Decision and Simulation Modeling in Systematic Reviews

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Methods Research Report

Decision and Simulation Modeling in Systematic Reviews

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Decision and Simulation Modeling in Systematic Reviews

Structured Abstract

Purpose. The purpose of this study is to provide guidance for determining when incorporating a decision-analytic model alongside a systemic review would be of added value for decisionmaking purposes. The purpose of systematic reviews is to synthesize the current scientific literature on a particular topic in the form of evidence reports and technology assessments to assist public and private organizations in developing strategies that improve the quality of health care and decisionmaking. However, there is often not enough evidence to fully address the questions that are relevant for decisionmakers. Decision models may provide added value alongside systematic reviews by adding a formal structure, which can be informed by the evidence.

Methods. Our framework is informed by two sets of interviews and a focus group discussion; literature reviews to summarize best modeling practices and to profile the modeling literature; and an exploration of the feasibility of developing a database of published models. We interviewed Evidence-based Practice Center (EPC) members, some of whom have successfully incorporated models in EPC reports, to document lessons learned from those experiences. We also interviewed members of the U.S. Preventive Services Task Force (USPSTF) and cancer modelers who were involved in the recent efforts to use modeling with a systematic review to update USPSTF cancer screening guidelines, to evaluate the process of conducting a simultaneous systematic review and modeling exercise, and to evaluate stakeholder-perceived needs and whether needs were met. We reviewed and summarized the literature on best practices for modeling. This was supplemented by a focus group discussion with modeling experts to elicit, characterize, and precisely qualify best practices in decision and simulation modeling. These included: model formulation and characterization, model development and construction, handling and presentation of modeling assumptions, definition and presentation of parameters, outcomes to incorporate into the model, model analysis, model testing, validation, and implementation (including results presentation and communication). We developed a profile of the current modeling literature by conducting a systematic review of the medical literature and the grey literature to document publications that used a decision model and for what purpose (e.g., disease of interest, interventions evaluated). We also developed a prototype database to serve as a preliminary step in developing a resource that could be used to determine if, and how many, models exist on a particular disease of interest.

Results. The resulting report consists of six chapters. Decision and Simulation Modeling Alongside Systematic Reviews provides an overview of models and describes the differences and synergies between systematic reviews and decision analysis. In Overview of Decision Models Used in Research, we provide a "scan" of the medical literature over the past 5 years in terms of the use of models in studies that compare intervention strategies using multiple sources of data. Use of Modeling in Systematic Reviews: The EPC Perspective documents the extent to which EPCs have incorporated models into data and presents results from key informant interviews with EPC members. We present a framework for deciding when a decision model can inform decisionmaking alongside a systematic review in Suggested Framework for Deciding

When a Modeling Effort Should Be Added to a Systematic Review. Potential Modeling Resources explores several possible approaches to use when undertaking a modeling effort and discusses some of the challenges. Lastly, Best Practices for Decision and Simulation Modeling reviews the literature on best practices for modeling, supplemented by a focus group discussion with modeling experts, and lessons learned about the process of conducting a modeling exercise alongside a systematic review using recent experience with the USPSTF.

Conclusion. We suggest a process for deciding when conducting a decision analysis in conjunction with a systematic review would be of value to decisionmakers.

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Executive Summary

Overview of Report

The overarching goal of our report is to provide guidance to determine when incorporating a decision-analytic model alongside a systemic review would be of added value for decisionmaking purposes. The purpose of systematic reviews is to synthesize the current scientific literature on a particular topic in the form of evidence reports and technology assessments to assist public and private organizations in developing strategies that improve the quality of health care and decisionmaking. However, there is often not enough evidence to fully address the questions that are relevant for decisionmakers. Or, there may be enough evidence on several components to the decision (e.g., diagnostic test characteristics, test risks, risk and effectiveness of treating disease), but no studies that evaluate the relevant clinical strategies that incorporate all of these components. In this example, the most relevant question for decisionmaking purposes is to address the comparison of alternative test-and-treat strategies, which synthesizes all of these data elements. Our framework is informed by two sets of interviews and a focus group discussion; literature reviews to summarize best modeling practices and to profile the modeling literature; and an exploration of the feasibility of the developing of a database of published models.

We present our findings in six chapters. Decision and Simulation Modeling Alongside Systematic Reviews provides an overview of models, and describes the differences and synergies between systematic reviews and decision analysis. In Overview of Decision Models Used in Research, we provide a "scan" of the medical literature over the past five years in terms of the use of models in studies that compare intervention strategies using multiple sources of data. Use of Modeling in Systematic Reviews: The EPC Perspective documents the extent to which Evidence-based Practice Centers (EPCs) have incorporated models to data, and presents results from key informant interviews with EPC members. We present a framework for deciding when a decision model can inform decisionmaking alongside a systematic review in Suggested Framework for Deciding When a Modeling Effort Should be Added to a Systematic Review. Potential Modeling Resources explores several possible approaches to use when undertaking a modeling effort and discusses some of the challenges. Lastly, Best Practices for Decision and Simulation Modeling reviews the literature on best practices for modeling, supplemented by a focus group discussion with modeling experts, and lessons learned about the process of conducting a modeling exercise alongside a systematic review using recent experience with the U.S. Preventive Services Task Force (USPSTF).

Decision and Simulation Modeling Alongside Systematic Reviews

Objective: To clarify the role of decision analysis and decision-analytic models in health care, specifically within the context of the current emphasis on evidence-based medicine and the proliferation of systematic and comparative effectiveness reviews.

This chapter sets the stage for the remainder of the report. We provide the historical context for the field of medical decisionmaking, documenting the growth of this relatively new discipline and noting the persistent concerns raised about its value in practice. Decision analysis is a systematic, quantitative, and transparent approach to making decisions under uncertainty. While

the methods of decision analysis have been applied to medicine for over 40 years, their use has only had modest impact on real-world decisionmaking.

The role of systematic reviews is to inform decisionmakers and policymakers about the current evidence pertaining to a clinical question that is aimed at improving the quality of health care and the lives of patients. Often situations arise where there is not enough evidence to fully address the clinical question, or where there are multiple sources of evidence available. In the absence of a systematic and formal approach to assist the decisionmaker(s) in the processing of the often disparate and complex evidence, the processing occurs in a more informal way, which may involve implicit value judgments and cognitive biases.

Decision-analytic models are mathematical structures that can be used to simulate the health outcomes of individual patients or populations under a variety of scenarios. They represent the core methodology of clinical decision analysis. Decision models can be a powerful tool for assessing public health and clinical policies for improving quality of health care and decisionmaking. Models can be used to: (1) project out beyond the time horizon of intervention studies, (2) extrapolate to other population subgroups not directly observed within a study, (3) incorporate data from multiple sources (e.g., clinical and health-related quality-of-life endpoints), (4) evaluate relevant comparators that have not been included in trials, and (5) project intermediate outcome measures (e.g., cases of cancer) used in trials to long-term outcomes, such as quality-adjusted life expectancy. One area where models may provide added value is alongside systematic reviews by adding a formal structure that could be informed by the evidence. The development of a decision model requires the analyst to synthesize all of the relevant literature that pertains to the question, including parameters for the natural history of (or risk of) a disease, effectiveness and risks of alternative interventions, and health-related quality of life. Thus, a modeling endeavor often relies on much of the same information provided by a systematic review, but it typically needs to be supplemented by clinically reasonable assumptions where data may be limited or nonexistent.

If done in a transparent manner, the methods of decision analysis provide a systematic and explicit way to examine a decision process and are an obvious companion for systematic reviews when there are limitations in the evidence base or multiple sources of evidence that require synthesis. Several types of decision models are appropriate for different types of clinical questions. However, they are all used for the same purpose: to assist in decisionmaking under uncertainty when a decision must be made.

Key Findings
- Decision models are mathematical structures that can synthesize multiple sources of evidence in a logical framework and project additional clinical outcomes that could be of value for decisionmaking.
- Although decision models have been used in medicine for over 40 years, their impact on decisionmaking has been modest.
- Systematic reviews are more commonly used to inform decisionmaking for a range of different clinical questions.
- The methods of decision analysis provide a systematic and explicit way to examine a decision process and are an obvious companion for systematic reviews when there are limitations in the evidence base or multiple sources of evidence that require synthesis.

Overview of Decision Models Used in Research

Objective: To profile the use of decision models in the published medical literature over the past 5 years. Decision modeling studies are defined as those that compare clinical outcomes associated with two or more strategies and incorporate data from multiple sources.

In this chapter, we present the results of a systematic review of the medical literature and the grey literature that documents and synthesizes all articles that used a decision-analytic model, including relevant cost-effectiveness analyses, conducted during 2005–2009. While there have been studies that document the use of cost effectiveness analyses or cost utility analyses, there has not been a comprehensive documentation of the use of decision analysis models in the literature. The purpose of this review was to get an overview of how prevalent the use of decision-analytic models is in the medical literature; to learn whether there are any patterns in their use, including country of origin; and to document what types of questions are typically addressed with a decision model.

We identified 1,773 articles in 2005–2009 that included the use of a decision model to compare the clinical outcomes associated with two or more strategies. The home country of the primary author was the United States for 42 percent of the articles. This was fairly consistent across years. The second most common home country of the primary author was the United Kingdom (16 percent), which was also consistent across this time frame. The journal Health Technology Assessment published the most articles (5 percent) in 2007–2009, followed by Pharmacoeconomics (4 percent).

The majority of the interventions modeled were treatment-related, representing 70 percent of the total articles. The second most common intervention type (12 percent) was prevention. These findings were consistent across the 5 years. The most common disease category evaluated was cancer (20 percent of the articles), followed by cardiovascular diseases (14 percent of the articles), and this was consistent across the 5 years. Approximately 11 percent of the articles specifically stated that the focus of the analysis was on a pediatric population, while 5 percent stated a focus on the elderly, and 15 percent had a stated focus on women only. The majority of the articles reported adjusted life years as an outcome (62 percent), most often quality adjusted life years. Other outcomes reported included life years, survival, and cases detected. While 20 percent of the overall articles focused on cancer, 33 percent of the screening articles focused on cancer. Some diseases were associated almost exclusively with treatment-related interventions (>90 percent of disease-specific articles related to treatment). These included mental diseases, kidney diseases, and multiple sclerosis. The diseases that were more commonly associated with prevention interventions (>25 percent of the disease specific articles) were lung diseases, influenza, and rotavirus. Most of the interventions pertaining to gastrointestinal diseases were related to diagnostics.

Key Findings

- Approximately 350 articles are published annually that use a decision model to compare alternative strategies.
- The majority of the interventions examined pertain to treatment, representing 70 percent of the total articles.
- The most common disease type evaluated is cancer (20 percent of the articles), followed by cardiovascular diseases (14 percent of the articles).

Use of Modeling in Systematic Reviews: The EPC Perspective

Objective: To review past EPC reports that have incorporated models and outline the specific reasons for incorporating models, the outcomes examined, and model contributions to the conclusions of the report. To complement the review of EPC reports, we also interviewed relevant EPC members about lessons learned from incorporating decision models in EPC reports.

This chapter documents the work done to date by EPCs to incorporate a decision model as part of a systematic review. We identified 11 EPC reports that used decision models. Only four used models as the prime methodology to answer key questions; the remaining seven used models to augment systematic review results. Reasons for incorporating models into the evidence reports include: (1) linking intermediate outcomes to clinical or patient-centered outcomes, (2) simulating head-to-head comparisons of interventions that were otherwise unavailable in the literature, (3) examining the cost-effectiveness of an intervention, and (4) modeling a novel hypothesis for disease progression to determine the impact on screening.

We developed a semistructured interview guide with four main themes: (1) what types of questions require a model, (2) what model outputs deliver the greatest utility to stakeholders, (3) what is the working definition of a model, and (4) how does one determine the quality of a model. We conducted phone interviews with EPC members from all EPCs. Interviewees with any degree of familiarity with models, whether firsthand or secondhand, tended to respond more similarly than those with no experience. Those interviewees with modeling experience unanimously held positive attitudes toward modeling with respect to its benefit in augmenting the evidence from systematic reviews. They stated that models are well suited to address gaps in the literature and to synthesize literature from differing sources and contexts into a single representation of the empirical evidence. The interviewees identified the lack of defined standards and methods as a major problem in the evaluation of models and hoped that this initiative would bring about some initial draft evaluation standards. A frequent issue mentioned was the ability to determine the opportunity or need for a model and/or simulation before the project has started, specifically before the question refinement phase has been completed and before an early stage literature review has been conducted. Lastly, all interviewees reported the desire for training resources.

Key Findings

- Eleven systematic reviews conducted by EPCs have incorporated a decision model.
- Interviewees with any degree of familiarity with models, whether first or second hand, tended to respond more similarly than those with no experience.
- Interviewees with modeling experience unanimously held positive attitudes towards modeling alongside systematic reviews.
- Interviewees stated that models are well-suited to address gaps in the literature and to synthesize literature from differing sources and contexts into a single representation of the empirical evidence.
- The interviewees identified the lack of defined standards and methods as a major problem in the evaluation of models and hoped that this initiative would bring about some initial draft evaluation standards.

Suggested Framework for Deciding When a Modeling Effort Should Be Added to a Systematic Review

Objective: To develop a framework for deciding when a decision model can inform decisionmaking alongside a systematic review of the evidence.

This chapter lays out a suggested framework for deciding when a decision model could be of added value to a systematic review. The purpose of systematic reviews is to synthesize the current scientific literature on a particular topic in the form of evidence reports and technology assessments to assist public and private organizations in developing strategies that improve quality of health care and decisionmaking. The addition of a decision analysis alongside a systematic review, as a separate yet integrated endeavor, would provide a tool for the decisionmaker that projects relevant health outcomes for all of the available options for several population subgroups. One of the most likely areas where a model could add value to a systematic review is for comparative effectiveness reviews.

The use of a modeling study should be supported and valued at the start by the relevant stakeholder(s). This may require that the stakeholder(s) be educated on what decision models are, how they have been used in practice, and their value. The timing of a modeling project in connection with a systematic review is important. One approach would be to have the report from the modeling study coincide with that of the systematic review. However, the results from the systematic review typically will be required to conduct the final modeling analysis. Thus, the addition of a decision model could delay the overall project. Another concern is the ability to determine the opportunity or need for a model before the project has started or before the question refinement phase has been completed. The proposal process could be augmented to include a more collaborative question refinement prior to proposal submissions, which would involve a relatively quick review of the literature to determine if there were aspects of the disease and interventions that were suitable for modeling.

Although decision models provide synergies with systematic reviews, the skills required to develop and analyze decision models are not typically well represented by groups that conduct systematic reviews. Because decision modeling requires a different skill set, it would be limiting to require that modeling work be done by the same team of researchers conducting a systematic review. Modeling is a multidisciplinary field that requires a nexus of experts in order to conduct credible modeling exercises on a wide variety of topics in timelines typical of a systematic review.

The several checklists available for determining best practices for evaluating decision models provide a minimum requirement for models. We propose that a checklist be used more to guide the documentation of a model and less to help distinguish "good" models from "bad" models. Again, if we focus on using models to assist the decisionmaker, a good model is one that includes inputs and outputs that are relevant to the decisionmaker and is ultimately useful and used by the decisionmaker. Model outcomes should always include those deemed relevant by the decisionmaker. However, we also recommend that a standard set of model outputs be developed to help with comparisons across models and aid in the acceptance of models over time. We recommend that quality adjusted life years (QALYs) be included as standard output, even though this may not be the most useful to a decisionmaker. In addition, life years (LYs) should also be included, as well as output that adds insight into the differences between the QALYs and LYs. For example, model output on the average amount of time spent in different health states could be provided to provide insight into QALYs. That is, , average QALYs are equal to the average time spent in each health state multiplied by the quality-of-life weight assigned to each state.

Findings from our interviews highlight the need for training users of decision models to educate them about the value, uses, and misconceptions of modeling. Opportunities for educating potential users of decision models could be created by incorporating a mechanism to conduct modeling alongside systematic reviews. Specifically, as a result of the interactive nature of the proposed framework, the modeling teams would be required to communicate the value of the decision modeling approach in a way that appeals to and is understood by the nonmodeling community. Part of the challenge to using decision analysis for real-world decisionmaking has been in communicating their value to policymakers and other nondecision analysts.

Key Findings
- The use of a modeling study should be supported and valued at the start by the relevant stakeholder(s), which may require that the stakeholder(s) be educated on what decision models are, how they are used in practice, and their value.
- Because decision modeling requires different skills than that needed to conduct systematic reviews, it would be limiting to require that modeling work be done by the same team of researchers conducting a systematic review.
- We propose that a checklist be used more to guide the documentation of a model and less to help distinguish "good" models from "bad" models.
- Model outcomes should always include those deemed relevant by the decisionmaker. However, we also recommend that a standard set of model output be developed to help with comparisons across models and aid in the acceptance of models over time.

Potential Modeling Resources

Objective: To explore several possible approaches to take when undertaking a modeling effort and discuss some of the challenges.

In this chapter, we compared three basic approaches for incorporating decision modeling alongside a systematic review: (1) a synthesis of the results of previous modeling studies, (2) modification of an existing model(s) so that it can be used to complement a systematic review, and (3) request the development of a de novo model. The first approach would provide a good first step to understanding the modeling issues pertaining to a disease and treatment area, but has several limitations in that it may not fit the question precisely, and it does not allow for input from the stakeholders. The second approach would require that modelers be willing to make changes to their models that are consistent with the values of the stakeholder, which may involve significant reprogramming in some cases. A key advantage to the third approach over using existing models is that it would limit any influence from prior modeling assumptions and would allow perhaps more unbiased input from stakeholders and the systematic reviews. This approach would be the most time consuming and costly, and may not be feasible for disease areas that require a fairly sophisticated modeling approach, such as cancer screening strategies.

To assist in identifying existing modelers, we explored the feasibility and potential value of a modeling database that includes some basic details about the existing models in the literature. There is potential value to developing a searchable database of models. However, more research is required to determine the most useful data fields and the best process of development and updating.

> **Key Findings**
> - There are three basic approaches that could be used once a decision has been made to use a decision model alongside a systematic review: (1) a synthesis of the results of previous modeling studies, (2) identify modeling groups that have an existing model that would be relevant for the particular systematic review, and (3) request the development of a de novo model.
> - There is potential value to developing a searchable database of models. However, more research is required to determine the most useful data fields and the best process of development and updating.

Best Practices for Decision and Simulation Modeling

Objective: To review and elicit best practices and recommendations for developing, validating, and using decision-analytic models in general as well as in the context of systematic reviews to inform decisionmaking of stakeholders such as the USPSTF.

This chapter focuses on best practices for decision-analytic models. We took a multipronged approach to gather information on best practices and recommendations for decision models. To identify existing recommendations for best practices in decision and simulation modeling we conducted a literature search. We identified 39 articles that provided guidance on key elements of what constitutes a good decision or simulation model. Of those 39 papers, 7 discuss good modeling practices; 4 discuss the roles, uses, or value of modeling in general; 20 focus on specific aspects of modeling; 3 propose comprehensive guidelines for modeling in a specific clinical domain; and 5 review and compare models in specific clinical areas. A compilation of all elements led to a structured list of 24 dimensions of model quality organized along four dimensions: structure, data, consistency/validation, and communication.

To complement our search of the current literature, we conducted a focus group of expert modelers to further discuss, characterize, and qualify best practices in decision and simulation modeling in general. The experts framed the discussion of modeling within the context of a decisionmaking framework, reiterated the results from the literature review regarding quality of models, further developed the need for interaction between the model and the decisionmaker(s) the model is intended to inform, and further developed the importance of model and model results communication.

To profile potential best practices of coordinating the simultaneous or sequential systematic review and modeling exercise, we interviewed breast, cervical, and colorectal modelers as well as USPSTF members about lessons learned from conducting decision and simulation models alongside systematic reviews to inform USPSTF recommendations. Three main themes emerged from these interviews: (1) communication and presentation of model results, (2) modeling literacy, and (3) recommendations for future projects. Despite the variability in how the modeling efforts were conducted across the three cancer projects, there was a high degree of consistency among interviewees regarding communication and modeling literacy. Interviewees stress difficulty in communicating models and results as a critical issue that needs to be addressed to improve success and acceptance of models. Interviewees also cited the need for some degree of modeling literacy among decisionmakers to increase understanding, acceptance, and use of models. There were differences among the respondents regarding recommendations for future projects. Overall, interviewees formulated a variety of recommendations along five basic categories: (1) goals and objectives for the project, (2) outputs and results, (3) USPSTF

interactions with modelers and/or reviewers, (4) project lead on the USPSTF, and (5) interactions between modeling and systematic review teams.

Key Findings
- A compilation of all best practices for modeling articles led to a structured list of 24 dimensions of model quality organized along four dimensions: structure, data, consistency/validation, and communication.
- A focus group of modeling experts highlighted the need for interaction between the model and the decisionmaker(s) the model is intended to inform, and further developed the importance of model and model results communication.
- Interviews with USPSTF and modelers involved with the cancer screening recommendations revealed that the difficulty in communicating models and results is a critical issue that needs to be addressed to improve the success and acceptance of models.
- Interviewees also cited the need for some degree of modeling literacy among decisionmakers to increase understanding, acceptance, and use of models.

Decision and Simulation Modeling Alongside Systematic Reviews

Overview

This chapter discusses the role of decision analysis and decision-analytic models in health care, specifically within the context of the current emphasis on evidence-based medicine and the proliferation of systematic reviews. Decision-analytic models are mathematical structures that can be used to simulate the health outcomes of individual patients or a population under a variety of scenarios; they represent the core methodology of clinical decision analysis. The goal of systematic reviews is to synthesize the current scientific literature on a particular topic in the form of evidence reports or technology assessments to assist public and private organizations in developing strategies that improve the quality of health care and decisionmaking. However, there is often not enough evidence to fully address the questions that are relevant to decisionmakers. Or, there may be enough evidence on several components of the decision (e.g., diagnostic test characteristics, test risks, risk and effectiveness of treating disease) but no studies that evaluate the relevant clinical strategies that incorporate all of these components in a manner that is most important for decisionmaking purposes, e.g., how does one test-and-treat strategy compare with an alternative test-and-treat strategy? Models may provide added value alongside systematic reviews by adding a formal structure, which can be informed by the evidence. The methods of decision analysis can provide a transparent, logical framework for structuring a decision process; decision analysis synthesizes all of the available evidence and projects outcomes that are relevant to the decisionmaker(s). One type of decision analysis is a cost-effectiveness analysis, which incorporates both the benefits and the costs of competing alternatives and explicitly considers a limited budget. Our report is focused on modeling more broadly and not on economic evaluations that use modeling to project costs and health benefits. Our framework would, in general, allow for inclusion of costs as an outcome.

Decision analysis is a quantitative discipline that can complement the fields of biostatistics and epidemiology. While the goals of biostatistics and epidemiology center on making inferences, or inferential statements about the truth, the goal of decision analysis is to make sound, rational, systematic decisions under conditions of uncertainty. Thus, decision analysis helps to understand the inherent tradeoffs that are present in complex decisions. It can identify those variables that most affect the decision and can help guide future research. In analyses that involve inference, a possible conclusion could be that there is not sufficient evidence to conclude that there is an effect and thus, no conclusive statements about the true effect can be made. In decision analysis, we start with the premise that a decision must be made and thus, there is no option to simply state that there isn't enough evidence to make the decision. A decision to not take action is indeed a decision, with potential consequences that are important to the decisionmaker and that can be quantified.

In the absence of a systematic and formal approach to assist decisionmakers in the processing of the (often disparate and complex) evidence, the processing occurs in a more informal way. It has been shown that individuals do not do a very good job processing multiple pieces of data in their heads. Tversky and Kahneman describe several biases and heuristics that may influence people when processing evidence informally, that is, in their heads.[1] For example, a policymaker may place too much weight on the diagnostic performance of a test and not enough weight on the

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prior probability of disease. Rittenhouse outlined several challenges that occur with the direct use of efficacy studies for policymaking.[2] Because many trials use a placebo comparison, it may not be an appropriate comparator for purposes of decisionmaking. In addition, because many patients in a trial receive protocol-driven care, the trial results may not be able to be generalized to a community setting (i.e., trials tend to have higher levels of adherence), and there may be other outcomes that are relevant to the decisionmaker that are not reported in a clinical trial, such as late outcomes that are not adequately captured due to the time horizon of the trial. Lastly, trial populations typically only represent a subset of patients for whom a decision is relevant. Thus, decision analysis can reduce the cognitive biases of informal decisionmaking and can project outcomes that are the most relevant to the decisionmaker, informed by the best available evidence.

Historical Overview of Decision Analysis

Decision theory has very early roots in mathematics, ethics, game theory, and economics.[3] In 1944, von Neumann and Morgenstern proposed the mathematical foundations for decision theory, which is based on four axioms of expected utility theory and which provide the framework for "rational" decisionmaking under uncertainty.[4] They synthesize the concepts of probability and value using the framework of preferences for lotteries. Since the publication of this historic work there have been many applications of decision analysis in business, policy, economics, industrial engineering, and other fields. The first application to medicine occurred in 1959, when Ledley and Lusted published an article titled "Reasoning foundations of medical diagnostics: Symbolic logic, probability, and value theory aid our understanding of how physicians reason" in the journal Science.[5] This landmark article focuses on diagnostics (i.e., how does a physician make a medical diagnosis?) and discusses three key concepts: logic, probability, and value. The authors discuss the importance of applying Bayes's formula to calculate the probability that a patient has a particular disease conditional on a set of signs and symptoms. (They use the terms "medical knowledge" to represent the concepts of sensitivity and specificity.) In addition, they apply the framework of expected utility theory to the choice of treatments, recognizing the probabilistic nature of the diagnosis (e.g., the diagnosis is Disease A, though there is a 70 percent chance of Disease A and a 30 percent chance of Disease B given the patient's signs and symptoms), and the relative effectiveness of alternative therapies. They propose that treatment decisions are based on the expected value of a valued outcome. In their examples, the outcomes were cure versus no cure in one and physician's assessment with regard to the pros and cons of treatment for each possible disease (ranging between −10 and 10) for the other. Drawing upon game theory, the authors note: "The process of choosing the best treatment can be described in the terminology of games. There are two players, the physician and nature. The physician is trying to determine the best strategy from his limited knowledge of nature. The … values … constitute the payoffs, what the physician will 'win,' and what nature will 'lose'."

The first publication of a medical application of decision analysis was Henschke and Flehinger's article titled "Decision Theory in Cancer Therapy," published in 1967.[6] The question addressed in that paper is whether or not prophylactic neck dissection should be done in the treatment of patients with cancer of the neck and head and no palpable metastasis to neck nodes. They note the high degree of risk associated with performing neck dissection among these patients and that the question "has plagued surgeons for more than 50 years and always produces spirited disagreement at medical meetings."[6] Neither this paper nor the examples in the Ledley and Lusted paper presents a formal decision tree, as these early examples were fairly simple and

could be solved analytically. Much of the authors' discussion was focused on their experience with opposition to their approach. They faced concerns such as "human values are not suitable for quantitative analysis" or that the available evidence is limited. Other concerns noted were that these methods would not be applicable in practice ("It would not be possible to induce the cancer specialist to use a sophisticated mathematical procedure in his daily work.") and the conclusions from decision theory only confirm what we already know and don't provide anything new.

In 1975, The New England Journal of Medicine focused an entire issue on articles and editorials pertaining to medical decisionmaking. Franz J. Ingelfinger, M.D., the editor at the time, stated in his editorial, "Analysis of the decision process is far from a new idea, but perhaps it is an idea whose time has come for those who deal with clinical medicine, whether as planners or practitioners."[7] By 1979, there was enough interest in the field of medical decisionmaking that a small group of researchers, mostly physicians, founded the Society for Medical Decision Making. The Society was formed "to promote the theory and practice of medical decisionmaking through scholarly activities, including research on and application of analytic methods to medical decisions affecting the care of individual patients, and to health policy decisions affecting the health of larger population."

The first textbook in decision analysis applied to medicine, Clinical Decision Analysis, was published in 1980.[8] In a foreword to the book, Howard Raiffa, Ph.D.—a prominent decision analyst at the Harvard Business School—writes:

"To me decision analysis is just the systematic articulation of common sense: any decent doctor reflects on alternatives, is aware of uncertainties, modifies judgments on the basis of accumulated evidence, balances risks of various kinds, considers the potential consequences of his or her diagnoses and treatments, and synthesizes all of this in making a reasoned decision that he or she decrees right from the patient. All that decision analysis is asking the doctor to do is to do this a lot more systematically and in such a way that others can see what is going on and can contribute to the decision process."

This textbook presents the construct of the decision tree as the basic analytic tool for decision analysis. The construction of the decision tree helps the decisionmaker display the logical sequences involved in the decision process, with decision nodes representing cases where the decisionmaker has a choice and chance nodes representing cases where the outcome is ruled by chance and beyond the control of the decisionmaker. The use of Markov models for medical decisionmaking was introduced in 1983 in the form of a Markov chain that can be solved analytically.[9] The primary difference between a Markov model and a decision tree is that the former models the risk of recurrent events over time in a straightforward fashion. This initial presentation of Markov chains formed the foundation for Markov processes,[10] which allow for the incorporation of time-dependent transition probabilities. Another key development in training decision analysts occurred in 1980 with the establishment of the Division of Clinical Decision Making within the Department of Medicine at the New England Medical Center Hospital (currently the Division of Clinical Decision Making, Informatics and Telemedicine at Tufts Medical Center) by Drs. Stephen Pauker and Jerome Kassirer. The purpose of this division was to conduct research, teach, train physicians, and provide consultations for physicians who are uncertain about the optimal management strategy for an individual patient. These consultations

included a literature review and formal decision analysis that explicitly weighed the risks and benefits of the available alternatives, and often resulted in publications. Two early DOS-based software packages designed to conduct decision analysis with trees and Markov processes (SMLTREE and DecisionMaker) were developed by fellows and faculty within this division during the 1980s.

Since 1980, there has been a steady increase in the number of decision analysis publications. Petitti reported an increase from approximately 20 decision analysis articles published in 1980 to approximately 250 articles published in 1997, based on a MEDLINE search.[11] This is likely an underestimate, as many of the cost-effectiveness analysis publications (about 420 in 1997) would be based on a decision analysis model. During the 1990's the Patient Outcomes Research Teams (PORTs) were one of the first initiatives to introduce modeling into policy. These multidisciplinary centers focused on particular medical problems and generally had an evidence synthesis component, a decision analysis component, and a dissemination component. Since 1992, the use of models for policymaking has risen dramatically as an increasing number of countries use formal cost-effectiveness analysis of interventions for coverage decisions (e.g., National Institute of Health and Clinical Excellence in the United Kingdom). The methods of decision analysis have advanced significantly with availability of personal computers that allow for the use of advanced methods which rely on faster computing speed and several textbooks with a focus on decision-analytic methods. There has also been an increase in training programs that offer courses and degrees in decision analysis and in professional societies that focus on decision modeling related areas. Also, a commercial software package has come to market (TreeAge). However, the fundamental goal of decision analysis has not changed—to assist decisionmakers in making complex decisions under uncertainty by providing a systematic, transparent, and quantitative approach to decisionmaking.

Taxonomy of Clinical Problems

In this section we present different types of clinical problems that are often addressed by systematic reviews, and for which decision-analytic models are used. We will introduce a taxonomy of clinical problems, based on one proposed by Kassirer et al. in a review of decision analyses prior to 1987.[12] Table 1 provides a summary of the different types of clinical problems. These categories may not be inclusive of all interventions, but they cover the vast majority.

Table 1. Summary of types of clinical problems

Type of Clinical Problem	Target Population	Intervention Goals
Prevention	Individuals without the disease or complication of interest; may be average risk or high risk.	Reduce the risk of disease or complication.
Screening/Prognostic	Individuals without the signs and symptoms of the disease of interest; may be average risk or high risk.	Detect underlying disease or marker for disease at an earlier and more treatable stage.
Diagnostics	Individuals with signs and symptoms of a disease.	Collect more information about the disease status to target treatment.
Treatment	Individuals with disease.	Reduce the risk of disease-related complications.

Prevention

Prevention includes all interventions targeted towards individuals without a disease or complication, where the primary goal of the intervention is to reduce the risk of the disease or

complication. The target population for interventions aimed at preventing disease would typically be a disease-free population, though they may represent those at high risk for the disease. The target population for interventions aimed at preventing complications is one with established disease, but the goal of the intervention is to prevent a complication and not treat the disease. An example of the latter would be predental antibiotic prophylaxis for patients with mitral-value prolapse.

One the most common prevention interventions is vaccination. Ideally, models that evaluate vaccinations against communicable diseases would utilize a dynamic model to capture the herd immunity effects. Interventions aimed at preventing noncommunicable diseases would typically involve modeling the risk of the disease over time. Evidence of the effectiveness of interventions that prevent disease typically involves long-term trials with large sample sizes with study populations that may not be generalizable to the population of disease-free individuals found in practice. Prevention trials can be costly compared to treatment trials and typically require a longer followup time to show a significant effect.

Screening/Prognostic

Many people who do not show signs and symptoms of a disease actually have the disease, or may carry a marker for disease (e.g., genetic mutation, elevated cholesterol levels). The goal of screening is to identify those individuals who have underlying disease, or marker for disease, prior to the time when signs and symptoms appear. In general, screening is likely to be an effective approach if the following five criteria are met, as outlined by Russel:[13] (1) the disease represents a significant burden on the population, (2) there is a reasonably long and/or detectable asymptomatic phase for the disease, (3) effective treatments are available for the condition, (4) treatment is more effective if delivered early, and (5) a test is available with good diagnostic performance characteristics. Often, screening does not involve a one-time screen; exceptions are newborn screening or genetic screening.

Cancer screening has been an active area for simulation modeling. Clinical trials that evaluate cancer screening strategies need to be long term with large sample sizes, yet they can never evaluate all of the possible strategies.

Diagnostics

The use of diagnostic tests follows a classic example of the need for a formal approach to decisionmaking. The three basic types of decisions that one can make are: (1) take action, (2) do not take action, and (3) collect more information. This framework translates directly to the diagnostic testing situation. When a patient presents with suspected disease, he or she has a probability of having the disease that can be estimated based on the clinical and demographic characteristics of the patient. If the probability is high enough, the optimal decision will be to empirically treat the patient. If the probability is low enough, the optimal decision would be to not treat (and not test) the patient. However, there is a range of prior probabilities of disease (which can be quantified using the methods of decision analysis) for which collecting more information in the form of a diagnostic test has value because it allows the clinician to tailor his or her treatment decisions based on the test results. The expected value of clinical information (EVCI) is defined as the difference in expected outcome between testing and not testing. Hence, the testing option is only worth doing if the EVCI is positive.

What distinguishes diagnostic testing from screening is that in the former situation an individual presents with suspected disease based on his or her signs or symptoms. Testing

options may involve the use of one test versus another, use of a sequence of tests, or the use of one positivity criterion versus another within one test. Evidence regarding diagnostic tests typically involves studies that estimate the sensitivity and specificity of the test, or possibly the receiver operator characteristic curve and area under the curve, but very few diagnostic test strategies have been evaluated in an integrated study, that is, a randomized clinical trial with patients randomized to different test strategies and followed until long-term outcomes are observed. Thus, decision models are very applicable to evaluating alternative diagnostic strategies because they can synthesize information on prior probability of disease, test characteristics, and treatment decisions conditional on test results.

Treatment

We define treatment broadly, as any intervention that is available for an individual, who already has a clinical condition or disease, with an effect on the prognosis of that condition. Treatment decisions may include the choice of treatment versus no treatment, the choice among several available treatments, or the sequencing of treatment. Evidence on the effectiveness of treatments is usually fairly good, with adequate follow up. The added values of using a model when there is a good evidence base would be to extrapolate findings to other patient subgroups, extend intermediate endpoints to survival, or evaluate sequences of treatment without direct evidence.

Roles of Systematic Reviews

Questions from stakeholders pertaining to any of the different types of clinical problems often prompt a systematic review of the evidence. There are fairly strict criteria for what may be called evidence and for determining the quality of evidence. Systematic reviews provide summary measures of the available evidence, as well as indicators of the quality of the evidence, but may fall short of providing outcomes that are synthesized in a way that would be most relevant for the decisionmaker(s). One of the challenges in conducting systematic reviews is how best to integrate different types of evidence. Evidence encountered by systematic reviewers can be either direct or indirect.[14] Evidence is direct if it relates (in a single study) a health care intervention directly to the occurrence of a key health outcome that informs decisionmaking. For example, a randomized controlled trial that compares statin therapy with no therapy (placebo) with a primary endpoint of cardiovascular mortality provides direct evidence. Alternatively, a similar trial with an endpoint of low-density lipoprotein cholesterol levels would provide only indirect evidence. Indirect evidence requires two or more pieces of evidence to relate the health care intervention to the principal health outcome. The latter example requires evidence on the relationship between low-density lipoprotein cholesterol levels and cardiovascular mortality in addition to the relationship between statin therapy and low-density lipoprotein cholesterol levels.

Because much of the evidence pertaining to health care interventions is indirect, how the multiple bodies of evidence get synthesized, whether formally or informally, is critical to health care decisionmaking. Decision models provide a way to synthesize multiple pieces of direct evidence in cases where only indirect evidence exists on the relationship between an intervention and the health outcomes of interest. Decision models can be used to structure the linkages between the intervention and the key health outcomes, where direct evidence can be used to inform each link. Thus, even though both systematic reviews and decision models are used to combine data, we view systematic reviews as an interpolation of the evidence with a goal of

enhancing our knowledge, and decision modeling as an extrapolation of the evidence with the goal of decisionmaking.

Types of Models

In this section, we present the different types of decision-analytic model structures that are typically used in medical decisionmaking applications. We present a simplification of the taxonomy of model structures proposed by Brennan et al.[15] We describe the key structural elements and the advantages and disadvantages of the following model types: decision trees, Markov (cohort) models, microsimulation (individual) models, dynamic models, and discrete event simulation models. The choice of what type of model to develop is typically related to the particular question at hand. The first three model types assume independence between individuals, while the latter two can model interactions among individuals, such as infectious disease transmission and restricted supplies of organs for transplantation. For a question with a relatively short time horizon, such as prevention of postoperative infections with no long-term sequelae, a simple decision tree may suffice. Questions pertaining to the prevention of infectious (communicable) diseases, such as the benefits of a childhood vaccination program, would require a dynamic model in order to capture the effects from herd immunity. Table 2 provides a summary of the different types of models, which are discussed in more detail below.

Table 2. Summary of types of decision model structures

Model Type	General Description	Type of Decision Best Suited For
Decision tree	Diagrams the risk of events and states of nature over a fixed time horizon.	Interventions for which the relevant time horizon is short and fixed.
Markov (cohort) model	Simulates a hypothetical cohort of individuals through a set of health states over time.	Modeling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events.
Microsimulation (individual) model	Simulates one individual at a time; tracks the past health states of individual and models risk of future events stochastically.	Modeling complex disease processes, when Markov models are too limiting.
Dynamic model	System of differential equations that simulates the interactions between individuals and the spread of disease.	Modeling interventions for communicable diseases, such as vaccinations.
Discrete event simulation model	Simulates one individual at time as well as interactions among individuals or within a health care system.	Evaluating alternative health care systems (e.g., workflow, staffing) though flexible enough to address questions in several different areas.

Decision Trees

A decision tree provides a logical structure of the decision and possible events as they unfold over time. The decision tree is made up of series of nodes and branches, and begins with a decision node (represented by a square) with all of the branches off of this node representing the different options available to the decisionmaker, such as treat, no treat, or test. Following these branches one can represent the events that can happen (e.g., patient has a positive test result) and the various states of nature that exist (e.g., patient has the disease of interest, though this is unknown to the decisionmaker) by a series of chance nodes (represented by circles) and branches

(representing events or states). The probabilities of events or states of nature dictate the chance of going down one branch versus another, and can be estimated from data. Decision nodes can be placed "downstream" to represent a decision that is made later; for example, the decision to do an additional test if the first test is negative.

The terminal nodes that are placed at the end of each of the possible pathways in the decision tree represent the outcome(s) of interest after a specified time horizon. The outcome or set of outcomes that is specified should represent what is important to the decisionmaker. A decision tree can be computed either analytically (called a "rollback analysis") to obtain the expected value of the health outcome associated with each strategy, or stochastically (i.e., where the outcomes are sampled) to obtain a measure of the variability in health outcomes in addition to the expected value. In some cases the outcome is very easy to quantify, such as whether the patient is dead or alive, that is, the optimal strategy will be the one that maximizes survival. For other cases the valued outcome is more qualitative in nature, such as levels of pain. Decision analysis, which includes the use of decision trees, uses utility theory or multiattribute utility theory to attach a value to all possible outcomes, which allows for a quantitative value to be assigned to a qualitative outcome in a manner that is consistent with the axioms of decisionmaking.[4] The quantification of qualitative outcomes is, indeed, one of the criticisms of the decision-analytic approach. Suppose treatment A resulted in equal chances of no, mild, or severe pain, and treatment B resulted in equal chances of no or severe pain, with no chance of mild pain. A decision to go with treatment A implicitly values mild pain closer to no pain, whereas a decision to go with treatment B values mild pain closer to severe pain. Such implicit value judgments must be made all of the time in health care. Decision analysis provides the tools to make them explicit and transparent to the decisionmaker.

The primary advantage of using a decision tree over the other types of models is that decision trees are easy to follow and laid out in a very logical and linear fashion. Even in cases where the decision tree is quite "bushy," the decisionmaker can view each of the possible pathways following an option, as well as the pathway probabilities. The primary disadvantage of a decision tree is that it is only applicable to situations where there are no (or very limited) recurring events and where the relevant time horizon is relatively short and fixed.

Markov Models

Many clinical conditions involve recurring events at uncertain times over the lifetime of an individual. For interventions targeted towards these conditions, a decision tree is less suitable as it would become unwieldy if it had to represent all possible sequences of events over a lifetime (or alternative time horizon). For example, consider individuals with high cholesterol levels who are at increased risk for coronary heart disease. If we used a decision tree to evaluate the use of statin therapy for these patients we would have to specify a fixed time horizon. For example, we could model the likelihood of having coronary heart disease at 10 years and the likelihood of dying (from any cause) under the "treat" and "no treat" scenarios. However, this framework would not capture when the disease or death occurred within the 10-year time frame, which may be important. It would also not capture any events that may occur beyond 10 years. Hence, Markov models are ideal for modeling clinical problems that involve risk over time, or when the timing of events is important. Markov models consist of a defined set of mutually exclusive and collectively exhaustive health states, where a cohort of simulated individuals resides over time. Markov models also provide a useful tool for calculating life expectancy, as that is often an outcome in interest in medical decisionmaking. For example, simple Markov models can extend

the time horizon of a decision tree with the sole purpose of calculating life expectancy with a two-state model ("alive" and "dead" states) using annual probabilities from a life table or adjusted life table. As with a decision tree, a Markov model can be computed either analytically to obtain the expected values of the outcomes or stochastically (i.e., where the outcomes are sampled) to obtain a measure of variability in health outcomes in addition to the expected value.

The advantage of using a Markov model is that this relatively standard modeling approach can capture many of the features present in a clinical process, such as risk of disease over time, changing health states over time and episodic events. The primary disadvantage is the underlying assumption that the probability of moving from one health state to another only depends on being in that state and does not depend on past history, either states visited in the past or time spent in that state. This assumption is known as the Markovian property and can be a very limiting assumption for clinical applications. The way that modelers get around this "memoryless" property is to create health state descriptions that include past history. For example, health states can be defined according to whether a stroke has occurred in the past, or perhaps even the number of or type of stroke. Health states can also be defined to include the number of years spent in a particular state. The impact of this is that the number of states can increase exponentially as the analyst attempts to include all of the relevant history for a clinical problem, which can result in a very large model that is difficult or sometimes impossible to manage.

Microsimulation (Individual) Models

The distinguishing feature of a microsimulation model is that it simulates one individual at a time, also called first-order Monte Carlo simulations. There are other model types that involve individual sampling; we refer in this case to any model structure that assumes independence between individuals, that is, a decision tree-type structure or a Markov-type structure. A Markov model is most often analyzed as a single cohort progressing through the health states simultaneously, which does not allow one to distinguish one simulated individual from another except by the health state descriptions. A key feature of a microsimulation model, or more generically referred to as an individual sampling model, is that it allows the model to keep track of each simulated individual's history so that the number of health states can be greatly reduced. Microsimulation models can track multiple comorbidities, whether continuous or not, for each simulated individual and allow comorbidities to interact and affect patient outcomes. A microsimulation model can simulate events one cycle at a time, or can simulate time to an event by drawing from distributions, thereby modeling in continuous time.

The advantage of a microsimulation model is that it is flexible in how the disease process and intervention are modeled and overcomes many of the limitations inherent with Markov models. The disadvantages are that they can take a considerable amount of computer time to run, as they require sometimes millions of individuals to be simulated in order to get a stable estimate of the expected value. These types of models are also difficult to debug compared with traditional Markov models. Specifically, a Markov trace, which provides the proportions of the cohort in each state by cycle time, is a convenient tool for checking model accuracy and testing face validity.

Dynamic Models

Dynamic models, or infectious disease models, are used when the disease of interest is communicable. These models typically use differential equations to simulate the interactions

between humans (e.g., in the case of airborne or sexually transmitted infection), or humans and animals (e.g., in the case of zoonoses), and how these interactions affect that spread of a disease over time. These types of models can also include spatial details that are pertinent to the spread of communicable disease, such as the location of classes in a school affected by an influenza outbreak. The advantage of these models is that, since they include information on how interactions between individuals affect transmission, they can more accurately quantify the impact of different interventions on health outcomes, such as vaccination and its impact via herd immunity. Brisson and Edmunds demonstrate the differences between using a Markov (static) model and a dynamic model to model the effectiveness of the varicella vaccination.[16] A limitation of these models is that, due to the complexity of programming, and the exponential increase in the number of differential equations needed to deal with the added complexity, they may, at times, include simplifications of complex programs such as screening programs. Examples include dynamic models of human papillomavirus and cervical cancer; to date these have failed to incorporate the detailed screening and triage strategies recommended by different policy groups, such as the American Society of Colposcopy and Cytopathology.[17] They may also be less transparent than Markov models, since the programs used to develop these types of models include mathematics software such as MatLab or Mathematica.

Discrete Event Simulation Models

Discrete event simulations are used primarily to evaluate systems. They have been applied to patient scheduling and admission rules, as well as patient routing and flow schemes.[18] Unlike Markov models they do not model the likelihood of experiencing an event within a specified time step (i.e., Markov cycle) but model the distribution of time until the next event, using time as a continuous scale. An example of the type of applications for which discrete event simulation models are uniquely designed is the comparison of current laparoscopic surgical practice with a new model system in which patient care is handed off between two anesthesiologists in order to balance patient volume and safety.[19] Another example is the evaluation of workflow models of parallel induction of anesthesia in the operating room to optimize facilities and use of resources.[20] These types of applications are typically outside the scope of systematic reviews.

Concerns With Modeling

Since the beginning of the use of decision-analytic models there has been a healthy amount of skepticism about their value. Many of the concerns raised by Henschke and Flehinger in their 1967 paper[6] are still applicable today. In a 1979 "Sounding Board" article in The New England Journal of Medicine, Dr. William Schwartz discusses several major concerns of physicians, academicians, and students about decision analysis which echo those concerns raised by Henschke and Flehinger.[21] One common criticism is that decision analysis requires quantification of all model parameters, and often the data aren't sufficient for such quantification, or that some outcomes are not quantifiable. This concern reveals the fundamental misconception about the goal of decision analysis: that it is an explicit and transparent approach to assist decisionmakers with complex decision when a decision must be made. Decisions are made every day with limited data, and implicit values are placed on qualitative outcomes; decision analysis provides the tool to help with this process. Another criticism is the concern that decisionmakers might not agree with the answer. For example, if a decision analysis showed that the risks of an intervention outweigh the benefits, this may be at odds with the conclusions that the decisionmaker would draw without the formal decision-analytic results. Again, since the

goals of decision analysis are to assist the decisionmaker and not necessarily provide "the answer," this situation should make explicit the decision process, with sensitivity analysis showing the effects of varying model parameters. These commonly voiced concerns about the use of decision models pose challenges for developing a framework to incorporate decision models into practice and will require that the methods and goals of decision analysis be made transparent to the decisionmaker.

Models Alongside Systematic Reviews

Much of the discussion to this point has been focused on the structure and purpose of a decision model and the goals of decision analysis in general. However, the value of a model does rely to some extent on the quality and availability of the data available to inform the model parameters. One of the goals of systematic reviews is to promote evidence-based practice in everyday care in the form of systematic reviews conducted to assist key stakeholders with decisionmaking. While a thorough and systematic synthesis of the available evidence to date, along with information regarding the grade of evidence, is no doubt a powerful tool for decisionmakers, it may not always provide a sufficient amount of information to the decisionmaker. If the evidence is weak regarding one parameter/question (e.g., risks of mild side effects, specificity of a test), how much will that matter in the decisionmaking process of the stakeholder? If data are strong for one subgroup of the population, what can be said about other subgroups for which data are not particularly strong? If an intervention has a significant effect on a surrogate marker, how does that translate into endpoints that are most important to the decisionmaker? Decision analysis provides an explicit and transparent way to: (1) synthesize data from disparate sources, (2) extrapolate beyond the time horizons of available data, (3) extrapolate beyond surrogate markers, (4) quantify all of the relevant clinical outcomes, (5) evaluate parameter uncertainty, and (6) quantify the value of conducting further research.

Despite the obvious role that decision modeling can play in providing additional relevant data, the added value of a decision model alongside a systematic review has never been formally evaluated. For situations where the evidence base is sufficient for addressing the policy questions of interest, we would expect that the added value of a decision model would be minimal. For situations where data are insufficient for either some aspect of the question or for a population subgroup of interest, then we would expect that the potential value of adding a decision analysis to inform decisionmaking would be substantial because it would provide a rational and transparent framework. Without such a framework, the decisionmaker would need to fill in the data deficiencies using implicit values and judgments, or may opt for "not making a decision," which in turn has relevant harms and benefits that may not be transparent to the decisionmaker. The addition of a decision model provides an objective, systematic, and explicit approach to decisionmaking that would enhance and clarify the decisionmaking process.

An important question arises regarding the quality of the evidence that goes into a decision model, which should ideally be connected with how model results are used to inform decisions. Typically, decision models include the best available evidence under the assumption that a decision will be made. However, there are certain "decisions" that may be more nuanced. For example, should a guidelines committee make a recommendation for the best strategy and provide the overall quality of the evidence informing that recommendation? Or, as is often the case, should guidelines fail to recommend anything in cases where the quality of the evidence is poor? Braithwaite and colleagues evaluated the cost-effectiveness of directly observed therapy for individuals with newly diagnosed HIV infection using a decision-analytic model.[22] They

conducted a series of analyses where they used different stringency of criteria for selecting which sources of evidence to use in the analyses. Often, the optimal decision found under both approaches is the same, as it is based on the strategy that maximizes an expected outcome, for example, quality-adjusted life years. However, the confidence with which one can state that one strategy is better is diminished if evidence of poorer quality is excluded. The choice of what levels of evidence to include in a decision analysis, or conducting a sensitivity analysis of varying the inclusion of different levels of evidence, should be the choice of the decisionmaker. Braithwaite and colleagues concluded that different a priori approaches may appeal to different types of decisionmakers: the "any data are better than no data" decisionmaker versus the "my judgment supersedes all but the best data" decisionmaker.[22]

An example of when modeling informed a systematic review is the 2007 U.S. Preventive Services Task Force (USPSTF) update of its recommendations for colorectal cancer screening.[23] The Task Force requested a decision analysis for colorectal cancer to assist it in determining the age to begin and end screening, and intervals of screening for multiple screening tests, for which no direct evidence was available or likely ever to be available. This is the first time that the Task Force used a decision analysis in combination with a systematic evidence review to inform its decisions. Two modeling groups from the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium provided standardized comparisons of 145 screening strategies using the best available evidence for consideration by USPSTF. The Task Force recommendations were published in fall 2008,[24] along with the systematic review[25] and decision analysis.[26] The Task Force recommended a stop age for screening among those individuals who have screened consistently negative between ages 50 and 75; this is the first guideline for colorectal cancer screening to recommend a stop age.

Issues Pertaining to a Modeling Framework

What is a Model?

In order to explore the value of developing a model alongside systematic reviews, it is first important to define exactly what we mean by a model. Broadly speaking, a "model" can represent a physical structure that represents an actual entity (e.g., a model airplane) or can be a series of mathematical equations that describe supply and demand. See Weinstein et al. for a more detailed discussion of modeling for health care.[27] For the purposes of decision modeling in health care, we define a decision model as a mathematical structure that describes the sequences of events and states of nature that can occur over time under alternative scenarios, that is, the alternative strategies available. A model provides a "virtual public health laboratory" to project out the average health outcomes associated with alternative policies, incorporating all of the evidence available to the decisionmaker. A decision model often incorporates mathematical functions that represent what we know about the disease, or the relationships between risk factors and disease, or disease and clinical outcomes. The impact of these assumptions can be evaluated in sensitivity analysis.

Grading Models

To date there has been no development of a grading system to designate whether a decision-analytic model is "good" or "bad." The idea of a model grading system is appealing because there is a high degree of skepticism and misunderstanding surrounding the usefulness of a model.

However, it is commonly recognized that a grading system for decision models is unrealistic.[28] Nonetheless, there are checklists that one can use (usually provided for cost-effectiveness analyses but some criteria apply more broadly to decision models) that cover basic analytic steps which every decision analysis should include, but should be viewed as minimal criteria. An example of such a checklist, adapted from the one suggested by Sculpher and colleagues[28] is shown in Table 3. Even if one were to impose a criterion that models should include a natural history component, this may be difficult to judge in all cases.

Table 3. Minimal criteria for a high-quality decision model (adapted from Sculpher et al., 2000)[28]

Dimensions of Quality	Attributes of "Good Practice"
Structure	Model structure should be consistent with the stated decision problem. The structure should be dictated by theory of disease, and not by data availability.
Disease states	Model should reflect the time dependence of the disease process. States should reflect the underlying biological process of the disease and the impact of intervention, rather than health services inputs. The number of states should be manageable, reflect all important aspects of disease, and not be omitted on the basis of lack of data.
Options	Options and strategies should not be limited by constraints of currently accepted clinical practice. A balance is needed between full range of options and keeping decision problem manageable.
Time horizon	The time horizon should be sufficient to capture all important health outcomes. Lifetime time horizons will be appropriate for many models; shorter time horizons can be justified according to understanding the disease process (e.g., impact on morbidity and not mortality) and effect of interventions.
Cycle length (if relevant)	The length of a cycle should be the minimum interval over which pathology and/or symptoms in patients is expected to alter. The analyst should justify the selection of the cycle length in terms of disease process.
Data identification	It is inappropriate to criticize a model because of lack of data. "Best available" data should be referred to as "optimal available" data as it is an empirical question whether acquiring all existing evidence is a good use of resources. Models can be used to undertake formal value of information analysis to determine the optimal data to incorporate. Analyst should make clear all low-cost sources have been searched for the appropriate parameter values. Methods used for parameter identification when no data are identified should be fully detailed.
Data incorporation	The process of data incorporation should follow accepted methods of epidemiology and statistics. Different sources of uncertainty should be distinguished (uncertainty, heterogeneity, first- and second-order uncertainty). Interval rates should be translated into transition probabilities using appropriate formula. Models should use half-cycle correction.
Internal consistency	The model should be checked and tested by the analyst (debugging).
External consistency	If possible, the model outputs should be compared to the results from relevant primary research studies (not used to inform model inputs).

Modeling Results

The process of building a decision model can be instructive to the decisionmaker, as it requires one to be explicit about the uncertain events and the true states of nature. It also requires careful thinking about what the possible comparison strategies are and for whom. Once a model is developed and the relevant parameters are quantified (ideally informed by a systematic review, when applicable) there are several analyses that can be conducted with the decision model, as outlined below.

Base-Case Analysis

This analysis estimates the expected values of the clinical outcomes associated with each strategy. The outcome could be a composite outcome that combines length of life and quality of life (e.g., quality-adjusted life years) or it could be a disease-specific outcome (e.g., number of acute events over a person's lifetime). The base-case analysis provides a ranking of all of the strategies using the best estimates for all of the input parameters.

Sensitivity Analysis

In one-way sensitivity analysis, the analyst varies each of the parameters one at a time within a clinically plausible range (or 95 percent confidence interval) to determine which parameters have the most impact on the base-case results. Two-way (or three-way) sensitivity analysis can be performed by varying two (or three) parameters simultaneously, though this type of sensitivity analysis gets impractical above three parameters.

Probabilistic Sensitivity Analysis

To evaluate all of the parameter uncertainty simultaneously, point estimates in the model can be replaced with probability distributions, where the mean of the distribution reflects the best estimate of the parameter and the variance reflects the uncertainty of the mean. For example, a commonly used distribution for probability estimates is the beta distribution since it is bound between 0 and 1. The model is then run many times (e.g., 1,000 simulations). For each simulation model, parameter values are randomly drawn from each of the distributions and the expected model outcome is recorded. The 1,000 simulations result in a distribution of expected model outcomes (e.g., quality-adjusted life expectancies for each strategy), which reflects the overall parameter uncertainty in the model.

Value of Information Analysis

While probabilistic sensitivity analysis describes the uncertainty in the model outputs based on the uncertainty in the model inputs, value of information analysis describes (in health terms) the "value" associated with reducing the uncertainty (in the form of conducting further studies) of one or more parameters. The notion is that by gathering more information on a parameter, we would reduce the variance of the distribution for that parameter and thus increase our chances of making a better decision. Hence, the increase in the probability in making a better decision leads to better clinical outcomes. Value of information analysis is most often done within a cost-effectiveness framework, where the value of further research is valued in terms of costs (using a specified willingness to pay threshold for a quality-adjusted year of life gained).

Summary Statement

While the underpinnings of decision analysis have a long history, the applications to health care have only occurred within the last 5 decades. The methods of decision analysis provide a systematic and explicit way to examine a decision process and are an obvious companion for systematic reviews when there are limitations in the evidence base, or multiple sources of evidence that require synthesis. There are several types of decision models available that are appropriate for different types of clinical questions. However, they are all used for the same purpose: to assist in decisionmaking under uncertainty when a decision must be made.

Overview of Decision Models Used in Research

Introduction

Decision analysis is a systematic, quantitative, and transparent approach to making decisions under uncertainty. The fundamental tool of decision analysis is a decision-analytic model, most often a decision tree or a Markov model. A decision model provides a way to visualize the sequences of events that can occur following alternative decisions (or actions) in a logical framework, as well as the health outcomes associated with each possible pathway. Decision models can incorporate the probabilities of the underlying (true) states of nature in determining the distribution of possible outcomes associated with a particular decision. These probabilities are not known to the decisionmaker but are critically important. For example, the value associated with the decision to do a diagnostic test depends on the probability that the patient has the disease of interest (i.e., the prior probability of disease), which in turn determines the probabilities of true and false positive findings, as well as true and false negative findings. Ultimately, the relative values assigned to these different outcomes determine the clinical value of a test, for example, how bad is it to fail to treat a person with disease relative to treating a person without disease? While the evidence requirement for a diagnostic test focuses on its diagnostic performance (e.g., sensitivity, specificity), the clinical value of the test, which should underlie the decision to use or recommend the test, depends on clinical evidence well beyond measurements of test performance. For example, does the information obtained from the diagnostic test change the decision that would be made, and does this change in decision lead to improved health outcomes? The methods of decision analysis have been found to be particularly useful in settings where multiple data inputs from a variety of studies are relevant in a particular decisionmaking context.

Since the first application in 1967, decision-analytic models have been increasingly used to evaluate and compare competing public health and medical interventions. Decision models can vary from a very simple "back of the envelope" type of calculation to extremely complex computer-based microsimulation models. While the term "model" has different meanings in different clinical settings,[27] such as a statistical model, the fundamental feature of a decision model is that the goal of a decision model is to assist with decisionmaking and not to make statements about truth. Statistical study designs such as randomized clinical trials and case control studies are focused on gathering evidence; however, decision analysis studies are aimed at processing evidence. In the absence of a systematic and formal approach that assists the decisionmaker in the processing of the (often disparate and complex) evidence, the processing occurs in a more informal way.

There has been little documentation of the use of decision models in the literature. Hence, the goal of our analysis was to profile decision-analytic models published in the literature over the past 5 years, and to provide a summary of who is publishing models, in what disease areas, in what journals, and for what types of interventions.

Methods

Overview

We sought to obtain a "bird's eye" view of the number of articles in the medical literature that used a model for medical decisionmaking purposes. Our goal was to capture studies that used the methods of decision analysis to project health outcomes associated with two or more competing strategies for purposes of decisionmaking. We were not interested in studies with a goal of estimating efficacy or effectiveness parameters, nor were we interested in studies that evaluation environmental interventions or regulatory policies. Our goal was to document the current use of decision models in the medical literature (within the past 5 years) and document basic information about the authors and analyses.

Literature Search

We conducted a systematic review of the medical literature and the grey literature to document and synthesize all analyses that used a decision-analytic model, including relevant cost-effectiveness analyses, conducted within the past 5 years.

We searched Medline for articles that used some form of decision model. We relied on key word searches to locate decision models since medical subject headings (MeSH) terms are not well indexed for decision modeling topics. Searches employing a model term other than "decision analysis" or "decision analytic model" required filters to eliminate nonrelated articles. For these filters, we used some form of quality adjusted life OR some form of incremental cost effectiveness ratio OR some form of disability adjusted life OR some form of modeling technique to further specify related articles. In addition, since cost-effectiveness models are the most commonly noted form of economic modeling references in the literature, we created a filter to further limit cost-utility and cost-effectiveness models to those that were not reported as simple extensions of a single clinical trial, as these were viewed as not incorporating multiple sources of data. Articles were limited to English language and human subjects. The full search string is provided in Appendix A. The search was performed on October 15, 2009, with an update search performed on February 18, 2010, for articles published from 2005 through 2009.

Inclusion/Exclusion Criteria

Articles were not excluded by country of origin, type of disease condition, or treatment provided. We also did not include decision aids or statistical analyses for estimating effect size, inference, or prediction. We included cost-effectiveness analysis as long as the model was used to project the costs and the effectiveness of two or more strategies, but excluded papers that evaluated costs only. Since our focus was on the effectiveness/comparative effectiveness of health care interventions at the individual level, we did not include dynamic models, or infectious disease models, which focus on describing epidemics rather than on evaluating strategies for decisionmaking purposes. We also excluded papers that reviewed current evidence around a topic, which may include pertinent decision analysis models, but did not use a model explicitly.

Screening and Data Abstraction

Model Definition

To ensure a broad look at the use of models in the literature, we defined a decision model as a mathematical structure developed to synthesize two or more sources of evidence, used to project out the health outcomes associated with alternative policies. This model definition is broader than what was applied to determine eligibility for the database discussed in the Potential Modeling Resources section of this report. Again, the purpose here was to generate a broad sense of the state of the literature.

Abstract Review

References generated from the search string were imported to Refworks for screening. Two reviewers screened all reference titles and abstracts for inclusion or exclusion. Conflicts were reconciled by a third reviewer through consensus. Included references were retained for abstracting. For excluded abstracts, the reason for exclusion was noted. Each abstract retained was reviewed independently by two readers. The reviewers abstracted the following information: title, journal, country of primary author, type of intervention, class of intervention, target disease, country of the target population, age group of the target population (children, adult, elderly), and the type of health outcome reported. The reviewers met to compare abstraction results; conflicts were reconciled through consensus, using a third reviewer if necessary.

Intervention Classification

The modeling analyses were classified according to the type of interventions that were evaluated: prevention, screening, diagnosis, and treatment.

Models were classified as "prevention" if the model studied an intervention aimed at a population with no symptoms with the express intent to prevent a certain disease. This most often includes models to evaluate the effectiveness of vaccinations, but also included pharmacological and other types of interventions, e.g., bed nets for malaria prevention.

Models were classified as "screening" if the intervention pertained to patients with no specific symptoms or diseases but was a method to determine a certain affliction from a general population. There were some caveats allowed in this definition in cases where a higher-risk population could be identified by factors other than signs and symptoms of a disease or condition. For example, we would categorize colonoscopy screening every 5 years among individuals who have had a polypectomy in the past as screening. Although this group is at higher risk of having colorectal cancer or an adenomatous polyp than the general population, members do not have signs and symptoms of disease at the time of the colonoscopy. (Note that in practice, this is referred to as surveillance and not screening.) Screening also includes those models that examine strategies of screening versus treatment of certain disease.

The "diagnosis" categorization includes models that target a population with a set of signs and symptoms related to a disease. Diagnostic interventions include the use of a diagnostic test to gather more information about the disease status of the patient and to target subsequent treatment or further testing based on the test results. This category includes lab testing, radiological test, and genetic tests.

Models were given the categorization of "treatment" if the model examined a certain intervention to be used on patients who had a specific disease. This can include pharmacological interventions, procedural interventions (surgery, noninvasive device), or organizational

interventions, such as stroke unit care. Treatment can also include strategies aimed at preventing complications in the normal course of treatment for disease, such as using a certain kind of surgical instrument to avoid infections when treating a patient.

Disease Classification

The articles were also classified according to the diseases targeted with the interventions. These diseases represent either the disease that the target population already had (in the case of treatment), the disease that the target population might have (in the case of screening or diagnostic interventions), or the disease that the intervention is aimed at preventing, (in the case of prevention.) Table 4 shows the disease categories that we used.

Table 4. Disease categories

Disease Type	Comments
Cancer	Excludes benign tumors, polyps.
Cardiovascular diseases	Includes heart and vascular disease, stroke, embolisms, aneurysms.
Bones/joints	
Lung diseases	Includes COPD, pneumonia, pneumococcal TB, asthma. Excludes lung cancer.
Hepatitis/liver diseases	Excludes cancers of the liver.
Mental disorders	Includes MDD, dementia, Alzheimer's, ADHD.
Kidney diseases	Includes CKD, renal hypertension, kidney injury. Excludes renal cancers.
Pregnancy/infertility/birth defects	
Rotavirus	
Gastrointestinal	Excludes gastrointestinal cancers.
Vision/eyes	
Diabetes	Includes type I and type II.
HIV/AIDS	
Influenza	
MRSA/nosocomial infection	
Multiple diseases/conditions	
Smoking/smoking related illnesses	Includes only studies with self-defined "smoking related disease" groupings; may include lung cancer.
Multiple sclerosis	
Hearing/ears	
Other	Diseases or conditions not covered above.

COPD = chronic obstructive pulmonary disease; TB = tuberculosis; MDD = major depressive disorder; ADHD – attention deficit hyperactivity disorder; CKD = chronic kidney disease; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; MRSA = methicillin-resistant *Staphylococcus aureus*.

Summary Statistics

For the 5-year time period, we calculated the distributions of the home country of primary author, the journal, type of intervention, disease categories, the target population, and outcomes measures.

Results

We present an overview of the use of decision-analytic models in the medical literature over the past 5 years. We identified 1,773 articles published in 2005–2009 that included the use of a decision model to compare the clinical outcomes associated with two or more strategies and excluded an additional 1,075 articles. Of the 1,075 articles excluded, the majority (56 percent) were deemed to be outside the scope of the review because they did not involve the comparison of two or more health care interventions. Other reasons for not including articles are shown in Table 5.

Table 5. Reason for rejection (2005–2009)

Reason	Number of Articles	Percent
Outside scope of review	601	56%
Review	171	16%
Statistical analysis	163	15%
No abstract	65	6%
Costs only	62	6%
Decision aid	11	1%
Comment letter	2	<1%
Total excluded articles	1,075	

The home country of the primary author was the United States for 42 percent articles, and this was fairly consistent across years. The second most common home country of the primary author was the United Kingdom (16 percent), which was also consistent across this timeframe. Table 6 shows the distribution of the home country of the primary author of the 2005–2009 modeling articles.

Table 6. Home country of primary author (2005–2009)

Country	Number of Included Articles	Percent
United States	741	42%
United Kingdom	291	16%
Canada	133	8%
Netherlands	98	6%
Australia	65	4%
Sweden	59	3%
Japan	40	2%
Switzerland	39	2%
Germany	37	2%
France	33	2%
Belgium	32	2%
Spain	30	2%
Italy	24	1%
Taiwan	12	<1%
Denmark	11	<1%
China	10	<1%
Thailand	10	<1%

Table 6. Home country of primary author (2005–2009) (continued)

Country	Number of Included Articles	Percent
Greece	8	<1%
Korea	7	<1%
Finland	7	<1%
Austria	7	<1%
Ireland	7	<1%
Israel	7	<1%
Brazil	6	<1%
Not specified	5	<1%
Argentina	4	<1%
Norway	4	<1%
Columbia	4	<1%
Slovenia	3	<1%
South Africa	3	<1%
New Zealand	3	<1%
Kenya	2	<1%
Paraguay	2	<1%
Portugal	2	<1%
Hong Kong	2	<1%
Chile	2	<1%
Turkey	2	<1%
Other* (1 article)	17	<1%
Total included articles	1,773	

* India, Haiti, Bulgaria, Estonia, Russia, Hungary, Saudi Arabia, Egypt, Sendai, Ecuador, Republic of Congo, Mexico, Serbia and Montenegro, Ghent, Jordan, Indonesia.

Health Technology Assessment published the most articles (5 percent) in 2005–2009, followed by Pharmacoeconomics (4 percent). Table 7 shows the distribution of articles by journal name. Table 8 shows the type of interventions modeled in the 2005–2009 modeling papers. The majority of the intervention types were treatment, representing 70 percent of the total articles. Among the articles that targeted a diseased population, 46 percent of the interventions were pharmaceutical interventions, and 14 percent of them evaluated procedural interventions. The second most common intervention type (12 percent) was prevention, most of which pertained to the evaluation of vaccinations. Screening strategies were evaluated in 12 percent of the articles and diagnostic interventions were evaluated in 6 percent of the 2005–2009 articles. These findings were consistent across years. (Data not shown.)

Table 7. Journals represented with more than seven articles (2005–2009)

Journal Name	Number of Articles	Percent
Health Technology Assessment	95	5%
Pharmacoeconomics	78	4%
Current Medical Research & Opinion	61	3%
Value in Health	50	3%
Vaccine	49	3%
International Journal of Technology Assessment in Health Care	40	2%

Table 7. Journals represented with more than seven articles (2005–2009) (continued)

Journal Name	Number of Articles	Percent
Clinical Therapeutics	31	2%
European Journal of Health Economics	22	1%
Medical Decision Making	21	1%
Annals of Internal Medicine	20	1%
Cancer	20	1%
Pediatrics	19	1%
Alimentary Pharmacology & Therapeutics	18	1%
Journal of Clinical Oncology	17	<1%
British Medical Journal (BMJ)	16	<1%
Osteoporosis International	16	<1%
Breast Cancer Research & Treatment	15	<1%
Obstetrics & Gynecology	15	<1%
Archives of Internal Medicine	14	<1%
JAIDS: Journal of Acquired Immune Deficiency Syndromes	14	<1%
Gynecologic Oncology	13	<1%
Sexually Transmitted Diseases	12	<1%
Clinical Gastroenterology & Hepatology	12	<1%
American Journal of Obstetrics & Gynecology	12	<1%
Clinical Drug Investigation	11	<1%
Radiology	11	<1%
Journal of Bone & Joint Surgery – American Volume	10	<1%
Rheumatology	10	<1%
Hepatology	9	<1%
AIDS	9	<1%
Health Policy	9	<1%
Gastrointestinal Endoscopy	8	<1%
American Journal of Preventive Medicine	8	<1%
Annals of Oncology	8	<1%
All other	1,000	56%
Total included articles	1,773	

Table 8. Type of intervention modeled (2005–2009)

Intervention Type	Number of Articles	Percent
Treatment	1,240	70%
Pharmacy	809	46%
Procedure	248	14%
Other	168	9%
Multiple	3	<1%
N/A	2	<1%
Vaccination	1	<1%
Prevention	209	12%
Vaccination	131	7%
Pharmacy	29	2%
Other	45	3%

Table 8. Type of intervention modeled (2005–2009) (continued)

Intervention Type	Number of Articles	Percent
Multiple	1	<1%
Procedure	2	<1%
Screening	219	12%
Diagnostic	104	6%
Multiple	1	<1%
Total included articles	1,773	

N/A = not applicable

Table 9 shows the classes of disease types that were the focus of the 2005–2009 articles. The most common disease type evaluated was cancer (20 percent of the articles), followed by cardiovascular diseases (14 percent of the articles), and this was consistent across the 5 years (data not shown).

Table 9. Diseases addressed by models (2005–2009)

Disease Group	Number of Articles	Percent
Cancer	348	20%
Cardiovascular diseases	256	14%
Bones/joints	113	6%
Lung diseases	91	5%
Hepatitis/liver diseases	82	5%
HIV/AIDS	73	4%
Diabetes	69	4%
Mental	69	4%
Gastrointestinal	69	4%
Pregnancy/infertility/birth defects	55	3%
Kidney diseases	45	3%
Multiple diseases/conditions	45	3%
Influenza	37	2%
Vision/eyes	32	2%
Smoking/smoking related diseases	29	2%
Rotavirus	20	2%
MRSA/nosocomial	16	<1%
Multiple sclerosis	9	<1%
Hearing/ears	9	<1%
STDs (other than HIV/AIDS)	7	<1%
All other	299	17%
Total Included articles	1,773	

HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; MRSA = methicillin-resistant *Staphylococcus aureus*; STDs = sexually transmitted diseases.

Table 10 shows the age (in broad categories) and sex of the target populations for those modeling articles that specified age and sex in the abstracts for 2005–2009. Approximately 10 percent of the 1,773 articles specifically stated that the focus of the analysis was on a pediatric population, while 6 percent of the stated a focus on an elderly only population and 15 percent with a stated focus on women only.

Table 10. Target populations (2005–2009)

Target Age Group	Target sex				Total Included Articles	Percent
	Both sexes	Female	Male	Not specified		
Adults	395	162	50	31	638	36%
Children	143	21	2	10	176	10%
Adults and elderly	185	58	13	11	267	15%
Elderly	62	17	16	8	103	6%
All ages	108	-	-	-	108	6%
Children and adults	26	11	-	1	38	2%
Not specified	140	21	2	280	443	25%
Total included articles	1,059	290	83	341	1,773	
Percent	60%	15%	5%	19%		

Table 11 shows the primary outcome measures reported in the 2005–2009 modeling articles. The majority of the articles reported adjusted life years as an outcome (62 percent). Other outcomes reported included life years, survival, and cases detected.

Table 11. Primary outcome measures (2005–2009)

Measure	Number of Articles	Percent
Adjusted life years	1,085	62%
QALY	1,027	
DALY	57	
VALY (visual acuity)	1	
Life years	144	8%
Mortality/survival	80	5%
Cases/cases detected/cases diagnosed	63	4%
Sensitivity/specificity	27	2%
Live births	8	<1%
Utility	7	<1%
Incidence/prevalence	5	<1%
All others (including no primary measure abstracted)	354	20%
Total included articles	1,773	

QALY = quality-adjusted life year; DALY = disability-adjusted life year; VALY = visual acuity-adjusted life year.

Table 12 shows the intervention types by disease category. While 22 percent of the overall articles focus on cancer, 36 percent of the screening articles focus on cancer. Some diseases are associated almost exclusively with treatment-related interventions (>90 percent of disease-specific articles are related to treatment). These include mental disease, kidney diseases, and multiple sclerosis. The diseases that were more associated with prevention interventions (>25 percent of the disease-specific articles) were lung diseases, influenza, and rotavirus. Most of the interventions pertaining to gastrointestinal disease were related to diagnostics.

Table 12. Intervention types modeled by associated disease (2005–2009)

Disease Group	Intervention type					Total Included Articles	Percent
	Treatment	Prevention	Screening	Diagnostic	Multiple		
Cancer	211	32	72	33	-	348	20%
Cardiovascular diseases	216	8	14	18	1	256	14%
Bones/joints	92	6	11	4	-	69	6%
Hepatitis/liver diseases	52	17	10	3	-	82	5%
Lung diseases	50	23	8	10	-	91	5%
Diabetes	59	3	7	-	-	69	4%
HIV/AIDS	46	10	16	1	-	73	4%
Mental diseases	66	-	2	1	-	69	4%
Kidney diseases	44	-	-	1	-	45	3%
Gastrointestinal	53	3	3	10	-	55	3%
Pregnancy/infertility/birth defects	34	6	11	4	-	55	3%
Vision/eyes	21	-	10	1	-	32	2%
Influenza	10	26	1	-	-	37	2%
Rotavirus	-	20	-	-	-	20	2%
Smoking/smoking related diseases	20	8	1	-	-	29	2%
Multiple diseases	32	7	4	2	-	45	3%
STDs (other than HIV/AIDS)	-	-	7	-	-	7	<1%
MRSA/nosocomial infection	11	2	3	-	-	16	<1%
Multiple sclerosis	9	-	-	-	-	9	<1%
Hearing/ears	6	1	2	-	-	9	<1%
All other diseases	204	32	72	33	-	299	17%
Total included articles	1,240	209	219	104	1	1,773	
Percent	68%	14%	12%	5%	<1%		

HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; STDs = sexually transmitted diseases; MRSA = methicillin-resistant *Staphylococcus aureus*

Summary

We provide a bird's eye view of the articles that used a decision model to incorporate data from multiple sources to evaluate two or more strategies for decisionmaking purposes. Over a 5-year period, we identified more than 1,700 articles in several disease areas and intervention types published in journals listed in Medline. It is possible that we missed some studies as we did not search other databases (e.g., EconLit, Heath Economic Evaluations Database). The diseases areas and interventions types are fairly representative of those evaluated by systematic reviews. The majority of the decision analysis papers evaluated an intervention aimed at individuals with existing disease, and surprisingly few were focused on diagnostic-related strategies.

Overall, 42 percent of the articles came from the United States, though over 45 countries were represented (home country of primary author). A wide variety of journals publish decision analysis papers. The journal that published the greatest number of articles, Health Technology Assessment, only represents 5 percent of the total papers. However, it is not surprising that Health Technology Assessment is a leading journal for publishing models because they publish peer-reviewed reports from the Health Technology Assessment program in the United Kingdom.

The most common disease type evaluated was cancer (20 percent of the articles), followed by cardiovascular diseases (14 percent of the articles). The majority of the target populations were adults, with approximately 10 percent of the 1,773 articles with a focus on a pediatric population, and 6 percent with a focus on an elderly population. In addition, 15 percent of the articles were targeted towards women only. The majority of the articles reported adjusted life years as an outcome (62 percent), the majority of which used quality-adjusted life years as the outcome.

The search algorithm we developed for this analysis could be useful in the future to identify studies that use a decision model within a disease area. (See Potential Modeling Resources.) We found that the search algorithm has a reasonable yield (61 percent) in terms of the percent of papers subsequently found to include a decision model. However, we are not certain how many decision models we have missed.

An overview of the decision analysis field, as detailed by this analysis of the decision modeling literature, provides a first step in the development of a framework for using models with systematic reviews. While there are a relatively large number of papers that have used the methods of decision analysis in the past three years, they tend to be published in journals whose audience is modelers, or in somewhat lower-tiered clinical journals. There are exceptions to this, of course, but one goal for the field of decision analysis is to reach a broader audience through publication in high-impact clinical journals. Development of a model alongside a systematic review may help move the field in this direction, as there would be opportunities to publish in the Annals of Internal Medicine. Also, the connection to a well-done systematic review and formal decisionmaking process will likely add to the credibility and understanding of the use of decision models for policymaking.

Use of Modeling in Systematic Reviews: The EPC Perspective

Introduction

In this chapter, we review past Evidence-based Practice Center (EPC) reports that have incorporated models and outline the specific reasons for incorporating models, the outcomes examined, and model contributions to the conclusions of the report. To complement the review of EPC reports, we also interviewed relevant EPC members about lessons learned from incorporating decision models in EPC reports.

Review Methods

Search Strategy

We searched each of the 193 evidence reports available on the Agency for Healthcare Research and Quality (AHRQ) EPC Web page (www.ahrq.gov/clinic/epcix.htm) using the keyword "model." Surrounding text was read to distinguish between statistical models, which are excluded from this review, and decision analytic (simulation) models. We also queried EPC staff participating in interviews for modeling performed in conjunction with EPC or other AHRQ projects. (See section below for reports in which models were used.) Our search was targeted towards identifying models developed by EPC members in conjunction with a systematic review.

Abstraction

Report title and identifiers, date published, EPC, model type, reported reason for incorporating the models, outcomes examined, and model contributions to report conclusions were abstracted into a summary table by one reviewer. The table was quality checked by a second reviewer. Any disagreements were resolved through consensus discussion by the reviewers.

Review Results

Out of 193 evidence reports, 10 reports and 1 supplement to a technology assessment were identified through the search process. Details of the 11 reports are provided in Table 13. Tufts Medical Center was the most frequent modeling EPC, with four reports covering the period of 1999 to 2007.[29-32] The Duke University EPC was the next most frequent, with three reports during 2006 to 2007,[33-35] followed by one each from Southern California RAND (2003),[36] University of Alberta (2004),[37] and Stanford-UCSF (2009).[38] All but two developed new models as part of the study leading to the evidence report. One evidence report adapted a previously published model,[34] and later refined the model further for a second evidence report.[35] Seven reports modeled diagnostic tests or screening strategies along with subsequent treatments,[29-34] while three reports modeled treatments only.[36-38]

Table 13. EPC reports that used decision models

Evidence Report/Technical Assessment Number Short Title	Publication Date EPC	Model Type Developed or Revised	Reason Incorporated Model	Outcomes Assessed	Model Contribution
#130 Adnexal Mass[34]	February 2006 Duke University	Diagnosis Developed Disease progression Revised	Predict outcomes Implications for screening if disease spreads from stage I directly to stage III	# of missed cancers, # of missed surgeries Estimated incidence, stage distribution	Serial tests resulted in fewer missed cancers and surgeries. Parallel tests had fewer missed cancers, more surgeries and tests. Reduced time available for detecting cancer at Stage I, which would adversely affect the potential effectiveness of screening.
#82 Heart Failure, Pharmacologic Management[36]	July 2003 Southern California-RAND	Treatment, cost effectiveness Developed	Examine cost-effectiveness of screening and treatment for asymptomatic left ventricular systolic dysfunction	Lifetime health, lifetime cost of care, cost per life year gained, QALY	ACE inhibitor treatment is more cost-effective than many other standard treatments. Screening with BNP followed by echocardiography cost-effective compared to other standard screening strategies.
#106 Cardiac Resynchronization Therapy (CRT)[37]	November 2004 University of Alberta	Treatment, cost effectiveness Developed	Examine cost-effectiveness of treatment for congestive heart failure with CRT	Lifetime effects, QALY	Insufficient long term and cost data to support broad implementation of CRT. Probability of cost effectiveness less than 59%, model sensitive to reasonable changes in variables.
#176 Elective Induction of Labor, Outcomes[38]	March 2009 Stanford University–UCSF	Treatment, cost effectiveness	To identify aspects of elective induction of labor that warrant further investigation in future prospective studies. Address consequences of labor induction and examine what particular outcomes drive clinical situations	QALY and cost per QALY for six maternal and neonatal clinical outcomes such as number of cesarean with possibility of maternal mortality	Elective induction had better overall outcomes (cesarean rates, meconium staining) and higher QALY than those expectantly managed. Induced labor was cost effective for 41 weeks gestation, insufficient evidence for weeks 39 to 40. Model deemed exploratory, not definitive due to low strength of evidence for inputs.

Table 13. EPC reports that used decision models (continued)

Evidence Report/Technical Assessment Number Short Title	Publication Date EPC	Model Type Developed or Revised	Reason Incorporated Model	Outcomes Assessed	Model Contribution
#145 Ovarian Cancer, Genomic Tests[35]	October 2006 Duke University	Screening Refinement of revised model used for report #130	Implications for screening if disease spreads from stage I directly to stage III	Estimated incidence, stage distribution	Screening less effective in reducing mortality if disease progresses from stage I to stage III. Screening frequencies of less than 12 months needed to reduce cancer mortality by more than 50%.
#150 Hereditary Nonpolyposis Colorectal Cancer[29]	May 2007 Tufts-New England Medical Center	Screening Developed	Evaluate different screening strategies	Sensitivity, specificity, number of tests used, for each screening strategy	Combination of 3 clinical predictors combined with either immunohistochemistry or MSI tissue testing identified similar number of patients as other more complex strategies.
(N/A) Obstructive Sleep Apnea-Hypopnea Syndrome[32]	December 2007 Tufts-New England Medical Center	Diagnosis/ Treatment Developed (companion report to technology assessment)	Simulate simultaneous head-to-head comparisons of diagnosis and treatment strategies	Proportion of people offered CPAP, time to final diagnosis, time to successful titration of CPAP level	Illustrative of tradeoffs between number of people offered CPAP and time to diagnosis or technically adequate CPAP level titration.
#146 Depression, Cytochrome P450 Testing for Adults Treated with SSRIs[33]	January 2007 Duke University	Diagnosis Developed	Evaluate circumstances under which testing for CYP polymorphisms improve clinical outcomes or favorably impact costs	Success of initial treatment/ resolution of depression without adverse effects.	No plausible scenario for testing strategies was predictive of improved outcomes at 6 weeks. Cost of testing not offset by treatment savings if treatment duration is less than approximately 9 months.
#9 Diagnosis and Treatment of Acute Bacterial Rhinosinusitis (original report)[31]	March 1999 Tufts-New England Medical Center	Diagnosis, Treatment, Cost effectiveness Developed	Evaluate diagnostic tests and treatment strategies for managing patients. Estimate cost-effectiveness of common treatment strategies	Symptom days, cost of care, quality adjusted days.	Symptomatic treatment alone had fewer symptom free days but most cost effective for prevalence up to 25%. Most cost effective treatment strategy depended on prevalence.
#26 Evaluation of technologies for Identifying Acute Cardiac Ischemia in Emergency Departments[30]	May 2001 Tufts-New England Medical Center	Diagnosis, Cost effectiveness Developed	Examine tradeoff between test performance and their costs	Appropriate triage, 30-day survival, QALY	Model should be used not for clinical recommendations but for understanding the interactions among the variables studied.

EPC = Evidence-based Practice Center; QALY = quality-adjusted life year; ACE = angiotension converting enzyme; BNP = plasma brain natriuretic peptide; CRT = cardiac resynchronization therapy; UCSF = University of California, San Francisco; MSI = microsatellite instability; CPAP = continuous positive airway pressure; SSRI = selective serotonin reuptake inhibitor

Only three reports used models as the prime methodology to answer key questions[36,37] or address the main research aim.[32] The remaining seven reports used models to augment systematic review results in cases where the preliminary literature search results suggested the literature would be unable to address the key question directly. The report language often did not clearly state the purpose of incorporating decision-analytic models into the systematic review. One of the main stated purposes of incorporating models into the evidence reports was to provide a link between intermediate outcomes and clinical, or patient-centered, outcomes. Other stated reasons included: simulating head-to-head comparisons otherwise unavailable in the literature, examining cost-effectiveness, and modeling a novel hypothesis for disease progression not previously mentioned in the literature to determine the impact on the effectiveness of screening.

Models contributed to conclusions through a few main paths. Seven evidence reports concluded from model results either more optimal practices or no clinically important distinguishable differences.[29,31,33-36,38] The conclusion made from one analysis was that there was insufficient evidence to state anything conclusive about the optimal strategy.[37] Models that relied on evidence that was considered to be of low quality were reported as exploratory.[38] Two modeling exercises were performed to promote understanding of the interactions between the variables of an analytic framework, rather than to provide a basis for clinical recommendations.[31,32]

One evidence report summarized an attempt to perform a decision model to evaluate which diagnostic modalities were useful in differentiating seizure types commonly mistaken for epilepsy from true epileptic seizures.[39] Diagnostic performance data from multiple sources were to be pulled together to accurately model the clinical differential diagnosis. However, the model was not developed because of a stated lack of available evidence with which to build the model.

Interview Methods

We contacted all EPC directors and arranged telephone interviews to (1) discuss whether EPC activities have involved any decision modeling activities, whether "successful" (i.e., incorporated in reports) or not and (2) identify key informants (name, current affiliation, and contact information) who were instrumental in considering, developing, and completing/abandoning modeling activities; whether those individuals are in the same institution, are past/existing partners/collaborators, and/or have moved somewhere else.

The rationale for interviewing members from all EPCs (as opposed to focusing only on EPCs that have incorporated models) was that lessons learned are more complete and informative if we also interview EPC members who have considered and attempted to incorporate modeling but decided (for reasons we wanted to discover) not to complete such tasks; EPC members who have not considered developing or incorporating models at all; or those not familiar with modeling at all.

We developed a semistructured interview guide to be used in conducting all interviews, whether by phone or face to face. The final interview guide was developed after review of the EPC reports that incorporated models with iterative participation of the Technical Expert Panel and Task Order Officers (TOOs). The interview guide is listed as Appendix B of this report. Twenty potential respondents were identified as shown in Table 2. Telephone interviews were conducted from December 15, 2009 through March 2010. In several cases, as shown in Table 14, EPC directors included additional EPC staff in the interview, requested that we speak to other EPC staff members in addition to themselves, or referred us to EPC staff members who were better able to represent that EPC's experience with the topic.

Table 14. Elite interview participants

Participant	EPC	Title
Jon Treadwell	ECRI	Associate Director
Dan Jonas	RTI-UNC	Associate Director
Naomi Aaronson Mark Grant David Samson	BCBS	Director EPC Staff Associate Director
Michael White Craig Coleman	University of Connecticut Hartford Hospital	Director Director, Pharmacoeconomics and Outcomes Studies Group
Eric Bass	Johns Hopkins University	Director
Meera Viswanathan	RTI-UNC	Director
Parminder Raina	McMaster University	Director
Tom Trikalinos	Tufts University	Associate Professor
Rick Meenan	OHSU	Contract Modeler from Kaiser Permanente
Evan Myers	Duke University	Professor and Chief OB/GYN
David Moher	University of Ottawa	Director
Doug Owens	Stanford-UCSF	Director Stanford-UCSF EPC
Gillian Schmidler (Sanders)	Duke University	Director
Robert Kane	University of Minnesota	Director
Mark Hefland	OHSU	Director
Ben Vandermeer	University of Alberta	EPC Staff
Katherine Hartmann	Vanderbilt University	Director

After three interviews were completed, the interview guide was shortened into a discussion guide with four main questions that focused on four themes as an organizing principle. This revised discussion guide is provided in Appendix C and summarized below.

1. What research questions are most appropriate for inclusion of a decision model?
2. What model outputs deliver the greatest utility to stakeholders?
3. What is your working definition of a model?
4. How do you determine the value of a model?

Tables of verbatim quotes for key themes were created to organize the material. The tables are provided in Appendix D.

Interview Results

Nineteen out of 20 (95 percent) individuals contacted agreed to be interviewed, representing 12 out of 13 EPCs (92.3 percent). Seven main themes emerged from the discussions with the EPC directors and designated staff.

These themes are:

1. Attitudes Toward Modeling and Appropriateness of Modeling in Systematic Reviews
2. Research Questions and Contexts Best Suited for Modeling
3. Definitions of Decision and Simulation Models
4. Evaluation of Models and Assessment of Model Outcomes
5. Decision and Simulation Models Results as Evidence
6. Impact of Decision and Simulation Models on Systematic Reviews
7. Training Needs

Most, but not necessarily all, themes were addressed across all EPC discussions, depending on the EPC and respondents' experience with modeling. Overall, interviewees' opinions and responses tended to fall into one of two groups:

1. Fifteen interviewees with experience, including individuals with personal modeling experience/expertise and those with no personal modeling experience but who are members of an EPC with modeling experience; and
2. Four interviewees without experience, interviewees with no personal experience/expertise who belong to an EPC with no modeling experience as well.

Thus, interviewees with any degree of familiarity with models (first group), whether firsthand or secondhand, tended to respond more similarly than those without experience or exposure (second group). For convention, we will refer to the former group as those "with experience" and the later the group as those "without experience" as we discuss these findings. Table 15 summarizes the key differences between interviewees with and without modeling experience with respect to the seven major themes that emerged from the interviews.

Table 15. Difference between responses of interviewees with and without modeling experience

Interview Theme	Interviewees With Experience (N=15)	Interviewees Without Experience (N=4)
Attitudes Toward Models and Appropriateness of Modeling in Systematic Reviews	• Important set of techniques and strategies for analysis and should be incorporated into systematic reviews. • Natural extension of the systematic review by addressing gaps in the literature and extending information about intermediate benefits and harms to terminal outcomes.	• Systematic review should be limited to synthesis and meta-analysis of all available empirical and observational evidence. • Models are outside the scope and purpose of the systematic review.
Research Questions and Contexts Best Suited for Decision and Simulation Modeling	• Comparison of testing strategies (start, stop and interval). • Determination of complicated net benefit calculations by linking intermediate to terminal benefits and harms with additional data sources. • Questions with high degree of uncertainty. • Application of findings to subpopulations not included in original study.	• Situations with high degree of uncertainty. • Difficulty enumerating, but agreed with the "with experience" examples when prompted.
Definition of Decision and Simulation Models	• Mathematical representation of a decision based on empirical input parameters, supported by a framework, and subject to a set of identifiable assumptions.	• Confusion on where modeling is defined differently from statistical inference.
Evaluation of Models and Assessment of Model Outcomes	• Quality and expertise of the modeler(s). • Lack of defined standards. • Inspection of assumptions and theoretical framework (natural history of disease representation).	• Focus on the quality and "believability" of the output parameters, and whether multiple models generated similar results. • Lacked familiarity with any empirical measures of model quality.
Decision and Simulation Models Results as Evidence	• Outputs generated from models merit inclusion in systematic reviews as evidence. • Modeling offers access to parameters that might not otherwise be available (e.g. subpopulations).	• Model evidence is "manufactured" or "model produced" and thus must be kept separate from empirical evidence (RCT or observational) • There is no evidence grading for model-based parameters.
Impact of Decision and Simulation Modeling on Systematic Reviews	• Models require additional time and expense, and are not always able to be anticipated at the initiation of a project. • Likely to add 20–40% to the time and expense of a typical systematic review. • Need a mechanism to include a model after the question refinement phase has been completed.	• Would require expertise that some EPCs do not have in-house, and thus must contract for externally. • Need to have guidelines from the Methods Manual.
Training Needs	• Increase training opportunities for doctoral and post-doctoral positions to train modelers.	• Need for seminars and programs to train existing EPC staff. • Identify modeling groups with specific expertise to contract with for model components of systematic reviews.

RCT = randomized controlled trial; EPC = Evidence-based Practice Center

Attitudes Toward Modeling and Appropriateness of Modeling in Systematic Reviews

Those interviewees with modeling experience unanimously held positive attitudes towards modeling with respect to its benefit for systematic reviews. All reported that modeling was an important set of techniques and strategies that were applicable to the work they were engaged in, and were generally supportive of incorporating these techniques into systematic reviews. Among these interviewees, some mentioned a struggle in considering whether models were "appropriate" within a systematic review, as opposed to models being developed after a systematic review has been completed, and as a separate project. They seemed to struggle with two main issues concerning models within systematic reviews. First, is the development of a model within or beyond the scope of a systematic review of the literature? Second, should published models and related output constitute valid information that could be included in systematic reviews, and if so, how does one go about incorporating and evaluating the evidence provided by such modeling studies?

Regarding the first issue, development of a model as part of a systematic review, interviewees without experience felt that a systematic review should be limited to the synthesis and meta-analysis of all available empirical and observational evidence regarding the key questions set forth for the review. For those respondents, models are perceived to go beyond this scope of synthesizing the literature and, as a result, they prefer to make conclusions based solely on the empirical and observational evidence. While most felt modeling is a worthwhile endeavor and can play a unique role, sometimes making recommendations even possible, some felt that modeling is in fact beyond the scope of the "spirit" of a systematic review and should be a separate endeavor. Specifically, they pointed to the limited number of reviews with models, the infrequent inclusion of model requests, and the absence of a standard methodology for modeling in systematic reviews.

Interviewees with experience, however, were very supportive of including models in systematic reviews and felt modeling is a natural extension or augmentation of the purpose and intent of systematic reviews. In fact, many described situations in which modeling greatly improved the systematic review by addressing gaps in the literature, extending benefits and harms beyond intermediate outcomes to terminal outcomes and offering comparisons of strategies. (This will be discussed in more detail when addressing the research questions that models are best prepared to address.) These interviewees discounted the "scope" issues, identified above as the result of limited EPC experience with models, and the recent focus in the methods manual and in methodology discussions of evidence review, grading, and meta-analysis. They all felt that, as attention switches to modeling, reference materials and standards could be created. In fact, most interviewees looked to the results of this project as the first step toward such an end. Thus, several interviewees indicated that models, when needed and appropriate, can be essential tools that belong to the realm of systematic reviews and that provisions should be made to enable the development and utilization of models within that context. They pointed to important hurdles that need to be addressed to make this possible and effective. Those hurdles are addressed within other themes below.

With respect to the second issue, considering the output generated by published models as a potential source of evidence in systematic reviews, the consensus among the interviewees seemed to be that such information should probably be treated and graded differently. Respondents were unsure how to approach this situation. While model outputs cannot be used in meta-analyses, they can still be incorporated and discussed in the review.

Research Questions and Contexts Best Suited for Modeling

In addressing the research questions and contexts where modeling offered the most benefit, interviewees with experience again demonstrated high concordance while those without experience, for the most part, did not offer suggestions regarding this theme. Models are well suited to address gaps in the literature and to synthesize literature from differing sources and contexts into a single representation of the empirical evidence. Often research questions involve harms or benefits that are measured with intermediate outcomes as opposed to the terminal outcome of interest, such as survival or disease prevention. In many cases, studies demonstrate quantitative findings for intermediate outcomes, but studies of the long-term or terminal outcomes are underway, inconclusive, or even not feasible to conduct. These present opportunities for modeling to link intermediate outcomes with estimates of terminal benefits and harms, thus allowing systematic reviews to make conclusions about terminal outcomes of interest. The comparison of testing, prevention, and diagnostic strategies was also noted as a primary area in which modeling can be of great benefit. Most remarked that the comparison of strategies and the establishment of net benefit, that is, benefit less harms, can only be determined through the use of a decision model. More generally, models are well suited for research questions in which there is a high degree of uncertainty in assumptions or input parameters or in situations in which there is a great amount of discordance between estimates in empirical studies. In many cases, large randomized controlled trials or observational studies have not focused on specific subpopulations. In these situations, modeling can be used to simulate findings where subpopulation characteristics are believed to impact or change conclusions for a specific subpopulation. Modeling affords a timelier and less expensive option to address subpopulations, than repeating an empirical study for the subpopulation. Lastly, there is great interest in the benefits modeling can bring to determining the value of information, and specification of research priorities and directions. In many cases, systematic reviews conclude with recommendations for further research and models can be used to quantify the "value" that an additional research recommendation would contribute to the key questions of interest.

Definitions of Decision and Simulation Models

The definition of what constitutes a model also had a high degree of similarity among those interviewees with experience, although the specifics about where statistical inference ends and decision modeling begins were a source of some controversy. Interviewees without experience did not have a consistent view of model definitions and had difficulty distinguishing them from statistical techniques. Most converged on a general definition of decision modeling and simulation as the mathematical representation of a decision (or series of decisions) based on empirical input parameters, supported by a specified framework or mechanism (e.g., a particular representation of the natural history of a disease), and subject to a set of identifiable assumptions. While the majority reported a similar definition of a model, there was greater disparity in the ability to differentiate between modeling and the domain of traditional statistics. These responses exhibited some of the greatest variance within the "with experience" group. Some drew distinct lines between any statistics used for "inference" and the set of techniques used in decision analysis. This group believed that the distinction between modeling and other mathematical techniques was the intended use, that is, inferential statistics versus recommending decisions between options. Others made more specific comments; such as decision models begin with Bayesian statistics and metaregression and extend to the techniques more commonly employed

in decision models, such as Markov modeling and simulation techniques. There was high agreement for the general definition, but the distinctions among techniques seemed to represent the interviewees' experience with particular techniques in particular situations.

Evaluation of Models and Assessment of Model Outcomes

The evaluation of a model or the determination of the quality of a model had high agreement among the group with experience. Albeit qualitative, the majority reported that their opinion about the "quality and expertise" of the actual modeler who developed the decision model weighed heavily on their overall and initial assessment of the model. Most identified the lack of defined standards and methods as a major problem in the evaluation of models, and again hoped that this initiative would bring about some initial draft evaluation standards. When pressed to describe the methodology used in their evaluation of a model, most reported that they routinely inspected the quality and reliability of the input parameters; the reasonableness of the assumptions; and, if available, (usually in a technical appendix) the structure of the model, for example, the representation of the natural history of the disease.

The discussion of model evaluation, in most cases, transitioned to a discussion of model outputs and the methods to assess these outputs. All interviewees (with and without experience) described the need for standardization of model outputs, as an important factor in accepting the models, but also in the practical usage of them across research questions and policy issues. Quality adjusted life years (QALYs) were the most frequently mentioned standard output, but interviewees were quick to critique its merits, especially the fact that it represents a population level output and is not immediately applicable at the individual level as a tool for practitioners and patients faced with important clinical decisions. Interviewees with experience also discussed the need for standardization of the way model characteristics and model results are presented independently of which specific outcome metrics are reported. They typically referred to the need for standard tables and graphs that would take on a specific form and contain a standardized set of information regarding the model, sensitivity analyses, and reported outputs. It was clear from the comments that many believed that some standardization was the best first step toward making models more accessible to a greater audience, and again saw this project as a critical step in creating such recommendations for EPCs to adopt. With regard to specific outcomes, while many of the interviewees with experience were critical of QALYs as a measure, there was no immediate response or direction towards any other measures that would be of greater value across a wide range of research questions and decisions. The strength of QALYs was the ability to use the measure to compare across diseases, treatments, and clinical issues. However, interviewees also suggested that additional outputs that were more actionable at the practitioner-clinician level needed to be reported and discussed. In conclusion, most interviewees reported that the output measures need be "tuned" to the decision to be made, and the same parameters and model structure may need to produce outputs at varying "levels."

Decision and Simulation Models Results as Evidence

An interesting, unanticipated discussion point from these interviews, among both groups with and without experience, was the consideration of evidence, and where modeling fit into the continuum of evidence, or did not fit. We can parse this feedback into two general components: (1) the use of models and simulation results as evidence in systematic reviews of the literature, where models may or may not then be developed to address the key questions, and (2) whether

the results from a model are evidence, which can be evaluated and graded alongside more traditional sources such as observational studies and randomized control trials, or should be considered as an orthogonal or even unrelated empirical finding. Although not included in the original interview guide, and thus not covered in all interviews, this was a rich topic even within the two groups and was mentioned in approximately two-thirds of the interviews. Beginning with the latter point, whether models produced by systematic reviews should be considered evidence, generally, those with experience stated that the outputs from a model that are included in a systematic review should be treated as evidence. The rigor of the systematic review methodology ensured high quality parameter inputs to these models, as well as sensitivity analyses and model assumptions that were consistent with the state of the science. Further, because modeling offers specific benefits (as mentioned earlier in this section), such as addressing literature gaps, subpopulations, extension of intermediate outcomes to terminal outcomes of interest, et cetera, such evidence would not be possible without the utilization of modeling and simulation. Many interviewees with experience made a distinction that this evidence was "manufactured" or "model produced" evidence, possibly indicating the need to categorize or somehow identify this as a different type of evidence.

With respect to incorporating modeling and simulation results into systematic literature reviews as evidence, both groups noted the lack of standards and direction, by the methods manual or the literature, in terms of how model and simulation results should be graded as evidence. Interviewees did not believe that the current evidence-grading methodologies addressed the issues that model and simulation evidence present to a reviewer. Those with experience recommended that this issue be linked to the model evaluation and assessment of outputs topic and saw this project as an opportunity to draft an initial set of grading standards, or at least initiate such a process as a next step. Interviewees without experience pointed to this lack of evidence standards as the principal reason to exclude any modeling studies from systematic reviews. Additionally, many reported that even if standards existed, the incorporation of models as evidence was beyond the scope of systematic review, which is charged with the compilation of all the available empirical evidence, and thus by definition excludes "modeled" or "simulated" data. Those without experience explicitly stated that models and simulations were not on the same "continuum of evidence" as other studies and sources and in fact represented a very different data source, which, when merged with traditional evidence, created a number of issues with respect to the validity of the reviews, and thus should not be included.

Impact of Decision and Simulation Modeling on Systematic Reviews

Feedback and comments regarding how modeling and simulations potentially altered the process, scope, and conduct of systematic reviews were also addressed. The most frequent issue mentioned by interviewees with experience was the ability to determine the opportunity or need for a model and/or simulation before the project has started, and specifically before the question refinement phase has been completed and before early stage literature review has been conducted. If modeling is considered a part of the review, this could present a major barrier to EPCs in competing for and then conducting systematic reviews. While individuals in EPCs with modeling experience were most vocal on this issue, even those interviewees with modeling experience but in EPCs that have not conducted modeling studies, reported this limitation. Often the ability to create a model is based on the availability of parameters and assumptions in the literature, the identification of which cannot be fully completed until the literature review is underway. This makes it difficult to include in a proposal without significant effort in the

proposal stage with no guarantee of contract award. In other cases, the need for a model is not fully understood and/or identified until the question refinement phase has been completed. Interviewees report that this is the natural phase to identify the actual question(s) of interest for the review and then the assessment of the best methods to address those questions.

Two general solutions were offered. The RTOP process could be augmented to include a more collaborative question refinement prior to proposal submission. Alternatively, many interviewees thought that the ability to amend a project if and when the opportunity or need for a model was identified would help mitigate these issues.

An essential issue is the resource intensiveness of models and modeling efforts. Most interviewees with experience with models in EPC reports responded that modeling efforts could easily consume 20–40 percent of the budget for a systematic review, and thus could not be accomplished without either inclusion in the budget at project inception, or an increased budget and timeline after the question refinement phase. If the ability or need for a model could be determined in the proposal stage it would be included in the proposal. Since even the most experienced EPCs and interviewees have only conducted models on a few recent EPC reports and projects, it was difficult for them to estimate the frequency models could be included in proposals. For this reason, and to not impact their EPC's competitiveness in proposal competitions, they defer models from most proposals and hope to convince TOOs on projects as to the merits of including a model after the projects have commenced, and rationale can be clearly established and communicated.

Training Needs

All interviewees reported the desire for training resources. Those with experience, and in EPCs with experience, reported a number of possibilities for training, including seminars for those who conduct systematic reviews, the identification of resources to train other staff members assisting with reviews, and availability of training grants to increase the capacity of model and simulation expertise through pre- and post-doctoral support. Interviewees without experience, and in EPCs without experience, felt that the training issue needed to be subordinated to a decision or "edict" by AHRQ to include more modeling and simulation into EPC projects and systematic reviews (or more favorably, to these interviewees, as separate projects after systematic reviews are completed). Once this is determined by AHRQ, then training in how to work with modelers and how to interpret models, along with other issues such as evidence grading and new methods manual chapters, need to be addressed to support the EPCs in this work. EPCs without experience have reported a reluctance to hire and develop model and simulation talent because of the lack of clarity about whether these skills are required by AHRQ and how it might impact their competitiveness among EPCs, as well as whether acquiring these skills should be prioritized above others.

Summary

The responses to interviews showed a high degree of consistency among interviewees that had experience, either personally or within their respective EPCs. There was more variability in responses among interviewees without experience. Further, interviewees without experience responded quite differently from interviewees with experience, both in the content of their responses and in their ability to respond to some of the questions and themes presented. In the above discussion, much of the reporting of opinions and responses is focused on the group with experience, simply because that is where the majority of the responses on the topics came from.

Overall, most interviewees had experience, either personally or within their EPC, with models and/or modeling techniques. Those with no experience, whether personally or within their EPC, expressed interest in modeling but as a separate activity beyond the scope of systematic reviews. Not surprisingly, they did not support the inclusion of modeling in systematic reviews and did not support the inclusion of model results as a potential source of evidence in the conduct of systematic reviews. The role of decision analytic results on the continuum of evidence deserves further research.

Overall, the EPCs, almost universally, seem to be seeking guidance about how to best handle models and simulations. All report an awareness of the growing popularity and application of models and simulations and many have ideas and opinions on how best to implement within systematic reviews. There was general consensus on the need for guidelines and extension of the methods training.

Suggested Framework for Deciding When a Modeling Effort Should be Added to a Systematic Review

Overview

This chapter provides a framework for deciding when a decision analysis should be conducted in addition to a systematic review. While the goal of a systematic review is to synthesize the current scientific literature on a particular topic to assist decisionmakers, there are often limitations with the evidence available to fully address the questions that are most relevant for decisionmakers. Decision-analytic models can be used to simulate the health outcomes of individual patients or populations under a variety of scenarios and they represent the core methodology of clinical decision analysis. Models may provide added value alongside systematic reviews by adding a formal structure, which can be informed by the evidence. We present several situations that would be appropriate to consider including a decision modeling project, and discuss the role of the stakeholder(s) within the framework. We also discuss issues pertaining to who would conduct the modeling studies, the timing of such studies, and the evaluation of existing models.

Proposed Framework

To help inform a framework to decide when a decision model should be added to a systematic review, we conducted key informant interviews with: (1) members from all of the Evidence-based Practice Centers (EPCs), (2) members of the United States Preventive Services Task Force (USPSTF), and (3) cancer modelers involved with recent modeling work with the USPSTF. Overall, we found strong support for establishing guidance for the use of models as an adjunct to systematic reviews. To that end, we address the many themes and concerns that arose during those interviews and make specific recommendations to consider. Details from the interviews are provided in other chapters, and a list of the types of systematic reviews is in Appendix E.

Scope

There was some discussion during the interviews about the distinction between using models within (as part of) a systematic review versus using a model alongside (as a separate project) a systematic review. Concerns about including models within a systematic review ranged from the fact that modeling is beyond the scope and "spirit" of an evidence review, and that it would add greatly to the time and resources (and skill set) required to complete the systematic review. Decision modeling can be viewed as a separate endeavor, but one that is fully integrated with the systematic review effort. This designation allows for an appropriate distinction between the "spirit" of modeling and evidence reviews. While the goal of a systematic review is to synthesize and grade all of the available evidence, the goal of a decision model is to provide a tool to the decisionmaker that projects relevant health outcomes for all of the available options for several population subgroups. A decision model should incorporate all of the available evidence (i.e., results from a systematic review) but is not limited to that evidence base. For example, a model can be used to extend the findings from a systematic review by addressing gaps in the literature, extending benefits and harms beyond intermediate outcomes (e.g., cancer incidence) to terminal outcomes (e.g., death from cancer), and offering comparisons of strategies that were not directly

compared in the literature. The decision modeling endeavor should also be integrated with the stakeholder and the systematic review team. This would ensure that the decision model is informed by the best available evidence and is relevant to the decisionmaker.

Engagement by the Stakeholder

We start with the premise that systematic reviews are conducted to assist stakeholders with decisionmaking. A model developed by a technical team, that was not informed by any interactions between the team and the decisionmaker, will not be successful no matter how sophisticated or well done the decision model is. Thus, the engagement of the stakeholder early in the question development and/or refinement phase is critical. If the stakeholder's goals are focused solely on the state of the evidence for the particular topic then there would be minimal value to including a modeling study. One exception to this might be using a model to conduct a formal value of information analysis, where a model can be used to quantify the value of conducting further research. If the goals of the stakeholder are to inform decisions; whether it is guideline development, coverage decisions, or other types of recommendations; then there should be consideration given to incorporating a modeling component.

Another important discussion to have during the question refinement stage addresses the distinction between two philosophically different approaches to decisionmaking. The first values empiricism with a hierarchy of acceptable "evidence," while the second values using "best available data" and utilizing, cautiously, expert opinion as well as poorer quality of evidence in models designed to inform decisions. In other words, is it acceptable for the decisionmaker to make decisions on the basis of a model that includes both good and poor quality data with clinically reasonable assumptions made when necessary to fill in evidence gaps? Stakeholders need to understand and weigh in on their decisionmaking philosophy, and understand the implications of moving forward with a modeling component.

The first step in the process should be to engage the stakeholder in discussions about the goals of decision modeling and how it could potentially add value to the topic being addressed (though there may be timing issues discussed below). This will likely require that the stakeholder be educated on what a decision model is, how they have been used in practice, and what their value is in this context. For example, for the modeling work done for the USPSTF, a "Decision Models 101" presentation was developed and presented to USPSTF members as a tutorial, in preparation for the discussion of results. This was viewed by several USPSTF members as an excellent session during our interviews. Because the goal of using a decision model is to assist the decisionmaker, it is important for the decisionmaker to be "on board" at the start and be willing to be engaged in the process. Ultimately, the success of using a decision model should be reflected in its value to the decisionmaker.

When Would a Modeling Study Be Helpful?

Of course to determine a priori when a modeling study would be helpful is a challenge. A modeling study would almost always be helpful, in that it provides decisionmakers with a logical and transparent framework for thinking about the tradeoffs between harms and benefits associated with two or more competing alternatives. A modeling study would also provide health outcomes that synthesize multiple sources of evidence, focusing on those outcomes most relevant to decisionmakers, and is well suited to address gaps in the literature. Exceptions would be cases where the interventions of interest have all been evaluated in head-to-head clinical trials with multiple study endpoints that capture all of the important outcomes in a diverse study

cohort. That being said, because a modeling study requires significant time and resources, it is prudent to consider those situations where a modeling study would be most useful in order to weigh the relative costs and benefits of moving forward with a modeling exercise. A relatively quick review of the literature could be done to get a brief scan of the state of the evidence for a particular topic of interest. The following paragraphs discuss specific settings in which a modeling study would likely add substantial value alongside a systematic review.

High Degree of Uncertainty in Evidence

Models are well suited for research questions in which there is a high degree of uncertainty in assumptions or input parameters or situations in which there is a great amount of discordance among empirical studies. Although decisionmakers are often interested in comparing several medical interventions in a particular setting, it is unlikely that all interventions have been compared in head-to-head trials, and there may be several different study designs and study populations across the different intervention studies. Models provide a transparent structure that represents the natural history of the disease of interest, and can specify how an intervention affects the natural history process in terms of both benefits and harms. For example, we have excellent clinical trial evidence regarding the effectiveness of annual fecal occult blood testing for colorectal cancer screening, but no direct evidence on the effectiveness of screening with colonoscopy every 10 years. Models have been shown to be well suited for evaluating the effectiveness of different cancer screening strategies in a variety of settings.

Intermediate Outcomes

Several intervention studies use intermediate, or surrogate, outcomes as endpoints. Surrogate endpoints are often desirable in a trial setting because they are either more likely to occur or they occur much sooner (or both) than the terminal outcome of interest (e.g., disease-specific mortality), and thus a study can be conducted in a shorter timeframe with smaller sample sizes. However, decisionmakers are interested in terminal outcomes that have a significant impact on patients. Studies with long-term or terminal outcomes are often inconclusive, not feasible to conduct, or still being conducted. Models are beneficial in these situations. For example, trials that evaluate interventions for patients with insulin-dependent diabetes often use intermediate outcomes such as retinopathy and neuropathy, because they are more common and more immediate. Decisionmakers interested in comparing alternative therapies for patients with insulin-dependent diabetes are also interested in the outcomes of blindness and amputation. Decision models are well suited to providing information on these outcomes because they synthesize the studies using intermediate results with epidemiological data on the relationship between intermediate and terminal outcomes, in this case, retinopathy and risk of blindness, and/or neuropathy and the risk of amputation.

Specific Subpopulations

Intervention studies are often focused on a highly selected population, and may exclude individuals such as those who are older or have comorbidities. In these situations, modeling can be used to simulate findings where subpopulation characteristics are believed to impact conclusions for that specific population. For example, a model would be appropriate to examine the benefits and harms of warfarin therapy in a subpopulation of patients not studied in a clinical trial, such as elderly patients at risk of falling.

Relevant Outcomes

The comparison of strategies typically involves the evaluation of benefits and harms (and costs) of available interventions. The establishment of net benefit (i.e., benefit less harms) or cost effectiveness can be determined through the use of a decision model. Models are also useful for incorporating variables that may be important in evaluating the benefit or cost of an intervention in real-world settings. For example, intervention studies don't always incorporate actual adherence rates; they may include a simplifying assumption of perfect adherence.

Diagnostic Test Strategies

Models are perhaps best suited for evaluating diagnostic tests or test strategies. Studies that evaluate diagnostic tests focus on estimating test characteristics (sensitivity and specificity) and not on long-term outcomes. However, the clinical value of performing one diagnostic test over another, or a sequence of diagnostic tests, should be judged by comparing long-term benefits and harms. Decision models incorporate the underlying risk that an individual has the disease and simulate the progression (natural history) of the disease over time to track the relevant terminal outcomes. A diagnostic test that detects the presence of disease (i.e., true positive result) will result in the patient getting treated and, depending on the effectiveness of that treatment; the diagnostic test will result in an overall benefit. A diagnostic test can also falsely detect disease (i.e., false positive result), which would lead to some degree of harm by inappropriately treating such an individual.

Value of Information

There is great interest in the benefits modeling can bring to determining the value of information and specification of research priorities and directions. In many cases, systematic reviews conclude with recommendations for further research and models can be used to quantify the "value" that an additional research recommendation would contribute to the key questions of interest. This is typically done in the setting of cost-effectiveness analysis.

Timing of Modeling Studies

When to conduct a modeling project in connection with a systematic review is a concern. Ideally, one would complete the systematic review first and then develop/refine a decision model that is designed to optimize the use of the evidence results. For example, the final results from a systematic review could inform modeling decisions about ways to categorize a disease that maximizes the use of the evidence. Or the results may indicate several options for categorizing a disease that would allow the modelers to build in different structural assumptions that could be evaluated in sensitivity analyses. This ideal situation, however, is unlikely to happen in practice and the modeling work will likely need to be completed at the same time, or close to the same time, as the systematic review. This is not an insurmountable problem and it is reasonable to assume that, with adequate interactions between the systematic review team and the modeling team, the modeling work could be done concurrently with the systematic review, with interim model parameter estimates used prior to completion of the reviews. Figure 1 illustrates this framework.

Figure 1. Diagram of framework
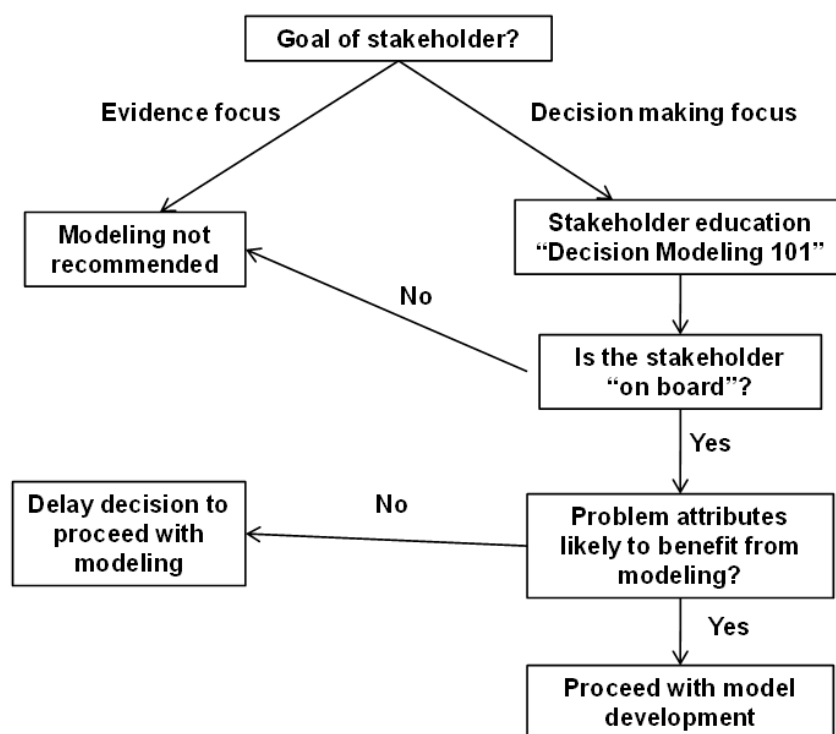
Who Does the Modeling?

Although decision models provide synergies with systematic reviews, the skills required to develop and analyze decision models are not well represented by researchers who conduct systematic reviews. Because decision modeling requires a different skill set, it is not always feasible to have the modeling work done by systematic review research teams, such as EPCs. Modeling is a multidisciplinary field that requires several disciplinary experts in order to conduct a credible modeling analysis on a wide variety of topics on timelines typical of a systematic review. It is beneficial for those conducting the modeling to have frequent interactions with researchers conducting the systematic review to ensure that the model is developed in such a way to incorporate the synthesized data, and that all relevant data are collected and synthesized to inform the model structure. In the ideal circumstance, the systematic review team and the decision analysis team would reside in the same place in order to facilitate a close working relationship.

Evaluating Existing Models

There are several checklists available for evaluating decision models. However, it is often difficult to judge whether published models adhere to the criteria because they are left to the interpretation of the reviewer. For example, one suggested criterion for model structure is that it "reflect the underlying biological process of the disease," which may be difficult to judge in many cases. Table 16 provides a slight modification of the framework proposed by Philips et al. (2004),[40] which is among the most comprehensive to date. A checklist such as this can help distinguish "good" models from "bad" models to some degree. However, if we focus on using

models to assist the decisionmaker, a "good" model is one that includes inputs and outputs that are relevant and ultimately useful to the decisionmaker.

Evaluating the model structure, including assumptions made, and assessing the completeness and quality of the input data (as described in Table 16) are clearly important components to evaluating models. However, it is also important to recognize that models can be very effective in predicting what could happen even when faced with limitations in the quality of the input data. In addition, for models that are evaluated for potential use alongside a systematic review, the quality of the input data is less relevant since much of the input data will come from the systematic review. A model that has a well-grounded structure (i.e., much is known about the biological nature of the disease) can be used to systematically vary the key parameters over plausible ranges to inform further studies needed to refine estimates of such key parameters.

All modeling efforts, at a minimum, should clearly display and discuss: (1) testing performed on the model (both structure and results), (2) assumptions and their impact on the results, (3) data input and parameters and their joint impact on the results, and (4) key drivers of the results. The latter point is important as, usually, a handful of key elements drive the results of a model. Those need to be made very explicit and such discussion should make sense to clinicians who are expert in the clinical domain addressed by the model and should be consistent with the underlying theory and natural history of the disease and its progression.

The involvement of clinical experts in the development of the model should be evident especially as it relates to the natural history of the disease; the formalization of the disease progression; the identification of, and rationale for relationships between key variables; and other "a priori structuring" tasks. Ideally, a visual depiction of the underlying disease mechanics would enhance the perception of content validity of the resulting model.

Just as the development of a model should integrate modeling and clinical expertise, the evaluation of a model needs to be conducted by both modeling and clinical experts. A modeler without the proper clinical expertise would naturally focus solely on the technical aspects of the model, but, if unfamiliar with the clinical domain, would not be in a position to judge face validity. A clinical expert would be in a position to judge whether the clinically important decision points have been captured and whether the underlying disease theory is appropriately integrated into the structure of the model.

This section focuses on the evaluation of existing models; Best Practices for Decision and Simulation Modeling focuses on best practices for developing new models.

Table 16. Framework for quality assessment of decision models, modified from that proposed by Philips et al. (2004)[40]

Dimension of Quality	Questions for Critical Appraisal
Structure	
Statement of decision problem	Is there a clear statement of the decision problem? Is the objective of the evaluation and model specified and consistent with the stated decision problem? Is the primary decisionmaker specified?
Statement of perspective	Is the perspective of the model stated clearly? Are the model inputs consistent with the stated perspective? Are the outcomes of the model consistent with the perspective and overall objective of the model?
Rationale for structure	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation? Have any competing theories regarding model structure been considered? Are the sources of data used to develop the structure of the model specified? Are the causal relationships described by the model structure justified appropriately?
Structural assumptions	Are the structural assumptions transparent and justified? Are the structural assumptions reasonable given the overall objective and perspective of the model?
Strategies/comparators	Is there a clear definition of the options under evaluation? Have all feasible and practical options been evaluated? If not, is there justification for the exclusion of feasible options?
Model type	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?
Time horizon	Is the time horizon of the model sufficient to reflect all important differences between options? Is the time horizon of the model, the duration of treatment, and treatment effect described and justified? Has a lifetime horizon been used? If not, has a shorter time horizon been justified?
Disease states/pathways	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?
Cycle length	Is the cycle length defined and justified in terms of the national history of disease and the interventions being evaluated?
Data	
Data identification	Are the data identification methods transparent and appropriate given the objectives of the model? Where choices have been made between data sources, are these justified appropriately? Has particular attention been paid to identifying data for the important parameters in the model? Has the process of selecting key parameters been justified and systematic (though not necessarily comprehensive) methods used to identify the most appropriate data? Has the quality of the data been assessed appropriately? Where expert opinion has been used, are the methods described and justified?
Premodel data analysis	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?
Baseline data	Is the choice of baseline data described and justified? Are transition probabilities calculated appropriately? Has a half cycle correction been applied? If not, has the omission been justified?

Table 16. Framework for quality assessment of decision models, modified from that proposed by Philips et al. (2004)[40] (continued)

Dimension of Quality	Questions for Critical Appraisal
Treatment effects	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques? Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified? Have alternative assumptions been explored through sensitivity analysis? Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?
Quality of life weights (utilities)	Are the utilities incorporated into the model appropriate? Is the source for the utility weights referenced? Are the methods of derivation for the utility weights justified?
Data incorporation	Have all data incorporated into the model been described and referenced in sufficient detail? Are the assumptions and choices made in cases of mutually inconsistent data been justified? Is the process of data incorporation transparent? If data have been incorporated as distributions, has the choice of distribution for each type of parameter been described and justified? If data have been incorporated as distributions, is it clear that second-order uncertainty is reflected?
Assessment of parameter uncertainty	Are the methods of assessment of parameter uncertainty appropriate? Has probabilistic sensitivity analysis been done? If not, has this been justified? If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?
Assessment of structural uncertainty	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?
Heterogeneity	Has heterogeneity been dealt with by running the model separately for different subgroups?
Consistency	
Internal consistency	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?
External consistency	Are the conclusions valid given the data presented? If the model has been calibrated against independent data, have any differences been explained and justified? Have the results of the model been compared with those of previous models and any differences in results explained?

Model Outcomes

Model outcomes should always include those deemed relevant by the decisionmaker. Relevant outcomes should be discussed at the start of the modeling project with a skeleton table of anticipated results. These should include both short-term and long-term measures that are considered by the decisionmaker to be of particular value to his or her decisionmaking process. We also recommend a standard set of model output be developed to help with comparisons across models and aid in the acceptance of models over time. We recommend that quality-adjusted life years (QALYs) be included as standard output, even though this may not be best understood by the decisionmaker. In addition, life years (LYs) should also be included, as well as output that adds insight into the differences between the QALYs and LYs. For example, model output on the average amount of time spent in different health states should be provided, i.e., QALYs are a weighted average of the time spent in each health state and the quality-of-life weight assigned to each state. Also it should be clearly stated whether these are outcomes from a lifetime horizon or a short-term horizon and, when possible, a lifetime horizon should be

included in the set of outcomes. When relevant, event outcomes should be provided in the outcomes table; for example, the lifetime risk of a simulated patient experiencing a particular event for each of the strategies being evaluated. Ultimately, there is a need for standard output tables and figures presented in a specific form and containing a standardized set of information and data regarding the model, sensitivity analyses, and reported outputs.

Training

ARHQ is already an important funder of training decision analysts. The T32 training grant mechanism in health services research has funded many predoctoral students and postdoctoral fellows at universities that have a training program in health decision sciences. Unfortunately, only a limited number of universities offer comprehensive coursework in decision analysis and decision modeling. There are other training needs that focus more on the users of decision models, including seminars for systematic reviewers and potential stakeholders and policy makers. Opportunities for educating potential users of decision models would be created by the incorporation of a mechanism to conduct modeling with systematic reviews as a result of the interactive nature of the proposed framework. Specifically, the modeling teams would be required to communicate the value of the decision modeling approach in a way that appeals to and is understood by the non-modeling community. While it would never be expected that policy makers would understand the details of the model, it is necessary that they understand and trust the output from the models.

Communication

Part of the challenge to using decision analyses for real-world decisionmaking has been in communicating their value to policymakers and other non-decision analysts. The issue with the acceptance of modeling is that modeling has been used extensively in cost-effectiveness analyses and thus is linked to the "rationing of health care." The use of modeling may be viewed as one step in that direction. Much of the success of the impact that the Cancer Intervention and Surveillance Modeling Network models have had on health policy has been influenced by the communications efforts by the National Cancer Institute with other federal agencies.

Future Recommendations

Table 17 lists some recommendations for future work in the areas of: (1) the role of modeling alongside systematic reviews, (2) standardized model output, (3) model validity guidelines, (4) training and communication, and (5) development of a modeling database.

Table 17. Future recommendations

Topic Area	Results Current Project	Future Recommendation
Role of modeling alongside systematic reviews	General support that this would be a beneficial endeavor.	The general guidance provided in the proposed framework would need to be refined as experience with the process of conducting modeling studies with systematic reviews is accumulated.
Standardized model output	There is not a currently agreed-upon list of model outputs, or a structured set of tables or figures that are recommended.	Model output should be, in part, determined by decisionmakers as part of a focused effort to learn what outputs decisionmakers value.

Table 17. Future recommendations (continued)

Topic Area	Results Current Project	Future Recommendation
Model validity guidelines	The existing checklists do not identify fatal flaws of a model (e.g., asymmetries).	Further develop best practice guidelines to help determine how best to assess model validity.
Training and communication	There is a need for more training in decision modeling, particularly with users of models. Their value and results are not well understood by potential users, which limits the opportunity to impact real-world policymaking.	Modeling workshops. Further refinement of "Decision Modeling 101" presentation. Development of ways to communicate findings from modeling studies.
Modeling database	Potential for valuable resource.	Recommend a focused research effort to develop and test a modeling database.

Potential Modeling Resources

Introduction

The purpose of systematic reviews is to synthesize the current scientific literature on a particular topic to assist public and private organizations in developing strategies that improve the quality of health care and decisionmaking. The resulting evidence reports may be used to inform practice guidelines, performance measures, educational programs, or coverage policies. Users of evidence reports include clinicians, health professional associations, health system managers, researchers, consumer organizations, policymakers, and other health stakeholders, such as the United States Preventive Services Task Force (USPSTF). Systematic reviews synthesize the existing evidence on a particular topic and thus may be limited by an incomplete evidence base. In cases where the stakeholders questions are not fully addressed by the evidence synthesis and when the questions asked by the stakeholders pertain to an action (e.g., what's the best course of action given the available data?) and not statements of truth (e.g., is one intervention statistically more effective than another?), the use of a decision analysis alongside the systematic review may be appropriate.

Using decision analysis alongside a systematic review requires one to ask different types of questions, ones that are less focused on evidence and more focused on decisionmaking and valued outcomes. Ideally, it requires a dialogue with the decisionmakers about their decisionmaking goals, and it lays out clearly and systematically the decision process, elements of the decision that are well supported by the evidence, elements that require explicit assumptions to be made, and results from sensitivity analyses that highlight which parameters and assumptions most influence the main findings.

Once it is determined that a modeling component would add substantial value to a systematic review, different approaches can be considered. We explore three such approaches in this chapter, and discuss some of the challenges. The first approach would be to conduct a systematic review of prior modeling studies on the topic of interest and provide a synthesis of the modeling study results to the decisionmaker(s). The search would attempt to find modeling studies that addressed the same questions, or similar questions, that the systematic review is addressing. A second approach would be to identify modeling groups that have an existing relevant model. Existing consortia or informal groups of modelers for some diseases could serve as a good resource. The Cancer Intervention and Surveillance Modeling Network (CISNET), funded by the National Cancer Institute, is a consortium of cancer modelers that has been involved in several analyses for national coverage determinations for the Centers for Medicare & Medicaid Services and guideline development by the USPSTF. The Collaborative Obesity Modeling Network (COMNet), funded by the National Institutes of Health and Robert Wood Johnson Foundation, consists of modeling groups from around the world (United States, Canada, United Kingdom, and Australia) who use simulation models to predict changes in population obesity trends and assess the cost-effectiveness of specified interventions to reduce obesity. A third approach would be to develop a de novo model (note there is some overlap in what might be considered a de novo model vs. a revision of an existing model). Table 18 summarizes these approaches.

Table 18. Approaches to conducting a modeling study alongside a systematic review

Approach	Advantages	Disadvantages
Conduct a systematic review of modeling studies	Provides a good first step to understanding the modeling issues pertaining to a disease/treatment area.	May not fit question precisely. Does not allow input from stakeholders.
Collaborate with investigators with existing model(s)	Allows for input from stakeholder.	May involve significant reprogramming in certain cases.
Develop model de novo	Allows for input from stakeholder; no influence from prior modeling assumptions.	May be time consuming and more costly.

Comparison of Approaches

Conduct a Systematic Review of Modeling Studies

At present, there are no rigorous methods for synthesizing and reporting modeling studies. Pignone and colleagues discuss the challenges associated with conducting systematic reviews of economic evaluations, much of which is relevant to decision analyses.[41] The challenge of identifying papers in the literature that use a decision analysis model was addressed in the Overview of Decision Models Used in Research section of this report, that is, what is a good search algorithm? One of the challenges in selecting papers to review among those identified from the initial search is to set the inclusion criteria broad enough to identify a sufficient number of papers to review (which tend to be small in number), yet have sufficiently stringent exclusion criteria to eliminate the low-quality papers, although there is no good system of grading models per se. While there are checklists for basic elements that should be included in a decision modeling study, such as "statement of the problem" and "list of assumptions,"[28,40] the overall quality of the model is a subjective assessment by the reviewer.

Assessing the quality of a model requires addressing the multiple categories of criteria, each of which must be assessed separately across several elements. For example, the category pertaining to model structure assesses the degree to which a model accurately reflects the natural history of disease, or whether the causal linkages between variables are explained and justified. Another category, which requires an independent assessment, pertains to data inputs into the model. This assessment determines whether data sources are clearly identified and level of evidence provided, as well as whether suitable justification is provided for base case values and ranges used in sensitivity analysis. A model could have high-quality structure and low-quality data inputs, and vice versa. A third dimension that is important in determining the quality of a model is the validation, that is, the degree to which a model has been "tested." This validation can range from simple debugging exercises to efforts to compare model output with other relevant studies.

Because decision-analytic studies vary in terms of the methods used (type of model, how or if natural history is defined, choice of defining and categorizing health states, choice of time horizon, etc.) the synthesis of model results can be problematic. Because the goal of a decision analysis is to assist in decisionmaking and not in making inferences, methods that combine results and provide confidence bounds are less relevant. Another disadvantage of this approach is that it does not allow the stakeholder to have any input. Again, because there are several modeling options when developing a decision model, the choices made by the analyst may not be consistent with the values and preferences of the decisionmaker/stakeholder. More importantly,

the process of constructing a decision model interactively with the decisionmaker helps with the decisionmaker's understanding of the model and builds trust in the model results (In this report, see Use of Modeling in Systematic Reviews: The EPC Perspective, and Best Practices for Decision and Simulation Modeling).

Several review papers of cost-effectiveness decision models have addressed specific disease areas.[42-46] However, the goal of those papers was not to summarize the findings (e.g., report a synthesized estimate and range of the incremental cost-effectiveness ratio or the incremental gain in quality-adjusted life expectancy of an intervention compared with a standard) as one would do in a systematic review of the evidence. Instead, the goal of those reviews was to compare and contrast the different approaches to modeling and to generate recommendations for best modeling practices. Table 2 summarizes five modeling review papers.

Although the types of reviews shown in Table 19 would not provide the necessary modeling information needed to supplement a systematic review, they do provide essential background information to any modeling endeavor requested by AHRQ, as well as identify existing modelers within a disease area. In fact, an initial review of models led to the modeling work that was done to assist the USPSTF in the updating of the 2008 recommendations for colorectal cancer screening. For the 2002 Task Force recommendations, Pignone and colleagues conducted a systematic review of the cost-effectiveness analysis studies of colorectal cancer screening.[47] They concluded that there was consensus among all of the studies that colorectal cancer screening was cost effective but there was no consensus regarding which strategy was optimal. They suspected the discrepancies were because of different assumptions in modeling the natural history of the disease, and also different estimates used for the input parameters. The findings from that review paper provided motivation for the Institute of Medicine (IOM) Workshop on Economic Models of Colorectal Cancer Screening,[48] which was convened to explore the discrepant findings across cost-effectiveness colorectal cancer screening models, using five of the models identified in the review. The workshop results showed that the discrepancies across models could be reduced somewhat by standardizing the inputs on adherence, test characteristics, costs, and follow-up assumptions. However, it was unable to further evaluate the uncertainties in the (untestable) natural history assumptions across the different models, such as adenoma dwell time. Two of the modeling groups that participated in the workshop conducted the decision analysis that provided outcomes to the USPSTF in 2008, and are part of the colorectal cancer CISNET group.[26]

Table 19. Examples of reviews of models

First Author, Year, Search Detail	Health Condition Model Type	Number of Models A Priori Model Definition	Disease Specific Key Modeling Aspects	Quality Indicators	Findings/Recommendations for Model Practice
Earnshaw, 2009[44] Searched 1990-2007	Acute stroke Treatment: treatment strategies or therapeutic intervention	13 models Markov models, decision-tree models, models based on mathematical equations	Model approach and health states; transition probabilities, short-, long-term, and indirect costs, utilities, post-stroke mortality, time horizon, model validation, estimation of parameter uncertainty	Not developed Summary and critical assessment per paper; criteria not provided	• Keep model complexity to minimum to avoid assumptions not supported by data • Use two phase models: acute treatment, long-term management and prevention • Report results in lifetime incremental cost per QALY • Include both one-way and probabilistic sensitivity analysis
Annemans, 2008[42] No dates provided	Breast cancer Treatment: aromatase inhibitors in early cancer	13 models Definition not reported	Absolute incidence of recurrence in control arm, risk reduction with intervention; cost of intervention; adverse events; patient subtypes	Model structure assessment guided by ISPOR modeling guidelines (Weinstein 2003)	• Work toward developing generic model that can evaluate both direct and indirect comparisons. • Models should be peer reviewed and made available with open access. • Calibrate with observational data • Multiple specific suggested elements which models should take into account
Campbell, 2008[43] Through 2005	Abdominal aortic aneurysm Screening: ultrasound of elderly males	9 models Definition not reported		Model structure assessment guided by HTA modeling guidelines (Philips 2004)	• Lack of agreement between models raises question of overall quality of models • Insufficient details of model inputs and structure inhibit validity assessment
Green, 2007[45] Through 2005	Alzheimer's disease Treatment: cost-effectiveness of drug treatments	22 CEAs, 20 models Use "clinical, economic, and epidemiological data" to study progression over time		Critical appraisal guided by Drummond et al. (1997) (Novel use of table data)	• 19 of the 20 models were supported by pharmaceutical industry • Literature is varied and models were largely drug-specific • Data inputs are sparse in all areas (epidemiology, resource use, outcomes) and clinical trials are all short term • Link between clinical effectiveness and modeling of longer term outcomes is not clear or explicit in many publications

Table 19. Examples of reviews of models (continued)

First Author, Year, Search Detail	Health Condition Model Type	Number of Models A Priori Model Definition	Disease Specific Key Modeling Aspects	Quality Indicators	Findings/Recommendations for Model Practice
Jones, 2000[46] No dates provided	Depression Treatment: antidepressants	10 models Definition not reported	Provided suggested decision tree, 5 year timeframe, impact of drugs coming off patent, depression severity, and other depressive disorders	Not developed. Summary and critical assessment per paper; criteria not provided	• Provides overall status of antidepressant modeling literature, examples of all relevant drugs and common modeling techniques • Intended audience is model user

QALY = quality-adjusted life year; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; HTA = health technology assessment; CEAs = cost-effective analysis.

Collaborate With Investigators With Existing Models

The decision to collaborate with investigators who have existing models may require some compromise to avoid the time and resources it takes to develop a simulation model from scratch. It may mean using a model that does not fit precisely, but it can allow for an interactive approach between the modeling group(s) and the stakeholder, as well as the systematic review team. As a first step in identifying a modeler or modeling group with an existing model, one could use the search algorithm developed in Overview of Decision Models Used in Research with a specified range of years and disease or condition. A review and abstraction of the articles found through this process would yield a summary of existing models that would compare several features of the models including: model design, time horizon, health states or health pathways (natural history), list of assumptions, health outcomes, uncertainty, and validation. Brief reports that summarize the existing modeling literature could be of value to the stakeholder(s) in understanding the range of model structures, modeling assumptions, data inputs, and model results for a particular topic. In addition, in-person workshops, similar to the two-day IOM workshop on models for colorectal cancer screening, could serve as an instructive first step for modelers and stakeholders.

To assist in identifying existing modelers, we explored the potential value of a modeling database that includes some basic details about the existing models in the literature. The modeling field has been interested for some time in developing a Web-based model registry platform.[49] To explore the time required to develop such a database, and the potential data fields to collect, we reviewed a subset of the 2009 modeling papers identified in Overview of Decision Models Used in Research to determine whether the model was appropriate for further data abstraction. We used two criteria: (1) natural history or slightly modified natural history (e.g., under usual care) was modeled, and (2) the model was complex enough to be flexible and generalizable in several settings. We collected the following information on a data-auditing form for each identified article:

- Reference citation
- Base-case population
- Strategies evaluated

- Model type
- Time horizon
- Cycle length
- Health outcomes
- Probabilistic sensitivity analysis (yes/no)
- Validation (yes/no)
- Model parameters (N=natural history; E=effectiveness; R=risk).

We noted the description of the model parameters included, usually as presented in the article's Table 1 (which, by convention, typically lists key model parameters, base case value, and ranges used in sensitivity analyses), but did not abstract any values, as we would expect those to come from a companion systematic review. We used three identifiers to distinguish the type of model parameter: (1) those that model the natural history of disease (N), (2) those that model the effectiveness of the intervention (E), and (3) those that model the risks of the intervention (R).

Among the papers published in 2009 that included a model, a subset was selected for further data abstraction. Abstracted information is shown in Appendix F. Such a database of abstracted information, once fully developed and maintained, could serve as a resource to determine if and how many models exist on a particular disease area. It also could identify investigators who could potentially conduct the decision modeling exercise alongside a systematic review. Another benefit of this type of resource is to identify multiple groups with models developed for the same or similar purposes to conduct comparative modeling. In comparative modeling, independently developed models are used to address the same clinical or policy question, which provides a type of sensitivity analysis on the underlying modeling assumptions made by the model developers.

Develop a De Novo Model

This approach requires the most time and resources, though it would provide the most flexibility and opportunity for input from the stakeholder and the systematic review team. This approach is optimal in cases where the structure of existing models is not flexible enough to simulate the interventions of interest. For example, suppose we are interested in a model that simulates the health outcomes of hypertension screening followed by targeted treatment for several pre-specified blood pressure levels. Markov models that simulate hypertension screening would have categorized levels of blood pressure, and likely include only systolic or diastolic levels. If the categories are not consistent with the targeted levels for treatment, the model would essentially need to be re-specified and re-parameterized.

Practical Considerations

EPCs

This report focuses on conducting a simulation modeling analysis in conjunction with a systematic review. One resource for conducting systematic reviews is the EPCs. While all of the EPCs have expertise in the areas of conducting systematic reviews, they do not all have expertise in decision modeling. CISNET is an example of coordinated modeling efforts that legitimize and promote use of models. Similar benefits may be found with other disease groups or policy/decisionmaking bodies.

Timing

The issues surrounding the timing of when a decision analysis is conducted alongside a review pose several challenges. Ideally, a decision analysis would not be done unless it was deemed to add substantial value to the questions being addressed by the systematic review. This may not become clear until after the systematic review has begun. However, it typically takes about the same time to develop and analyze a decision model as it does to conduct a systematic review, and the final decision analysis results should incorporate the results from the review. Thus the addition of a simulation model alongside a systematic review may add time to the overall project in some cases.

Summary

Three basic options are available for conducting a modeling study alongside a systematic review. One option is to use methods similar to the systematic review and summarize and synthesize the available modeling studies on a particular topic. This approach provides a good first step to understanding the modeling issues pertaining to a disease and treatment area, but has several limitations in that it may not fit the question precisely and it does not allow for input from the stakeholders. A second approach is to collaborate with investigators with existing models. This approach requires modelers to be willing to make changes to their models that are consistent with the values of the stakeholder, which may involve significant reprogramming in some cases. The third approach is to develop de novo models. A key advantage to this approach over using existing models is that it limits any influence from prior modeling assumptions and allows perhaps more unbiased input from the stakeholder and the systematic review. This approach would be the most time consuming and costly, and it may not be appropriate for disease areas that require a fairly sophisticated modeling approach (e.g., cancer screening strategies) because of the time required for model development.

Best Practices for Decision and Simulation Modeling

Overview

This chapter discusses best practices and recommendations for developing, validating, and using decision-analytic models in general, as well as in the context of systematic reviews to inform decisionmaking of stakeholders such as the United States Preventive Services Task Force (USPSTF). We took a multipronged approach to gather information on best practices and recommendations for the development decision models and their use in practice. First, we sought to identify existing recommendations for best practices in decision and simulation modeling by conducting a literature search to document the current best practice recommendations and identify gaps in the literature. To complement our literature search, we conducted a focus group of expert modelers to discuss, characterize, and qualify best practices in decision and simulation modeling in general. Included were issues such as model formulation and characterization, model development and construction, handling and presentation of modeling assumptions, definition and presentation of parameters, outcomes to incorporate into the model, model analysis, model testing, validation and implementation, presentation and communication of results, and perceived gaps in the literature. Lastly, we created a profile of potential best practices in coordinating a simultaneous systematic review and modeling exercise based on responses from interviewees selected because of their involvement in recent decision analyses used inform the recommendations of the USPSTF. We interviewed modelers involved in those analyses, as well as USPSTF members, about lessons learned from conducting decision and simulation models alongside systematic reviews.

Summary of Literature on Best Practices

Systematic Review Methods

A search was conducted in Medline from database inception to March 2010 to locate best practice recommendations for economic analyses and decision analyses. We relied primarily on key word searches, such as "decision analytic model" or "Markov model," since MeSH terms are not well designed to facilitate indexing of such literature. We also used the search strategy employed by Philips et al.[40] to update the search they completed for their review of good practice guidelines from 2005 to March 2010. Specific search strings are provided in Appendix 7. Articles were not limited by country of origin, but they were limited to the English language. The trial search, which does not include a language limitation, did not yield any relevant article titles in a language other than English. To complement the review, we searched the grey literature for published guidelines from professional societies, governmental bodies, and other health-related organizations using Google search engines.

Articles were initially screened by one reviewer scanning titles and abstracts. Papers were included if the paper provided either (1) general guidance on key elements that constitute a good decision or simulation model or (2) explicit criteria against which the quality or validity of a decision or simulation model might be assessed. While the goal was to identify articles that discussed best practices as applicable to decision analytic and simulation modeling in general, we also examined modeling practices for specific disease conditions. For the latter, papers were included if the paper provided either (1) insight on modeling that could be applicable to other

conditions or (2) a comprehensive and critical review for specific clinical domains. Full articles were pulled for selected papers and examined by three reviewers each for inclusion. Disagreements regarding inclusion status were resolved through consensus. Articles not satisfying any of the inclusion criteria were excluded.

Systematic Review Results

Figure 2 depicts the article flow chart of all searches. The initial search produced 616 articles. A total of 42 articles underwent full review, of which 39 were retained for the final set.

Figure 2. Literature flow diagram
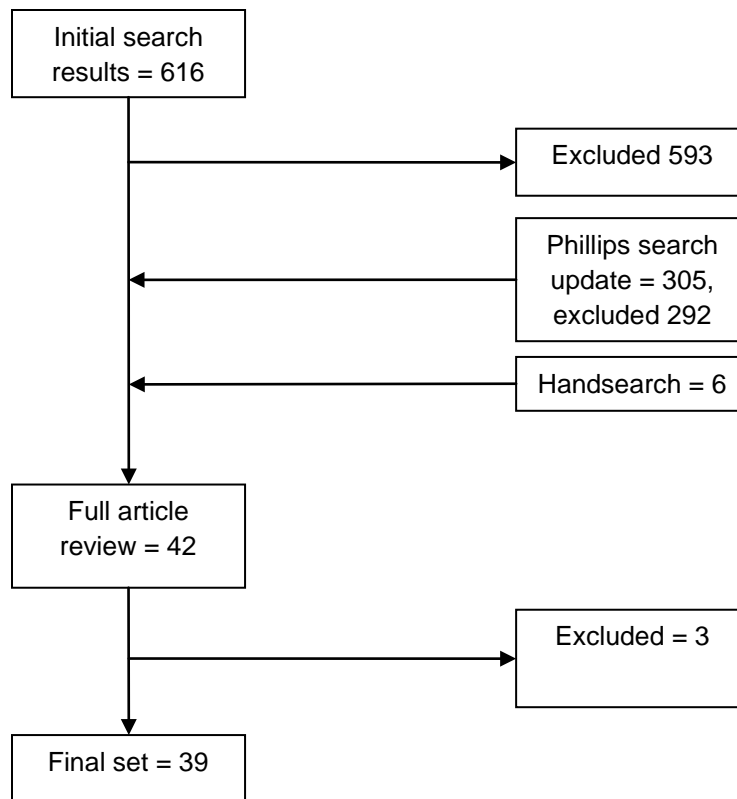
The final set of articles, listed in Table 20, was classified into five different categories:
1. Articles that propose and/or discuss good modeling practices (N=7).
2. Articles that discuss the roles, uses and/or value of modeling in general (N=4).
3. Articles that focus on a specific aspect of modeling such as uncertainty or validity (N=20).
4. Articles that propose comprehensive guidelines for modeling in a specific clinical area such as coronary care, screening (N=3).
5. Articles that review and compare models in specific clinical areas or comparative modeling (N=5).

Table 20. Articles offering best practice guidelines

Authors Year	Title	Journal	Comment
Good Modeling Practices			
Consensus conference on guidelines on economic modeling in HTA[50] 2000	Decision analytic modeling in the economic evaluation of health technologies. A consensus statement	Pharmacoeconomics	Short overview of best practices
Philips, Ginnelly, Sculpher, Claxton, Golder, Riemsma, Woolacott, Glanville[40] 2004	Review of guidelines for good practice in decision-analytic modeling in health technology assessment	Health technology assessment	Good practice guidelines for decision modeling
Philips, Bojke, Sculpher, Claxton, Golder[51] 2006	Good practice guidelines for decision-analytic modeling in health technology assessment	Pharmacoeconomics	Good practice guidelines for decision modeling
Sculpher, Fenwick, Claxton[28] 2000	Assessing quality in decision analytic cost-effectiveness models	Pharmacoeconomics	Provides attributes of good modeling practice
Tom, Schulman[52] 1997	Mathematical models in decision analysis	Infection control and hospital epidemiology	Overview of modeling as tutorial
Vale, Thomas, MacLennan, Grimshaw[53] 2007	Systematic review of economic evaluations and cost analyses of guideline implementation strategies	European journal of health economics	Review of best practices
Weinstein, O'Brien, Hornberger, Jackson, Johannesson, McCabe Luce[54] 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 in health	Best practice guideline
Role of Modeling			
Brennan, Akehurst[55] 2000	Modeling in health economic evaluation. What is its place? What is its value?	Pharmacoeconomics	Focus is on the roles of modeling
Drummond, Iglesias, Cooper[56] 2008	Systematic reviews and economic evaluations conducted for the national institute for health and clinical excellence in the United Kingdom: a game of two halves?	International journal of technology assessment in health care	Discusses the value of systematic reviews for models
Oddone, Samsa, Matchar[57] 1994	Global judgments versus decision-model-facilitated judgments: are experts internally consistent?	Medical decision making	Discusses value of models in expert judgment
Weinstein, Toy, Sandberg, Neumann, Evans, Kuntz, Graham, Hammitt[27] 2001	Modeling for health care and other policy decisions: uses, roles, and validity	Value in health	Discusses the role of models and a framework for evaluation models
Specific Aspects of Modeling			
Braithwaite, Roberts, Justice[22] 2007	Incorporating quality of evidence into decision analytic modeling	Annals of internal medicine	Evaluated impact of excluding lower quality evidence
Briggs[58] 2000	Handling uncertainty in cost-effectiveness models	Pharmacoeconomics	Focus on how to incorporate uncertainty
Claxton, Eggington, Ginnelly, Griffin, McCabe, Philips, Tappenden, Wailoo[59] 2005	A pilot study of value of information analysis to support research recommendations for the national institute for health and clinical excellence	Center for health economics research paper	Focus is on the role of value of information analysis

Table 20. Articles offering best practice guidelines (continued)

Authors Year	Title	Journal	Comment
Cooper, Sutton, Ades, Paisley, Jones (Working group on the use of evidence in economic decision models)[60] 2007	Use of evidence in economic decision models: practical issues and methodological challenges	Health economics	Editorial that focuses on evidence
Debicki, Ferko, Demarteau, Gallivan, Bauch, Anonychuk, Mantovani, Capri, Chou, Standaert, Annemans[61] 2008	Comparison of detailed and succinct cohort modeling approaches in a multiregional evaluation of cervical cancer vaccination	Vaccine	Discusses implications of simple vs. detailed models
Drummond, Manca, Sculpher[62] 2005	Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies	International journal of technology assessment in health care	Focus is on generalizability of modeling studies
Drummond, Barbieri, Cook, Glick, Lis, Malik, Reed, Rutten, Sculpher, Severens[63] 2009	Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report	Value in health	Focus is on transferability of modeling studies
Duintjer Tebbens, Thompson, Hunink, Mazzuchi, Lewandowski, Kurowicka, Cooke[64] 2008	Uncertainty and sensitivity analyses of a dynamic economic evaluation model for vaccination programs	Medical decision making	Discussed the choice of sensitivity analysis methods in dynamic modeling studies
Evans, Crawford[65] 2000	Expert judgment in pharmacoeconomic studies. Guidance and future use	Pharmacoeconomics	Focus is on the use of expert judgment
Faissol, Griffin, Swann[66] 2009	Bias in Markov models of disease	Mathematical biosciences	Focus is on biases that occur in modeling
Gallivan[67] 2008	Challenging the role of calibration, validation and sensitivity analysis in relation to models of health care processes	Health care management science	Argues against formulaic sensitivity analysis, calibration, and validation
Hughes, Cowell, Koncz, Cramer[68] 2007	Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations	Value in health	Focus is on modeling adherence and persistence
Karnon, Brennan, Akehurst[69] 2007	A critique and impact analysis of decision modeling assumptions	Medical decision making	Discusses implications of cohort vs. population modeling
Lilford, Girling, Braunholtz, Gillett, Gordon, Brown, Stevens[70] 2007	Cost-utility analysis when not everyone wants the treatment: modeling split choice bias	Medical decision making	Discusses the impact of bias due to treatment adherence
McCabe, Dixon[71] 2000	Testing the validity of cost-effectiveness models	Pharmacoeconomics	Discusses the challenges of validity tests for models
Stout, Knudsen, Kong, McMahon, Gazelle[72] 2009	Calibration methods used in cancer simulation models and suggested reporting guidelines	Pharmacoeconomics	Discusses the pros and cons of different calibration methods
Sun, Faunce[73] 2008	Decision-analytical modeling in health-care economic evaluations	European journal of health economics	Focus is on Markov models
Swan, Miksad[74] 2009	Measuring the quality of life effects of diagnostic and screening tests	Journal of American college of radiology	Focus is on quality of life

Table 20. Articles offering best practice guidelines (continued)

Authors Year	Title	Journal	Comment
Tavakoli, Davies, Thomson[75] 2000	Decision analysis in evidence-based decisionmaking	Journal of evaluation in clinical practice	Discusses the role of models in complex decisionmaking
Trikalinos, Siebert, Lau[76] 2009	Decision-analytic modeling to evaluate benefits and harms of medical tests: uses and limitations	Medical decision making	Discusses decision modeling in comparative evaluation of medical tests
Comprehensive Guidelines for Specific Modeling Area			
Bernstein, Hofer, Meijler, Rigter[77] 1997	Setting standards for effectiveness: a comparison of expert panels and decision analysis	International journal for quality in health care	General guidelines focused on coronary care
Karnon, Goyder, Tappenden, McPhie, Towers, Brazier, Madan[78] 2007	A review and critique of modeling in prioritizing and designing screening programs	Health technology assessment	Focus is on screening programs
Tappenden, Chilcott, Ward, Eggington, Hind, Hummel[79] 2006	Methodological issues in the economic analysis of cancer treatments	European journal of cancer	Modeling issues specific to cancer
Reviews of Modeling			
Annemans[42] 2008	Methodological issues in evaluating cost effectiveness of adjuvant aromatase inhibitors in early breast cancer. A need for improved modeling to aid decisionmaking	Pharmacoeconomics	Comparative modeling study
Campbell, Briggs, Buxton, Kim, Thompson[43] 2007	The credibility of health economic models for health policy decision-making: the case of population screening for abdominal aortic aneurysm	Journal of health services & research policy	Comparative modeling study
Earnshaw, Wilson, Mauskopf, Joshi[44] 2009	Model-based cost-effectiveness analyses for the treatment of acute stroke events: a review and summary of challenges	Value in health	Comparative modeling study
Green[45] 2007	Modeling disease progression in Alzheimer's disease. A review of modeling methods used for cost-effectiveness analysis	Pharmacoeconomics	Comparative modeling study
Jones, Cockrum[46] 2000	A critical review of published economic modeling studies in depression	Pharmacoeconomics	Comparative modeling study

Discussion of Selected Best Practices Articles

The articles shown in Table 20 provide insight into several key issues pertaining to the establishment of best practice guidelines; these include: (1) model definition, (2) purpose of a model and its appropriate use, (3) model evaluation, and (4) challenges in using models. These core concepts can be integrated into a set of recommendations and guidelines for the use of modeling alongside systematic reviews, and to inform key stakeholders, such as the USPSTF, regarding the employment of models in their studies and recommendations.

Model Definition

Weinstein et al. define a model as an "analytic methodology that accounts for events over time and across populations based on data drawn from primary and/or secondary sources"

(p.350).[27] This definition is further developed by Weinstein et al. as "a logical mathematical framework that permits the integration of facts and values and that links these data to outcomes that are of interest to health-care decisionmakers" (p. 9).[54] While similar, there are some differences to note between these two definitions. One difference is the specification of an "analytic framework"[27] versus a "logical mathematical framework."[54] The later specification of the use of mathematics versus stating a model as a framework suggests the later definition may be more restricted in its scope. Moreover, Weinstein et al. preface the definition with the requirement that a model "synthesize[s] evidence on health consequences and costs from many different sources."[54] This is an important point to consider in the definition of a model, the synthesis of multiple, disparate data in order to inform or support a decisionmaker. Specifically, the synthesis of multiple data sources makes decision modeling unique from other modeling methodologies, such as statistical modeling.

Model Purpose and Use

Beyond the definition of a model is the discussion of the purpose of a model as well as the appropriate application of a model to a particular situation. Weinstein et al. propose that the purpose of a model is to "structure evidence on clinical and economic outcomes in a form that can help inform decisions about clinical practices and health care resource allocation" (p. 9).[54] They go on to suggest that the "value of a model lies not only in the results it generates, but also in its ability to reveal theoretical connections between inputs (i.e., data and assumptions) and outputs in the form of valued consequences and costs" (p. 10).[54]

Brennan and Akehurst stress the fundamental cultural difference between biomedical researchers and the health technology assessment/health economics communities.[55] The latter have a paradigm of cost-effectiveness and the need to support policy decisions while the former have a paradigm of experimental data and hypothesis testing. As a result, as stated by Luce, health economists tend to recognize and accept "the necessity of various types of analytical models to enrich and broaden results from experimental research when it is available and to find substitutes for experimental data when it is not available".[80] Brennan and Akehurst propose that decision-analytic modeling plays a role through five different perspectives: (1) extending results from a single trial, (2) combining multiple sources of evidence to answer policy questions, (3) generalizing results from one context to another, (4) modeling to inform research strategy and design, and (5) modeling and analyzing uncertainties in the knowledge base.[55]

Models have been shown to be of considerable value to compare test-and-treat strategies in order to make recommendations on testing for a wide variety of diseases, helping to establish the links between the outcome of the test and the patient-relevant outcomes.[76] Trikalinos and colleagues explain the characteristics of many comparisons of test-and-treat strategies in which modeling is especially helpful.[76] These characteristics include: (1) integration of evidence from disparate sources, (2) evaluation of uncertainties and assumptions, (3) the analysis and evaluation tradeoffs, (4) determining the effect of succession of technologies, and (5) the consideration of hypothetical conditions for diseases with no effective treatment.

The assessment of both definition of a model and the purpose of a model sets the stage for an exploration of the condition or situations in which models are well suited to serve their purpose, namely helping decisionmakers make more informed decisions through the synthesis of information.

Model Evaluation

With the definition, purpose, and uses of models examined, it is then instructive to ask, "What makes a good model?" or "How does one evaluate a model?" The literature offers some answers to this question. Several baseline conditions are discussed in the literature, which specify the basic requirements for the use of a model; these can be considered a minimum threshold of characteristics. As stated by Weinstein et al., "models should be used only after careful testing to ensure internal accuracy (internal validity), to ensure that their inputs and outputs are consistent with available data (calibration), and to ensure that their conclusions make sense (face validity)."[27]

Weinstein et al. offer a summary of the key components of model validation, as well as evaluation: (1) transparency; (2) verification; (3) corroboration; (4) face validity; and (5) accreditation.[27] Much attention is placed on validity in this evaluation methodology. Strong emphasis is placed on assessing face validity, and using multiple modeling efforts to establish convergent validity. Regarding model validation, they also warn against important elements such as (1) the nature of change in contexts that are not accounted for in models, (2) the rapid pace of technological change, and (3) population and sub-population characteristics that may be subject to change not included in the model. They caution modelers to be aware of changing contexts and applicability of models to other populations, not initially studied.

In a subsequent article on the assessment of decision models, Weinstein et al. enumerates a more detailed set of criteria for model evaluation.[54] The structure of models must first be assessed to determine two main points, (1) the degree that the inputs and outputs are relevant to the decisionmaker and (2) whether the model follows the theoretical basis of the disease, especially the causal linkages among variables suggested in the literature. Additional evaluation dimensions include: (1) specific criteria for state-transition/Markov model structure, (2) an inspection of the data, (3) specific attention to the modeling and quantitative methods used, (4) the incorporation and exclusion of particular data, and (5) a robust validation process.

Sculpher et al. propose that criteria for assessing the quality of models be grouped in a framework that consists of three main categories: (1) structure, (2) data, and (3) validation.[28] In a subsequent review and consolidation of existing guidelines on the use of decision modeling, Philips et al. adopted similar categories in their proposed good practice guidelines for decision-analytic modeling in health technology assessment: (1) structure, (2) data, and (3) consistency.[51]

Beyond the "technical" quality of decision models, the 2000 consensus conference on guidelines on economic modeling in health technology assessment proposed additional characteristics of good decision analytic models. These characteristics expand the scope of the technical quality of a model and address the fact that models need to be: (1) useful for informing the decisions at which they are aimed, (2) clear, interpretable and readily communicated, and (3) parsimonious and not unnecessarily complex.

Table 21 summarizes key elements of the quality of decision and simulation models identified in the articles reviewed in Table 20.

Table 21. Assessing the quality of decision and simulation models

Type	Element of Quality	Comment
Structure	Statement of decision	Clearly state decision problem.
	Context and viewpoint	Specify perspective used. Inputs and outputs need to be relevant to that perspective.
	Statement of scope	Define purpose of model and domain of applicability including populations addressed and timeframe.
	Modeling approach and model type	Define nature and type model and explain/justify underlying theoretical approach.
	Structural assumptions	Clearly specify assumptions involved in the model. Discuss limitations of the evidence regarding structural assumptions.
	Options/strategies/comparators	Clearly state exhaustive and mutually independent options. Should not be limited by constraints of currently accepted clinical practice.
	Natural history of the disease	Structure of model should be dictated by a theory of the disease, not data availability.
	Causal relationships	Causal linkages between variables should explained and be consistent with underlying disease theory.
	Health/disease state	States should reflect the underlying biological process of the disease, rather than health service inputs. Should not be limited because of lack of data.
	Time horizon	Justify time horizon. Should be long enough to reflect important and valued differences between long-run consequences of alternative options/strategies.
	Cycle length	Justify choice of cycle length. Should be short enough so that changes in pathology, symptoms, and treatment decisions within a cycle are unlikely.
	Heterogeneity	Account for heterogeneity within modeled population. When appropriate, disaggregate populations into strata.
Data	Data identification	Clearly identify sources of data used and strength of evidence. Models are well suited to deal with and incorporate incomplete or insufficient evidence and can be used for value of information to determine optimal data to incorporate and/or collect. Expert opinions are legitimate but need to be duly documented. Justify excluded known sources of data.
	Parameters definition	Clearly define all parameters. Specify base-case estimates and ranges for all parameters.
	Data modeling	Explain mathematical steps perform to transform empirical observations into a form useful for decision modeling.

Table 21. Assessing the quality of decision and simulation models (continued)

Type	Element of Quality	Comment
Data	Data incorporation	Different sources of uncertainty should be distinguished (e.g., sample uncertainty vs. heterogeneity). Choice and form of distributions need to be set for all parameter values to reflect second order uncertainty.
	Exploration of uncertainty	All modeling studies should include extensive sensitivity analysis. All forms of uncertainty, including methodological, structural and parameter, must be explored. Probabilistic sensitivity analysis is the most appropriate method for handling parameter uncertainty.
Consistency/Validation	Internal consistency	Models should be subjected to thorough internal testing and debugging to trap any errors relating to data incorporation and modeling syntax. Models should be calibrated against data when possible.
	External consistency	Compare model outputs with any possible relevant study and/or model. Are results of the model consistent with information contained in relevant primary studies?
	Predictive validity	Outputs should always be interpreted contingent to inputs and assumptions. Since models are intended as aids to decisionmaking, there is no empirical test of predictive validity. Models should be updated, sometimes abandoned or replaced, as new evidence becomes available to inform their structure or input values.
Communication	Transparency	Transparency enables a user to examine the structure of the model and incorporated data without obstacle.
	Interpretability	The results should be clear, easily interpretable and understood for the decision the model is supposed to inform.
	Parsimony/Simplicity	Structure of model should be as simple as possible and avoid unnecessary complexity while capturing underlying essentials of disease process and interventions.

Challenges in Modeling

Modelers face many challenges as they seek to assist decisionmakers and improve the quality of decisionmaking. In the context of medical tests, Trikalinos et al. summarize these challenges and offer examples of situations where these challenges are faced.[76] These challenges include: (1) insufficient data on key input quantities (such as prevalence, test performance, effectiveness), (2) the potential non-transferability of performance across studies, (3) the choice of modeling outcomes (e.g., event-free survival, survival, QALYs), (4) the methods for meta-analysis, and (5) challenges in the parameterization and appraisal of complex models.

This list echoes Tavakoli et al., who also emphasize that one of the major difficulties in developing decision models lie in identifying data, specifically: (1) epidemiological data needed on the risk of subsequent outcomes in the natural history of a disease, (2) effectiveness data essential to estimate putative treatment benefits and harms as well as the probabilities of various outcomes given specific decisions over clinical pathways, and (3) health state valuation data necessary to estimate the utilities to be attached to specific outcomes.[75] By definition, models are simplified representations of a real problem and therefore are incomplete and inherently suffer limitations. However, they are precisely useful for that reason. They promote transparency by pinpointing the influential constituents of each problem and by providing systematic uncertainty analysis to fully appreciate the impact of parameter estimates. To capitalize on the potential

value of models, it is this necessary to clearly identify and communicate their assumptions, challenges and limitations.

Gaps in the Best Practices in Modeling Literature

There is extensive and fairly consistent guidance for model users, although it is vague at times. For example, while it is recognized that model structure is important, the guidelines are not explicit about how one judges this. Because the focus of good modeling practice guidance is on the technical aspects of models, they do not tend to provide guidance for the process of modeling, including the expertise required to conduct a modeling study, the best ways to illustrate and present models and modeling results, and best ways to develop capacity to understand decision models and overcome the black box problem. In addition, much of the modeling guidelines are focused on Markov models and less on other types of models such as dynamic models or discrete event models. Nor is there much guidance provided on the optimal approach to choosing the type of model for a particular problem.

The International Society for Pharmacoeconomics and Outcomes Research Society–Society for Medical Decision Making (ISPOR-SMDM) Joint Modeling Good Research Practices Task Force was recently convened (May 2010) with the goal of providing guidance for: (1) delineating the approach and design of modeling studies and the identification and preparation of required data, (2) selecting a modeling technique, (3) implementing and validating the model, (4) addressing uncertainty around model results, (5) reporting the modeling study results to assure transparency, and (6) using model-based study results to inform decisionmaking. This Task Force will produce several papers, including an overall summary paper, to be submitted for publication in 2011.

Expert Modelers Focus Groups

Introduction

The goals of conducting a focus group of modeling experts were to elicit, characterize, and precisely qualify best practices in decision and simulation modeling. These include model formulation and characterization, model development and construction, handling and presentation of modeling assumptions, definition and presentation of parameters, outcomes to incorporate into the model, model analysis, model testing, and validation and implementation (including results presentation and communication and perceived gaps in the literature). To complement the systematic review of best modeling practices, we used a focus group methodology to collect more in-depth information on how to characterize and qualify best practices in decision and simulation modeling in general. The focus group, with prior consent of the participants, was recorded, analyzed, and summarized.

The four participants for the focus group were identified by the Principal Investigators, Technical Expert Panel (TEP) and the Task Order Officers (TOOs). The focus group was conducted on May 16-17, 2010 in Atlanta, GA, in conjunction with the 15th annual international meeting of ISPOR. Focus group participants and instructions are provided in Appendix H. Prior to the focus group, participants were provided with a summary of preliminary findings from interviews with Evidence-based Practice Center (EPC) members (Appendix I) and with a selection of three articles on best practices from Table 1 (the articles are listed in Appendix I).

Findings

In looking at best practices in decision and simulation modeling along systematic reviews, three aspects of models were identified as the key components that need to be addressed:

1. The scientific and technical quality of the model.
2. The interaction between the model and the decisionmaker(s) the model is intended to inform.
3. The communication of the model and model results to a lay audience, beyond the decisionmaker.

Furthermore, the focus group felt that it is essential to put the discussion of modeling within the proper context of a decisionmaking framework, where the main goal of modeling is to generate an unbiased synthesis of available evidence on the basis of clearly stated assumptions to produce information not otherwise available to support, but not make, decisions made by individual(s) in charge of making complex but well-defined decisions and/or recommendations.

The focus group noted that, in their opinion, when specifically tasked with making a complex decision, most individuals, such as members of the USPSTF, value the availability of a decision analytic framework and welcome decision models to aid their decisionmaking process. The main issues regarding acceptance of models generally come from stakeholders and broader communities that are affected by the decision and may or may not welcome or accept the resulting decision and/or recommendations.

Regarding the technical quality of models, the focus group felt that existing guidelines identified in the review of literature performed in the first study captured all necessary dimensions of quality fairly well. Additional thoughts are summarized below.

Structure Versus Data

Evaluating the model structure, including assumptions made, and assessing the completeness and quality of the input data, as described in the literature on best practices are clearly essential prerequisites for using models alongside systematic reviews. However, it is also important to recognize that models can be very effective in predicting what could happen given input data and model structure. A model that has excellent structure but is impaired by lack of good parameter estimates for key inputs will not have high predictive ability but still has tremendous value in identifying and understanding (through sensitivity analyses) key drivers of outcomes and systematically studying the impact of key parameters. Thereby, at a minimum, informing further studies needed to refine estimates of such key parameters.

When data with different strengths of evidence are used jointly in a model, along the spectrum from expert opinion to strong evidence, it is important for modelers to clearly state and analyze the relative weight that different pieces of data carry in driving the outcomes. Equally important is the knowledge and disclosure of what was not included into the model, what factors or other variables are not taken into account.

Model Evaluation

In all modeling efforts, at a minimum, there should be a clear display and discussion of: (1) testing performed on the model (both structure and results), (2) assumptions and their impact on the results, (3) data input and parameters and their joint impact on the results, and (4) key drivers of the results. The latter point is important as usually, a handful of key elements drive the results of a model. Those need to be made very explicit and such discussion should make sense to clinicians who are experts in the clinical domain addressed by the model and should be consistent with the underlying theory and natural history of the disease and its progression.

The involvement of clinical experts in the development of the model should be evident, especially as it relates to the natural history of the disease, the formalization of the disease progression, the identification of and rationale for relationships between key variables, and other "a priori structuring" tasks. Ideally, a visual depiction of the underlying disease mechanics would enhance the perception of content validity of the resulting model.

Just as the development of a model should integrate modeling and clinical expertise, the evaluation of a model needs to be conducted by both modeling and clinical experts. A modeler without the proper clinical expertise would naturally focus solely on the technical aspects of the model, but, if unfamiliar with the clinical domain, would not be in a position to judge face validity. Only a clinical expert would be in a position to judge whether the clinically important decision points have been captured and whether the underlying disease theory is appropriately integrated into the structure of the model.

Gaps in the Best Practices Literature

The focus group perceived that an important neglected aspect of best practices in modeling alongside systematic reviews resides at the interface between the model and the decisionmaker the model is intended to inform. Four key issues were discussed: (1) nature of evidence produced by models, (2) nature and extent of involvement of the decisionmaker in the modeling effort, (3) transparency versus trust in the model, and (4) communication and visualization.

Not surprisingly, the consensus among expert modelers is that models do constitute "inferential" or "carefully manufactured" evidence that would not have been otherwise available and need to be incorporated along with other evidence generated through systematic reviews. The nature of the evidence generated may differ and may need to be viewed through different lenses, but it provides information to support decisions that other evidence cannot provide. Furthermore, one could argue that there is an implicit "mental model" that is being applied in reviewing and evaluating evidence in systematic reviews and that, theoretically, such mental model should be made more explicit.

One of the potential problems related to the acceptance, and therefore subsequent use and usefulness of models, is the notion that models are first developed by a technical team which passes on the results to decisionmakers without prior built-in interaction between the technical team and the decisionmakers. Such process may be ineffective and lead to the wrong model being developed, misunderstanding of the model and its results, and low acceptance and use. As stated above, in a framework of decision support, the development of a model should be a multidisciplinary effort that involves clinical expertise, modeling expertise, and the decisionmakers from inception to completion of the modeling project. A modeling report generally has multiple audiences and it is necessary to ensure that the model and its results are carefully explained and understood by the relevant stakeholders. Understanding, acceptance, and

use of models would be greatly enhanced with built-in interaction and involvement of the decisionmakers with the modeling team.

The issue of transparency is somewhat of a paradox. Transparency is certainly essential to allow review and evaluation of models by peer expert modelers. However, it is generally not what stakeholders want (i.e., to know every technical detail of the model), even though most say they want transparency. One could argue that when stakeholders say they want transparency, they really mean that they want to "trust" models. While model soundness and evaluation should be left to peer expert modelers, presentation of results is key in building trust and acceptance for stakeholders and users. Learning from, and researching novel methods and applications of, computer visualization in other fields would be very beneficial and lead to compelling ways of visualizing disease progression and the comparative impact of alternative interventions. We need more studies, perhaps performed by behavioral psychologists, to better understand how to present models and associated results so as to build such trust. For most lay people with respect to modeling, and hence the majority of stakeholders and users of the models (at the exception of researchers perhaps), transparency into the intricacies of a model would not help, in fact, they may even detract. Models are used for many purposes—from weather predictions to economic forecasting—with the focus being on the presentation of the model findings and not in the model specifications. Similarly, focusing on the visualization of output of decision and simulation models in health care would be a major step forward in increasing trust and acceptance of models by users and stakeholders.

Another issue with respect to the acceptance of models and model results is that a model might be very good, but users may have trouble interpreting the results of the model. In this case, the user might reject the model itself to avoid dealing with the tradeoffs revealed by the model. In addition, one could postulate that the well-known anchoring and adjustment bias[1] may play a role in how users "judge" the results of a model and eventually accept/reject such results. While it would be worthwhile testing such hypotheses, it is clear that the way models and results are communicated to users plays a critical role in user/stakeholder trust and acceptance. The ultimate test of how good a model is resides in its usefulness and actual use. Finding individuals who can clearly and simply explain what a model is and does to lay audiences is necessary to increase acceptance of models and associated results to the general public. The focus group did not have specific recommendations on how to find or train individuals in that regard but did stress the importance of building such expertise.

Research Gaps

Two additional elements were discussed by the focus group: the creation of a model registry and the need to incorporate human behaviors in models.

Creation and Management of a Model Registry

Just as ClinicalTrials.gov was created to form an organized registry of federally and privately supported clinical trials conducted in the United States and around the world, a similar registry could be created for models used. Such a registry would provide information about a model's purpose, the modelers, and provide a location where the model could be peer reviewed and possibly used and better disseminated. A number of issues would need to be addressed for such a registry to work, including secured access, intellectual property issues, computer codes, et cetera. It would, however, create tremendous value, increase acceptance, and accelerate dissemination of models.

Incorporating Human Behaviors in Models

A potential area of improvement for models is to capture critical human behavior that can influence outcomes as part of the model itself. For example, few models systematically attempt to incorporate issues such as treatment adherence, patient and provider behaviors, or compliance as part of the modeling of clinical pathways. Again, a model, with clearly stated assumptions, can inform such issues. For example, a model can provide estimates of benefits of a new intervention for a population of patients but only if full compliance is achieved. Comparing the results of such model to actual results, should they be available, might lead to the erroneous conclusion that the model is wrong if that assumption is not explicitly stated and is not subjected to uncertainty analysis. The model could be right and help focus efforts on (1) obtaining better estimates of actual compliance, or, even better, (2) how to increase compliance to reap the benefits of a new intervention.

Interviews of Cancer Modelers and USPSTF Members

Introduction

The goals of this study were to evaluate the strengths and weaknesses of current approaches to conducting a simultaneous or sequential systematic review and modeling exercise, evaluate stakeholder perceived needs and whether needs were met, and to make recommendations for the process of conducting future similar projects. To that effect, we interviewed relevant members of the Oregon Health & Science University EPC, modeling groups, and USPSTF members to evaluate the lessons learned from the colorectal cancer, breast cancer, and cervical cancer modeling projects that were conducted alongside systematic reviews, and their impact on USPSTF decisionmaking.

Interview Methodology

We worked with the TEP and the TOOs to select the most appropriate composition of respondents from among the Oregon Health & Science University EPC, the 16 members of the USPSTF, USPSTF partners, and selected cancer modeling groups and consortia. The final sample consisted of the leaders on each of the three cancer modeling projects (cervical cancer, breast cancer, and colorectal cancer), members of each modeling team, and members of the USPSTF who were involved in the development of the models and/or voting on recommendations (the evidence for which included modeling). Interviews, lasting approximately one hour each, were conducted via telephone over the course of April 5, 2010, through May 25, 2010. The interview participants are shown in Table 22. The interviews focused on lessons learned from the three cancer modeling efforts and the subsequent recommendations that were made.

The interview guide for this set of interviews focused on strengths and weaknesses of current approaches, perceived needs, degree to which needs are met, lessons learned from the cancer screening modeling projects, and perceived impact of these projects on USPSTF decisionmaking. The interview guide was then tailored to the different groups (modelers vs. USPSTF members). A general outline for the interviews is provided in Appendix J.

Table 22. Key informant interviews

Interviewee	Institution	Role
Natasha Stout	Harvard University	Breast Cancer Modeler
Don Berry	MD Anderson Cancer Center	Breast Cancer Modeler
Sylvia Plevritis	Stanford University	Breast Cancer Modeler
Shalini Kulasingam	University of Minnesota	Cervical Cancer Modeler
George Sawaya	University of California, San Francisco	USPSTF Member
Karen Kuntz	University of Minnesota	Colorectal Cancer Modeler
Mike LeFevre	University of Missouri School of Medicine	USPSTF Member
Tim Wilt	University of Minnesota/ Minneapolis VA	USPSTF Member
Steve Teutch	LA County Public Health	USPSTF Member
Diana Pettiti	Arizona State University	USPSTF Member

USPSTF = U.S. Preventive Services Task Force; VA = Department of Veterans Affairs

Findings

This section synthesizes the lessons learned from the interviews within the framework presented in the preceding section. Four key themes emerged from the interviews:

1. Modality
2. Communication and presentation of model results and rationale to stakeholders
3. Modeling literacy of stakeholders
4. Recommendations for future projects.

Modality refers to the primary design utilized, or that resulted, in each of the three cancer modeling efforts. The communication theme was universally discussed by all interviewees and was perceived as the most critical success factor for future projects. This theme involved issues ranging from written reports and documentation, to discussions with the media, to the visual presentation of results, and the rationale for the employment of models to address the key questions. Modeling literacy concerns stakeholders' dexterity with modeling and their ability to interpret the results and use them in order to make judgments and subsequent recommendations. Finally, all respondents expressed lessons learned and made specific recommendations for future efforts involving modeling alongside systematic reviews. While there was a high degree of consistency among respondents regarding communication and modeling literacy, there were differences among them regarding recommendations for future projects. Selected verbatim quotes from the interviewees are provided by theme in Appendix K.

Modality

Two dimensions were repeatedly used to describe each of the three cancer projects. First was whether the modeling effort was "coordinated," meaning the extent to which the systematic review team and modeling team coordinated their work for the USPSTF. Within the dimension of coordination, a temporal sub-dimension addressed whether the two components, systematic review and modeling, were conducted simultaneously with one another, or sequentially (i.e., the modeling effort following the completion of the systematic review). The second dimension that describes modality is the employment of a single modeling team or the utilization of a modeling syndicate, including multiple modeling teams, working to develop independent models to address the same questions, but using the same systematic review as a source of information.

The issue of modality framed the discussion of "lessons learned" from each project and was mentioned in each interview. In all of the interviews, the interviewees began the discussion with mention of the modality, and the majority described it in terms of coordination, sequence, and the number of modeling teams used.

There is high agreement among the interviewees that future projects should always employ multiple modeling teams developing different models. These suggestions ranged from a low of "at least two" to a high of "three to five," depending on how many people have been studying the disease," and the availability of modeling expertise for that condition. The rationale is simple: multiple modeling groups, using the same parameters from a systematic review, will develop models containing different assumptions, transitions, and representations of the natural history of a disease. To the extent that these differing models generate similar results, then the effort has high "convergent validity." Additionally, this method allows for detailed sensitivity analyses of the input parameters and assumptions that each model utilizes. Such an approach was described as the "foundation of CISNET [the Cancer Intervention and Surveillance Modeling Network]" and the "reason why CISNET is so well respected and the quality of its work is so highly regarded." This practice was also referred to as "comparative modeling" and was unanimously suggested as a best practice and recommended for future projects.

With regard to coordination between the modeling teams and the systematic review team, there was much agreement among the interviewees. All suggested that future projects employ a coordinated effort between modelers and systematic reviewers. There were several reasons given for this approach. There is benefit in both parties participating in the question refinement process and in defining the scope of evidence that will be reviewed. This ensures that evidence useful for the modeling effort is not neglected or ignored by the systematic review. Coordination allows for the standardization of many important project components, such as definitions and terminology and units of measure. In several cases, modelers mentioned that the lack of coordination isolated the modeling effort and detached the modelers from the key questions, needs, and goals of the USPSTF with regard to the utility of the modeling effort because of the inability to interact in detail with the systematic review team. This was reported as a "dissatisfying experience," but also one that "questioned the opportunity to improve the quality and robustness of the models." While there were differing degrees of commitment to a coordinated effort, suggesting a range of solutions from complete integration of the two groups to "several meetings during the systematic review process between modelers and reviewers," there was no dissenting opinion which suggested the efforts not be coordinated. The only mention of rationale for an uncoordinated effort is the reality that a systematic review may be completed and then used to inform model parameters for a different or subsequent effort. Additional subsequent efforts notwithstanding, future projects should strive to be coordinated efforts between the systematic review team and the modeling team(s). On the other hand, little to no communication is necessary between distinct modeling teams so as to preserve independence and maximize the value of multiple models examining the same questions.

While there was a high degree of agreement with respect to coordination, differences emerged when the temporal nature of coordination was addressed, namely sequential or simultaneous completion of the systematic review and development of the models. Those in favor of a sequential method cited two main reasons, first, that the systematic review needs to be completed so that key questions or assumptions have been established and that all key parameters have been identified. Once this is complete, then the modeling team can integrate the systematic review findings into the modeling effort. Although sequential, this remains

coordinated, in that the modeling team is involved in the systematic review, either as formal members of the team, giving guidance to the reviewers as to the evidence needs of the model, or in the form of several "readouts" of information and progress with the reviewers and modelers. In addition, many models already exist for many diseases. These models have certain assumptions, (e.g., natural history of disease), already established, so a new modeling effort might be more focused on updating and adding parameters to already established models, versus development of a new model. In this case, a sequential process may be more efficient, in that the extent of the modeling effort is new parameters, sensitivity analyses, and inspection of results. Several modelers supported a sequential process for this very reason. That said, in the development of a new model, where there is no existing basis to begin, those same modelers supported a simultaneous process during which the modelers would be interacting with the reviewers to develop the underlying model structure and assumptions in conjunction, and then using the systematic review as input parameters for the modeling effort. Additional rationale for a simultaneous process extended the supporting points for overall coordination, including the ability for modelers to impact the nature of the review and key questions, as well as for reviewers to help "identify nuances of the questions material to the model, such as natural history of disease or the identification of sub-populations of interest."

Communication to Users and Stakeholders

Communication of models and model-based results used as key evidence was cited most frequently as the top issue that needed to be addressed to improve the success and acceptance of these projects in the future. Regarding communication, we focus on the needs for improved communication with and between stakeholders for these projects and the subsequent recommendations that are generated. Although a tangential issue, we address stakeholders' overall "model literacy" in the next section. Communication can be segmented into a few salient issues: (1) USPSTF communication of recommendations whose rationale is based, to some degree, on results from a decision or simulation model versus with "evidence from more traditional sources"; (2) transparency and understandability of models and their results; and (3) discussion of models with the larger stakeholder population of providers and patients. Regarding the USPSTF communication of recommendations that include models, one interviewee captured the essence clearly, "The task force should tune their communications so that the science writer at The Washington Post or New York Times could understand, and then convey an accurate reporting of, the recommendation to the general public." Many of the USPSTF members claimed the media training recently provided to task force members was helpful in their interactions with the media, but more broadly in their communications with a variety of audiences.

USPSTF members cited the largest challenge was due to the actual models themselves. "The modelers need to [do] a better job at clearly and simply communicating the results of their models." Many interviewees mentioned the lack of standardization of model terminology, outputs, and results presentation as a challenge for the broader communications of results. One interviewee opined, "In the early 1980s, epidemiology faced this same issue…a group was formed and the science established an encyclopedia of epidemiology, which set the standard and began to allow for broader understanding and acceptance of epidemiology and results from epidemiological studies. Decision modelers should take this template and create their own encyclopedia." Further, one USPSTF member suggested that all projects should begin with a specification of what the outputs should look like, describing tables and figures in detail. Once this alignment has taken place, the expectations are set and the results are easier to communicate.

This improves the presentation and communication of results, but still leaves the description of the model, methodology, assumptions, structure, and techniques to be communicated. "Even with a high degree of transparency, it is still very difficult to describe these models to those that are not familiar with the models…technical appendices are indecipherable."

The question of communications with audiences beyond the USPSTF or other policymakers is even more complex. Many of the interviewees were unsure how to overcome this issue. Some recommendations are captured in the next section regarding model literacy, but the consensus solution seemed to be the reporting of standardized results (e.g., quality adjusted life years, number needed to treat, etc.) consistently for each model, along with "an accessible appendix that clearly and simply describes the metrics and the model." "Perhaps this is easier articulated, than actually achieved."

Model Literacy

After the discussion of communication, overall stakeholder literacy of modeling in general and the necessity of ongoing training and education were universally identified by all interviewees as a significant challenge to future projects. "Modeling is a unique discipline…it's not generally included in medical training, so even those that have used it for a while, need to have formal training by the experts." USPSTF members described a "decision models 101" that had been developed during one of the projects and presented to the Task Force members as a tutorial, in preparation for the discussion of results. This was graded by several USPSTF members as an excellent session, and one that should be routinely conducted as new members join the task force and when projects incorporate new techniques and methods not previously addressed. "A short manual needs to be developed as a reference guide for terminology, types of models, and standard outputs…like frontier curves and output tables." Some suggested that "Decision Models 101" should be included at the beginning of every results presentation that uses models."

The issue of training was identified in several of the interviews. First, the disparate nature of the training that many USPSTF members and other stakeholders have received to date was noted. "Most of us didn't say I want to be a modeler, we just starting using them in our work and learned." One solution, albeit longer term, is to "formalize training programs for decision modelers…if AHRQ [Agency for Healthcare Research and Quality] and the USPSTF want to use more models, then we need more resources to train the next modelers." Beyond training modelers, training for other stakeholders and policy makers was reported as being essential. "How do we incorporate this into medical training, or public health policy making, so that when physicians and policy makers see models they can understand them, and also that they can know when to ask for a model, instead of report[ing] not enough data to make or change a policy or recommendation."

Recommendations for Future Projects

Many of the lessons cited by both USPSTF members and the modelers were focused on the actual process of conducting the projects and analyses. Interviewees were prompted to reflect on the projects in which they were involved and report the top two to three lessons learned, either "what went right, or opportunity areas for improvement." Responses grouped into five basic categories: (1) goals and objectives for the project, (2) outputs and results, (3) USPSTF interactions with modelers and/or reviewers, (4) leadership from the USPSTF, and (5) interactions among modeling teams.

The goals and objectives that the USPSTF are trying to address with the modeling effort need to be explicit and understood by both the modelers and the task force leader. Within key questions, the areas where modeling is anticipated to have impact and be most beneficial need to be identified so that modelers can tune the analysis to those specific items. The largest opportunity for models to impact is in determining the start, stop, and interval for different testing strategies, an essential objective of the USPSTF. Beyond testing strategies, models need to be utilized in key questions to help the USPSTF assess the net benefit and the magnitude of the effect/benefit. When these goals and objectives are specific, clear, and have been aligned, the project should deliver the necessary results. Lack of clarity has been a problem in the past. Modelers need to be very specific with the task force lead and the systematic review team as to what key questions, or components of key questions, can modeling likely impact, and if the evidence is sufficient to develop a model to address that specific issue.

The design of outputs from a model needs to be conducted in a purposeful and careful manner. Essentially, the "outputs are the model," and as such need to be carefully constructed so that they answer the questions needed to inform and support decisionmaking. One interviewee suggested that "tables and figures be designed before the start of the project…this makes expectations clear and makes the goals clear, but it also ensures that the results will assist the decisionmaking." This point is important. It does not suggest that the modeling effort merely confirm an existing conclusion, but that the outputs are directly usable by decisionmakers to inform and aid in the specific decision or recommendation that is being addressed. There was some discussion that often modeling efforts provide too much or too little information, and in some cases, do not provide the necessary information that the decisionmakers need, thus leaving them to interpret or interpolate the results to address the recommendations.

Modelers desire an iterative process that allows interim "readouts of results with the USPSTF lead." "An iterative process is a much better discipline for modelers, especially with complex questions…interaction with the lead would have served us well, and allowed us to develop a better model." Further, in one case, the syndicate of modelers was completely disconnected from the USPSTF and the key questions, and was asked to perform specific "runs" based on standard parameters and to simply report the results of those runs. There was concern that, by not informing the modelers of the key questions and the ability to further "tune the model to address the key issues," unclear communication could result in less informative model results that may require additional analyses to be done. Such an iterative process will "hopefully give the task force members, or just the lead, more confidence in the model and a better ability to communicate the results."

Informed, model-literate leadership within the USPSTF was mentioned in two of the three projects reviewed as an essential component of success. In both cases, the modelers and the USPSTF lead reported a modeling project that impacted the USPSTF recommendations and allowed the task force to make either a "more detailed recommendation" or "to increase the certainty and/or the magnitude of the effects." Modelers noted that these USPSTF leads were familiar with models and had used them in their professional experiences, and thus were able to "be much more specific and answer detailed questions about their request…also they were able to challenge us on some of our logic." No team mentioned the lack of leadership, just the difference that strong, informed leadership can make to a project.

Interactions among modeling groups and with systematic review teams were a source of many recommendations. In terms of interactions among modeling teams, the CISNET structure and operations were consistently cited as a best practice by the interviewers, albeit "an expensive

undertaking that would require additional resources from AHRQ, the Task Force, or someone." The operations of CISNET were seen as providing the right balance between interactions and collaboration among the modeling teams on a frequent enough basis while still maintaining distinct and separate models that in fact demonstrate disparate representations of the disease. The CISNET structure was also seen as advantageous in terms of building repositories of expertise in specific diseases. "The Task Force knows where to go to get the best talent to address breast cancer." The interaction between the modelers and the systematic reviewers has been addressed previously in the discussion about coordination, but was seen as essential. Most modelers mentioned the advantages of frequent interactions with the systematic review teams. Interestingly, a few modelers suggested that such interaction made the "team more cohesive and…that improved the project." Perhaps, in addition to the value of the interactions from a purely empirical stance, interaction impacts some team dynamics and feelings of ownership of the project, which in turn improves the overall project, and allows for a more integrated systematic review and modeling effort to address the Task Force's issues.

Conclusion

In this chapter we discussed best practices and recommendations for developing, validating, using, and communicating decision-analytic models in general as well as in the context of systematic reviews to inform decisionmaking of stakeholders. Three separate studies were conducted to reach this objective: a systematic review of the literature on best practices, a focus group of expert modelers, and a set of semi-structured interviews with key modelers and stakeholders involved with three recent cancer models used alongside systematic reviews.

All three studies provided rich sets of information regarding the quality of decision and simulation modeling in general. They included issues such as model formulation and characterization, model development and construction, handling and presentation of modeling assumptions, definition and presentation of parameters, outcomes to incorporate into the model, model analysis, model testing, validation, and implementation (including results presentation and communication).

The literature on best practices provided an extensive list of 23 dimensions of quality of decision and simulation models classified in four main categories: structure, data, consistency/validation, and communication.

As a complement to the summary from the literature, the focus group proposed to frame models and systematic reviews in the context of a decisionmaking framework and identified three key issues to be addressed: the scientific and technical quality of the model, the interaction between the model and the decisionmaker(s) the model is intended to inform, and the communication of the model and model results to a lay audience, beyond the decisionmaker.

Finally, the interviews capturing lessons learned from the breast, cervical, and colorectal cancer models conducted alongside systematic reviews for the USPSTF provided insights in four key categories regarding the development and use of models alongside systematic reviews: modality, communication and presentation of model results and rationale to stakeholders, modeling literacy of stakeholders, and recommendations for future projects.

The information gathered through these three activities is reinforcing and complementary, and provides a solid basis for establishing guidelines for the successful development of models alongside systematic reviews.

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Acronyms/Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CISNET	Cancer Intervention and Surveillance Modeling Network
COMNet	Collaborative Obesity Modeling Network
EPC	Evidence-based practice center
EVCI	Expected value of clinical information
IOM	Institute of Medicine
LY	Life years
MeSH	Medical subject headings
NIH	National Institutes of Health
QALY	Quality-adjusted life years
TEP	Technical Expert Panel
TOO	Task Order Officer
USPSTF	United States Preventive Services Task Force

Appendix A. Search String and Results

1 decision analytic model$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	683
2 decision analys$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2,755
3 simulation model$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3,519
4 markov model$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3,184
5 state transition model$.mp. [mp=title, original title, abstract, name of substanceword, subject heading word, unique identifier]	152
6 markov cohort model.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	12
7 or/3	6 6,817
8 QALY.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2,108
9 quality adjusted li$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5,617
10 quality adjusted life.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5,613
11 quality adjusted days.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	23
12 quality adjusted month$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	13
13 quality adjusted survival.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	212
14 quality adjusted year$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	66
15 or/8	14 5,908
16 ICER.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	677
17 (incremental adj2 ratio).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	78
18 (incremental adj3 ratio).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1,221
19 or/16-18 Advanced Display	1,565
20 DALY.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	406
21 disability adjusted life year$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	572
22 20 or 21	733
23 monte carlo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	17,762
24 decision tree.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1,995

25 microsimulation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	185
26 15 or 19 or 22 or 23 or 24 or 25	26,611
27 7 and 26	1,441
28 cost utility.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1,432
29 cost effective $.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	48,974
30 28 or 29	49,475
31 limit 30 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial)	4,817
32 30 not 31	44,658
33 32 and 26	4,135
34 1 or 2 or 27 or 33	7,361
35 limit 34 to (English language and humans)	6,525
36 exp Environment/	682,103
37 exp Environmental Illness/ or exp Environmental Exposure/ or exp Environmental Pollution/ or exp Environmental Medicine/ or exp Environmental Monitoring/ or exp Environmental Pollutants/ or exp Environmental Health/	356,251
38 36 or 37	936,163
39 35 not 38	6,396
40 limit 39 to yr="2009" (before duplicates)	562
41 limit 39 to yr="2008" (before duplicates)	615
42 limit 39 to yr="2007" (before duplicates)	576
43 limit 39 to yr="2006" (before duplicates)	525
44 limit 39 to yr="2005" (before duplicates)	481

Appendix B. Semistructured Interview Guide

We interviewed EPC directors (and relevant staff) about lessons learned from incorporating, or not incorporating, models in EPC reports.

    a. Has considered and attempted to incorporate modeling but decided not to complete such a task

    b. Has not considered developing or incorporating models at all.

Key Themes

For all EPC members, we asked the following questions.

- Familiarity with models
  - Shared language set – how EPCs understand modeling terms
- Interest
- Access to modeling resources/expertise
- Usefulness
- Use of models
- Use of evidence generated by models (from others) as part of the systematic review
- How to recognize value/need for model at inception
- Impact on systematic review planning, timeline, budget
  - How would these differ for different EPC mandates, i.e., OMAR, CER, generalist topics, USPSTF-related projects
- Resources needed
  - Should modeling teams work separately from review team?
- Should training be offered?
- Impact of evidence generated by models on patients
- Impact of evidence generated by models on providers
- Impact of evidence generated by models on policymakers

For all EPC members who had experience with using models, we asked the following questions.

- Specifics on:
  - What, how, who – details of the model and modeling process
  - Effort, resources used
  - How to recognize value/need for model at inception
  - Impact on systematic review planning, timeline, budget
  - Training
- Are you <u>familiar</u> with employing decision and/or simulation modeling techniques to augment scope/use of evidence? How much?
- Are you <u>interested</u> in employing decision and/or simulation modeling to estimate outcomes when there is insufficient evidence to explicitly answer pressing policy needs? Why or why not?

- In your EPC work, have you <u>used</u> or <u>attempted to use</u> decision and/or simulation modeling to estimate outcomes when there is insufficient evidence to explicitly answer pressing policy needs? Why or why not?
- Have you reviewed models and their output for inclusion in systematic reviews? Have you included such information as part of the evidence? How do you "treat," weigh, and present that evidence in the reviews?
    <u>If YES:</u>
    - What were the opportunities?
    - What role did you play in the modeling effort?
    - Who else was involved, and what were their roles?
    - How well did it work?
    - What were your expectations? Were they met? Why or why not?
    - What were the main challenges?
    - Would you say the modeling activities were successful? Why or why not? How do you define "success" in this context?
    - Why did it work/fail?
    - How much effort was expended overall?
    - How much effort was expended relative to the total effort for this project (systematic reviews, etc.)?
    - How did modeling affect your planning for a systematic review? Timelines? Budget?
    - Did you incorporate the model in final report/recommendation? Why or why not?
    - How did you proceed?
    - Did you use other experts/resources to assist you? Who? How did you find assistance? How did you decide on who/what you needed?
    - Did you examine alternative modeling techniques? Which ones? If not, why not?
    - How did you/the team decide on the modeling approach?
    - What factors influenced the modeling approach?
    - Describe modeling activities from model formulation (including assumptions) to model development, testing, validation, and implementation. Comment on facilitators/barriers for each step.
    - What kind of models did you use?
    - Would you recommend to others to use similar strategies? Why or why not?
    - Would you try again in future projects? Why or why not?
    - If so, would you do anything differently? What? Why or why not?
    - How often do you think you can recognize the value/need for modeling at the inception of a review?
    - How do you recognize value/need?
    - Can you anticipate the need for modeling? How?
    - Should EPCs be offered training in modeling?
- Do you have <u>access</u> to necessary resources to develop, analyze, and implement decision and/or simulation models? Which ones?
- Do you believe decision and/or simulation modeling can be <u>useful</u> to augment evidence to explicitly answer pressing policy needs? Why or why not?

- Do you believe decision and/or simulation modeling to estimate outcomes can be successfully <u>used</u> to augment evidence to explicitly answer pressing policy needs? Why or why not?
- Do you think <u>patients</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by patients?
- Do you think <u>providers</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by providers?
- Do you think <u>policymakers</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by policy makers?
- How does modeling fit with the goals of stakeholders/partners?
- Have you reviewed models and their output for inclusion in systematic reviews? Have you included such information as part of the evidence? How do you "treat," weigh, and present that evidence in the reviews?
    <u>If NO:</u>
    - Have you read/seen reports/publications detailing the use of decision and/or simulation modeling alongside scientific reviews of evidence? If so, what is your impression/reaction to such approach?
    - How often do you think you can recognize the value/need for modeling at the inception of a review?
    - How do you recognize value/need?
    - Should EPCs be offered training in modeling?
    - Would you try modeling in future projects? Why or why not?
    - If so, how would you approach such effort?
    - How would modeling affect your planning for a systematic review? Timelines? Budget?
    - What challenges would you anticipate? How would you address them?
    - What do you think you would need? Do you know how to access such resources?
- Do you have <u>access</u> to necessary resources to develop, analyze, and implement decision and/or simulation models? Which ones?
- Do you believe decision and/or simulation modeling can be <u>useful</u> to augment evidence to explicitly answer pressing policy needs? Why or why not?
- Do you believe decision and/or simulation modeling to estimate outcomes can be successfully <u>used</u> to augment evidence to explicitly answer pressing policy needs? Why or why not?
- Do you think <u>patients</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by patients?
- Do you think <u>providers</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by providers?

- Do you think <u>policymakers</u> can rely on evidence (partly) based on decision and/or simulation modeling? Why or why not? How should such reports be developed/presented so as to gain trust/acceptance by policy makers?
- How does modeling fit with the goals of stakeholders/partners?

Appendix C. Revised Discussion Guide

1. What problems, research questions, or situations are most appropriate for the development and inclusion of decision models and/or simulation?

2. What model outputs (types and forms) deliver the greatest utility to the stakeholders (Policymakers, Patients, Providers)?

3. What is your working definition of a model? How do you distinguish it from other analytical techniques? How do you distinguish it from other forms of evidence? How do you evaluate model-based evidence from other empirical evidence?

4. How do you evaluate a model? How do you determine the "value" of a model and the evidence it provides?

Appendix D. Verbatim Quotes for Key Themes

This appendix summarizes the results of the Elite Interviews conducted with EPC directors and staff. Tables D1–D8 provide de-identified verbatim quotes for each theme presented along with clarifying comments and discussion from the interviewers.

Table D1. Theme #1: General attitude towards modeling

Respondent	Quote
16	"Lack of experience with modeling…when we have the need to incorporate modeling, we've had to seek outside expertise."
15	"We've been doing models for 8 years, going back to the inception of the EPCs…we feel that they are a very important part of EPC work, and a natural extension of EPC work."
10	"Default should be a model in every CER report."
7	"No modeling experience and no intent either."
4	"No clear guidance from methods manual on how to address…low modeling expertise within EPC…need guidance from AHRQ in order to assess."
	"Models are useful if they change the scope of CERs from systematic reviews to guidelines…any step closer to the establishment of a guideline…usage of the guideline by someone other than researchers."
1	"We have not done much modeling but we are quite interested… possibly through collaboration with others."

Table D2. Theme #2: When to utilize models

Respondent	Quote
16	"When the outcomes are in doubt, when there are many covariates that might affect the outcome… a model would be very helpful."
15	"Uncertainty about outcomes, benefits, harms…" "Extrapolation to groups that have not been well studied." "Determining the benefits of increased accuracy of tests versus decreasing access by recommending screening." "Situations where the evidence is poor, or where later stage outcomes are not well understood." "Task force review…these issues are particularly well suited."
13	"Anytime there is uncertainty in the data or the situation." "Addressing evidence gaps." "Unclear disease progression, like the ovarian cancer project, where the natural history of the disease is unclear." "Where there are not enough trials in the evidence, this makes the results from screening tests clearer." "Where results are insufficient but are handled as a positive indication."
11	"In the case of what works type of questions…in determining effectiveness from multiple RCTs." "In cases where there is less real data…like H1N1…to inform questions of prevalence or containment." "Where there is a lack of quality data about outcomes…where we have surrogate vs. terminal outcomes." "Value of information modeling is underexplored…this could be the most useful area."
10	"Quantify the effect of a lack of evidence…for example the characteristics of screening…frequency and costs. "In situations where there is a lack of evidence." "Low evidence situations where the causal chain and probabilities are difficult to assess without models."

Respondent	Quote
	"To assess value of information…and to allocate additional research resources."

Table D2. Theme #2: When to utilize models (continued)

Respondent	Quote
9	"Working to incorporate models in all proposals…understand the economic valuation of the RCTs." "Simulation models with underlying cost effectiveness should be included in reports." "Models should be used to update findings or to replicate results." "Clearly defined clinical questions."
8	"Evaluation of diagnostic tests beyond simple specificity and sensitivity…treatment decisions…comparing treatment strategies where optimal treatments are unclear…allocation of resources…cost effectiveness…value of information."
7	"CERs that have design or heterogeneity issues…use modeling, specifically simulation and bootstrapping to improve the value of evidence in CER." "When you need to synthesize evidence from multiple data reports, use simulation to understand the impacts these inputs have." "Determining the value of information." "Disease progression simulation helps understand the phenomenon."
6	"Weak evidence, very complex clinical issue…evidence is poorly documented…all complex clinical pathways." "Multiple outcomes…outcomes that are different among subgroups."
5	"Models are state of the art for cost-effectiveness…evaluation of diagnostic testing…treatment questions…linking surrogate to terminal outcomes" "Determining the treatment of subgroups of targeted populations with different outcomes."
4	"Comparison of alternative strategies…economic or clinical decisions." "Gap between intermediate and long-term outcomes." "Optimization decisions…defining treatment specifics."
3	"Situations where landmark clinical trials have not been conducted…unclear balance between evidence and harms…the focus of the decision is on costs…to determine the value of research gaps." "Models in technology assessments are a limited context."
2	"Extremely useful when we do not have all the answers from the literature. Very strong evidence form models for situations involving frequency of screening." "When we do not have an adequate answer from the systematic review but some of the evidence can provide input to a model." "When we get very good evidence on how different treatments compare on benefits and harms but we need to go to the next step of putting it all together in one common metric such as QALYs. Modeling is really useful to identify treatment that provides the best overall value." "Also to address to a question that is related to the value of information modeling especially when we are looking at questions of future research. With value of information modeling, we can figure out which one of those questions are really the most important to answer."
12	"Very useful when important tradeoffs exist and there is a need to balance them in some way… When there is uncertainty that is crucial to a decision, that is, the importance of ignorance, understanding what you do not know… modeling value of information to guide future research… cost-effectiveness.

Table D2. Theme #2: When to utilize models (continued)

Respondent	Quote
14	"One area is a situation in which studies available have only intermediate outcomes that do not reach clinical outcomes. The only way to make a stronger case is to do some modeling that looks at the relationship between the intermediate outcomes and the clinical outcomes. One could even use non-empirical data sources to build parts of the model." "Another area where you could use modeling very effectively is when you have infinite variation in small differences in techniques and where you have two literatures that converge. One literature is the clinical literature, which is very rich in information about the treatments and very poor in information about the client. The other literature is from epidemiologists, which is very rich in information about the patients and very sparse in information about the treatments. Modeling might at least help in pointing to where future work might be more useful in merging those two streams and actually get information about how different treatments might affect different kinds of patients." "The other area is in cost-effectiveness. In one study we developed a cost-effectiveness model which showed that the question of which type of outcome would be more beneficial from a policy standpoint depended on whose perspective one would take—the hospital perspective would be different from the insurer perspective." "When it appears that we have a number of disjoint findings but a sense of the pathway that leads to the outcome of interest, then some kind of modeling exercise would be very helpful in trying to pull of these things together."

Table D3. Theme #3: Model definition

Respondent	Quote
16	"Modeling the type of decisions make clinically? Actually, any type of meta-analysis is technically a model." "I am not used to the term around here, since we don't do much of it, so I don't have a good answer."
15	"Models are fundamentally a representation of a decision with respect to a hypothesis…versus an inference from statistical analysis." "It's the mathematical analysis of a decision."
13	"Mathematical representation of decision alternatives and outcomes."
11	"A predictive component and multiple inputs…meta-regression is a model."
10	"Simulation of the natural history of disease and strategies to treat the disease. "Not tools for cost effectiveness… more focused on clinical questions, clinical outcomes."
8	"Mathematics that link two pieces of evidence." "Define broadly to include more statistics beyond modeling." "Has to be something that pieces together different kinds of information… and uses something relatively complex… beyond a simple formula… For example, calculating the attributable fraction of a gene for a particular disease given X, Y, Z is not really a model." "Decisional context needs to be well thought of… if the context is not well defined or if information on treatments and/or treatment effects is lacking, a model would not help."
3	"Research contexts have not lent to the use of decision analytic models…we are eager to use modeling."
2	"A model is something that aims to answer a particular question using data input either available from empirical literature or based on assumptions that has a number of different options or comparisons. There is some type of comparison there, comparing one thing to another."
12	"Can be a relatively straightforward spreadsheet if benefits and harms are short term… Most of hard problems have either benefits or harms occurring over time… Need to use a decision analytic framework… Statistical models should not be included, the focus is on making a decision of some sort."
14	"A model is something that works around a decision tree with nodes and information that allows you to extrapolate from the data you have to answer a question for which there is no specific data. In many parts of medicine there are so many branches and potential points of disjuncture that you could not do empirical research that would capture all those things." "A model gives you guidance in ways you can fall back to say what things are going to make a difference and what things are not. It is partly a decision making tool, a planning tool, and an evaluation tool that gives you some insight into what is likely to happen or how big the difference is needed to actually make an ultimate difference. You can make some estimation of effects at various points of the care pathway to gauge whether there is a big enough difference or it is likely to be big enough to worry about it. Hopefully you can expedite the future research agenda you might want to recommend." "Comparing models and statistics, a model has a structure. Statistics may be a tool you would use in modeling and you may use statistics without modeling. For example, you would use statistics to calculate the likelihood of events representing real or significant events whereas a model really focuses on trying to look at the sequential effect of effects and/or activities on the prior probability of an outcome."

Table D4. Theme #4: Model outputs

Respondent	Quote
15	"QALYs are an artifact of the mid 90s as a result of the Gold book for CE." "Modeling is usually from a societal or population basis…that's the reason why QALYs make sense." "QALYs are to determine resource divisions at the broadest level." "QALY is really an omnibus measure for everything other than dollars." "Cost per QALY across services is the current method for reporting models." "Morbidity or mortality are very important, we just need a method to equate them to QALYs."
13	"Engaging the stakeholders throughout the process is key; that makes it easier to obtain support for the outputs or recommendations." "There should be two levels of output…simple metrics and a technical appendix." "Clearly stated assumptions, inputs and sensitivity analyses are essential." "QALYs and life expectancies are primary outcomes." "Outputs depend on the decisions being made." "Different stakeholders need different outputs…it's about the decisions they are making." "Models with multiple outputs…providers need NNTs…patients need life expectancy, risks for adverse events."
11	"AHRQ needs to standardize outputs."
10	"QALY is the accepted standard…so you need to make it an output of the model regardless". "QALYs do not provide a lot of utilities for specific issues." "Outputs that are denominated in intermediate versus terminal outcomes are difficult to interpret…not sure what conclusions can be drawn." "Developing tables that detail intermediate outcomes that change with different strategies can be very useful." "Patients and clinicians need outputs that illustrate the tradeoffs for specific decisions."
9	"Model results should not just be the model outputs…more about the over intent…relevant to the stakeholders." "Costs need to be considered." "Clinicians are detached from most economic components."
8	"QALY and expectancies, but they are difficult to determine." "Costs…but we've been asked to keep them out of scope." "Need to additional information." "Counts of events…like NNTs." "QALY is most effective, because it is what everyone uses." "Most reports stop short of QALYs to determine effect of different screening strategies." "Outputs are situation specific…surrogate versus terminal outcomes need to be understood and identified."
7	"Policymakers are more apt to use decision modeling…much more than clinicians."
6	"Presentation of the model is critical…all caveats about inputs and any poor quality data."
5	"Consistency and standardization are key." "QALY…can be a weak link to outcome decision…needs a consistent application of methods." "Patients and providers need a chain of understanding; clinicians don't understand QALYs and can't apply them to patients."
4	"Physicians prefer a narrative to a table of outputs or simulation results." "Health care decision makers do not like models…they want a recommendation."
3	"QALYs are the standard outputs…they are difficult for general audiences." "Direct or patient estimate probabilities would be very helpful…an explicit model that produced confidence intervals."

Table D4. Theme #4: Model outputs (continued)

Respondent	Quote
2	"Would love to see model output presented in terms of QALYs because that's an output that is extremely meaningful and can be compared across interventions." "Beyond that, outputs can be so varied depending on the situation, and some can be difficult to understand."
12	"It depends on purpose of the model. However, in general, I favor models with QALY as an output… For example for HIV intervention, treatment, or screening, one can look at infections averted as an output but then one cannot compare prevention with treatment." "QALYs capture changes in length and quality of life and allow comparison across interventions." "Other outcomes are important. Some metrics show benefits, others harms. One needs to delineate the pros and cons of different outcome measures. For example, successful treatment of HIV could _increase_ prevalence."
14	[In looking at output generated by a model as a source of evidence in a systematic review,] "We would probably treat it differently. Not sure exactly how, but it would depend on what we were doing… we can't really use model outputs in our meta-analyses, but you could certainly put them into a forest plot… and certainly if their findings were different, you would discuss the discrepancies." "What's interesting is that if a model that was used was using data from other studies that are part of the review, I am not sure what to do since the rules of the report are that each study can only be used once... This is a methodological issue that needs to be discussed." "For users—patients, clinicians, policymakers—showing a model is a waste of time… What you have to show them is what the model says… and make sure they understand what the model says and what the model does not say, and what it means… For patients… most patients do not distinguish anything about data sources or analysis sources… they are looking for a bottom line. A model for them is just another piece of information." "We, as academics, absolutely refuse to acknowledge that most users don't want to read more than a page of anything… as a result, we are terrible communicators."

Table D5. Theme #5: Evaluation of models

Respondent	Quote
16	"Formulation…how are they justifying the assumptions and the parameters…are they incorporating all the data…how was the weighting determined."
15	"Inputs, parameters, and sensitivity analysis are key to evaluating models." "The structure of the model must be well documented…it is important to be able to evaluate the underlying structure of the model…how well does it characterize the pathway or natural history of the disease." "What journals use as transparency vis a vis publishing standards is a good place to start." "Models need to be based on a good CER…credibility is lost when modelers use expert judgment."
13	"The structure of the model." "Do the results map to what we know about the data…modeling is an iterative process…how is the model performing?" "Who is the modeler…this is unscientific, but if I know who the modeler is, and if I know they do good work, then I am confident in the model." "Then there are specifics…representation of the available alternatives…assumptions and tests…exploring the uncertainty…a conservative view…what are the results of the sensitivity analysis…what are the inputs, evidence…what data was used."
10	"Review the structure of the model and the basic assumptions…what are the technical aspects of the model…review the data used as inputs."
9	"Understand the intervention…clear specification of the model and the framework."
6	"Inspect the analytical framework…clear model specification is critical." "The criteria is similar to that for any primary study."
5	"Traditional sources from decision analysis and cost effectiveness should be used." "The Weinstein text is a good source." "Model construction needs to be assessed…then sensitivity analyses need to be reported."
4	"Assumptions and where they break down…relative versus absolute nature of the measures…utility of the model outputs by non-modelers."
3	"We hope to be able to determine the model validity or quality…but it is very challenging."
2	"I like to see a detailed description of model inputs and assumptions that went into it." "A lot of description about sensitivity analysis especially for input and assumptions that were based on evidence that was not as strong." "Are data input valid? Is there an appropriate search strategy to find data? Are calculations adequate? Are appropriate sensitivity analyses conducted?"
12	"I look at both the structure and the fidelity of the model… The latter is to judge the representation and can be very difficult." "Need to judge the evidence of the input parameters… This can be done in just the same way as any other evidence review." "Judging the caliber of a model is very difficult… Checklists are OK, but more important is *who* developed the model." "For complex model, one should develop an enormous amount of time debugging, testing and exercising the model… It would be helpful to understand how much time modelers spent on this."

Table D5. Theme #5: Evaluation of models (continued)

Respondent	Quote
14	"Grading scheme for grading models has to be different from the grading scheme for grading empirical evidence. However, the grading scheme for the value of evidence needs a coherent whole but before you could really do that, you would need to define different types of models. For certain types of models, a proportion of data is empirical, some of it is opinion… the proportion would affect how you view the model as well as the evidence of the model." "If no modeling expertise, can only tell you whether the model is *useful*. So, first I need to understand the model. Are the right nodes in there? Is the important information used and addressed by the model? Then, have I learned anything? Leave it to other people to evaluate whether the right type of model is used and whether it is technically sound. I trust other people who have that kind of expertise."
1	"Definitely do a lot of sensitivity analysis. Should even be done with systematic reviews… For example would we get the same result in a systematic review if we take one study out? Sensitivity analysis in meta-analysis."

Table D6. Theme #6: Continuum of evidence

Respondent	Quote
16	"Most decision models incorporate evidence from RCTs and observational studies, so it's hard to distinguish them?"
15	"This is the gap between the U.S. and the U.K.…RCTs because of the FDA are predictable and that means credible. The value of RCTs is overstated, but the value is that they are predictable. If there were clear standards for decision models like at NICE, there wouldn't be such a perceived difference." "The tradition of the ACP is to use models as evidence to support decisions versus those in the Evidence-based/Cochran tradition that are more wedded to methodological standards and not decisions."
11	"I would never use modes in a CER." "Fifty percent of all CERs don't contain any analytics." 'Models are only pertinent with analysis…they are strictly quantitative."
10	"Where there is enough literature on a topic to create a good model, you don't need a model in the CER as evidence."
9	"Often there is not much evidence for the specific clinical area…many areas are uncommon."
8	"Typically excluded…research questions ask specifically for empirical evidence…often we comment on modeling studies, but don't include them." "There is no mandate to include models in reports…the evidence grading process doesn't work for models."
7	"Our TEP was recently against the use of evidence from models in the review…just a few years ago all AHRQ reports were based on RCTs…models can be used in literature review, but not for estimating effects."
6	"Depends on the research question."
4	"Models are reviewed in the discussion section in many reports." "Currently rated the same as no data, since the grading process doesn't allow for models." "It's critical to report the assumptions of the model…models are informative versus evidentiary."
3	"Our preference is for other type of evidence, except in the evaluation of pharma and cost effectiveness or comparative effectiveness studies." "Intermediate uncertainly is when modeling has the highest utility."
2	"Not quite the same level of evidence. In comparing output of a model and output of a well-designed effectiveness study, I would rate the level of evidence lower."
12	"I disagree with the statement that "*models are not evidence*"… modeling does extent evidence. Modeling studies should be included as evidence, as long as the models are good. In fact, they can be the most informative type of evidence… The USPSTF has models. The problem is that there is no well developed system for incorporating models as evidence." "Nobody is doing an RCT to follow HIV people for 20 years. Modeling, if carefully appraised, should be included as evidence… Modeling is not a substitute but there are situations where it is the only way. We typically would not use a model for comparing drug A versus drug B, but there might be some tradeoffs for drug A versus drug B that can lend themselves to modeling."
14	"The weight of information/evidence provided by a model in the context of a systematic review will vary greatly with the audience. Different audiences will give different amount of credence to these models depending on what they need. As everything we do, it has to be explained in terms that are meaningful to the person you are trying to communicate with." "Models are not empirical research, nor are we going to all the empirical research to support every clinical decision. So, somewhere we have to find some way to work our way through this. It may well be that models, either on a temporary or quasi permanent basis, may be useful in some cases in writing guidelines." "Placed in some sort of evidence hierarchy, something that is purely empirically based will be at the top, and something that is opinion-based would be at the bottom. Something that uses modeling, even where some of the nodes rely on opinion, would be better than purely relying on opinions."

Table D6. Theme #6: Continuum of evidence (continued)

Respondent	Quote
1	"People should realize that even an RCT has underlying theoretical perspective, just as models do." "There seems to be a chasm between research based on empirical data and theoretical research such as modeling… Maybe the Bayesian approach can help bridge that gap."

Table D7. Theme #7: Appropriateness of models in comparative effectiveness research (CER)

Respondent	Quote
15	"Models are a natural extension of CER work…all models need a strong CER as the basis for inputs, assumptions and parameters."
13	"This is an important question…we need guidance on how to consider models in these reports." "Models can add support to existing RCTs included in reviews…They identify opportunities for more information…This is critical in determining the value of information."
11	"It's reasonable to consider and include models, especially when updating previous CERs…when implementing the findings from a CER." "Could be useful to perform rapid reviews when new information is available…like from a new RCT…how does it impact the current state of the literature?"
7	"We need guidance from AHRQ on this issue…and guidance on how to evaluate models."
5	"Reluctant to include in CER…it's a substantial effort and we have limited resources." "Purpose of the CER …identify, review and synthesize original data from empirical studies…outputs from models are a very different evidence type." "For cost effectiveness, models are the only type available." "We have enough problems integrating the empirical studies…we need to use careful justification for selective inclusion of models."
4	"CERs are well accepted by payers and providers and provider organizations. They influence the development of guidelines…we need to be cautious if we substantively change them." "Models should be a separate part of the report…the other sections should not rely on them and should be able to stand alone."
3	"AHRQ needs to issue some guidance to EPCs about when the use of modeling is appropriate." "Modeling has the ability to inform the decision…many situations have a modest body of information to model from."
12	"Comparative effectiveness is more than looking at the literature… Models are extremely appropriate and needed… There are many instances where the value of a systematic review would be significantly enhanced by integrating it into a model… especially in how we weigh harms and benefits… in this situation, a model increases the usefulness of the review but it needs to be transparent."
14	"In the context of systematic reviews the appropriateness of models varies with where you are. Some reviews are pretty straightforward and you do not need models. At one extreme you have reviews with strong evidence and the other extreme the literature is terrible and all you can do is make recommendations for future research. Then you have a group in the middle where you could extend the clinician's appreciation of what would be worthwhile at the next step of research by estimating the likely effect of the next increment of information along with some boundaries on how large that effect is likely to be or would have to be to make a substantial difference in the outcome of interest." "The other way to do it is to say we have information up to this point but in fact we want to go beyond this point so then we need to extrapolate the information you have and modeling can be useful to do that." "Guidelines about what are the ranges of models and situations that they would be appropriate for would be useful… Something about what should go into a model. However there is no consensus about what constitutes a good model… Disconcerting that the best indicator of the quality of a model seems to be who did it! It does not feel me with optimism that guidelines are the way to go but there may be some principles that you may want to get across. Alerting people that there is more than one kind of model and what it does and what it does not do would be valuable."

Table D8. Theme #8: Impact of modeling effort on resources, training, timelines etc.

Respondent	Quote
16	"Models add to the time burden completing reviews…We don't have much time to get these projects completed." "Modeling increased the timeline for the project 20–40 percent, but we outsourced to another center." "Decision to use modeling came very early in the project."
15	"Modeling doubles the effort and time on a CER for AHRQ." "It requires the division of the team into two parts…people focused on evidence review, and then the people building the model." "This requires both teams to collaborate." "Models require upfront development of the scope and definition…you need to know the availability of the parameters in order to specify the model." "We need to use the VA model, where there's a national center to disseminate the expertise and methods and support and consult with the other centers."
13	"Identifying the opportunity for a model is difficult before the question refinement stage." "TOs need to be more flexible to changes after this phase." "Models take 1–2 additional team members." "Modelers need to be involved in the CER…they need to participate in the general investigation." "Models can be built simultaneously…it doesn't require a sequential process."
11	"Modeling needs to be handled in a separate TO…it's just too hard to predict the costs during the initial process." "Modeling has a moderate impact to timelines and budgets…data need to be looked at in order to determine if models are appropriate."
10	"Models need to be a collaborative between clinicians and modelers." "Collaboration builds expertise in the modelers for specific clinical issues…modelers need to focus on specific areas where they have some background-specific diseases or patient populations." "Models need to be specified upfront and incorporated into the RFP responses." "Model approaches and uses need to be identified ahead to time…otherwise the questions in the TO are so numerous that they consume all the report resources." "Recent models…approximately 30 percent of the total effort." "Expertise should be in the EPCs to conduct the modeling." "We should be identifying subject matter modelers that can contract with other EPCs if necessary."
8	"A comprehensive modeling approach is resource intensive." "Modeling is complementary to CERs…it leverages CER evidence…but it has a life of its own." "Training is fine, but it can't substitute for experience." "In-house modeling expertise is great, but at least EPCs need access to the talent and resources."
7	"Models must be considered at the inception of the project." "Training is critical if AHRQ wants more models, or to include models as evidence…training is needed to build capacity…a methods manual for models would be helpful." "Need clear requirements." "Modelers need to be involved at the start of the project...joint development of analytics and review framework."

Table D8. Theme #8: Impact of modeling effort on resources, training, timelines etc. (continued)

Respondent	Quote
5	"Scope of work needs to specify whether models need to be included…with commensurate increases in funding and timeline." "There needs to be agreement that there is a need for the increased level of evidence from models." "Needs to be integrated into the overall review…must be used to define the questions…reviewers need to understand what the modelers need." "An addendum or separate methods manual is required…needs to specify how to include models in the review report."
4	"Separate groups into reviewers and modelers."
3	"Models need to be specified in the question refinement phase of the project." "CERs are very time consuming, modeling significantly increases the scope."
2	"Modeling will affect timeline much less if we knew up front that a model needs to be done. Could affect the timeline by two to four weeks from the time." "Much like we have a methods manual for comparative effectiveness, there could be a method manual for commonly used types of modeling." "Challenges include whether the right people are available on short notice since modelers are not currently part of our EPC core staff." "Our initial approach is to have the modeling team involved from start to finish… One person from the modeling team is there more intensively at all meetings and then we'll have two other senior modeling individuals involved once a month."
12	"Not cheap to do this… It depends on the problem… Our most complicated models easily cost in the hundreds of thousands of dollars… Some models are the result of over 15 years of development… Engaging in a modeling effort should not be an afterthought… Developing a good model is substantial work." "I would estimate a model can take a third to a half of the budget and effort of a systematic review. It can be a substantial additional effort depending on what the model is addressing and what the problem is, infectious disease, chronic disease, long term outcomes or not, etc." "Not all EPCs have modeling resources… We should have collaboration between EPC in that regard… It would be useful to train additional people to do modeling. For example, we could have a CER fellowship program to increase capacity and send selected individuals to centers of excellence or institutions capable of training such people. It is a significant issue, there simply does not exist many people who have the training and skills to develop models."
14	"The need for a model can be recognized early on in a systematic review but you may or may not recognize it at the beginning… Probably three months in when you have done preliminary review of the literature, you can pretty much tell what your outcome variables are and if they are not the outcome variables you are looking for, then you know something like a model might be needed." "Need to negotiate bigger budget, or ask for additional budget, or build in contingency clause for additional budget if both sides recognize the need, or do add-on after project is done." "Obviously need some model-based training… but that's only one piece. Part of this is just to broaden people's horizon… At least, at one of those EPC meetings, there should be a modeling 101 that may be would start with some panel discussion of the various roles that models can play."
1	"Training will be useful but the need can vary greatly from EPC to EPC."

Appendix E. Types of Systematic Reviews

Overview

There are two broad categories of AHRQ-funded synthesis reports, Technical Briefs and Research Reviews. Technical Briefs are short reports on the type of information available to answer a question, whereas Research Reviews are more traditional comprehensive systematic literature reviews with quantitative and qualitative summaries of the actual evidence for each key question. AHRQ funds several different types of Research Reviews, including Comparative Effectiveness Reviews (CERs), National Institutes of Health (NIH) Consensus and State-of-the-Science Conference reviews, U.S. Preventive Services Task Force (USPSTF) reviews, and some additional Generalist Program reviews. Below are descriptions of each of these different types of reports.

Technical Briefs

The aim of a Technical Brief is to provide an overview of the information available on a given topic. Typically these are early stage products for which there is only limited evidence. The goal is to explain what is known and not known about new or emerging health care tests or treatments. These reports can be used to help set priorities for future research needs and to help develop questions for future more comprehensive reviews. It is not anticipated that modeling would be done for a Technical Brief.

Comparative Effectiveness Reviews (CER)

The CER is the core product of the Effective Health Care (EHC) Program and an area where we would anticipate a great deal of interest in the use of decision models. The aim of a CER review is to depict how the relative benefits and harms of a range of options compare, rather than to answer a narrow question of whether a single therapy is safe and effective. This requires a clear understanding of the clinical context to ensure that the review focuses on the appropriate population and interventions among which clinicians are currently choosing.

There is rarely a sufficient body of head-to-head trials to support easy conclusions about comparative benefits and harms. Providing useful information requires examining a broader array of literature, including placebo-controlled trials and observational studies. The latter are especially useful for looking more completely at harms, adherence, and persistence. In addition, reviews may examine whether, in the absence of head-to-head trials, indirect comparisons may be useful, e.g., comparing results of placebo-controlled trials of A and placebo-controlled trials of B.

Carefully examining the applicability of evidence is especially important. A useful review compares the tradeoffs of multiple alternatives, each of which may vary with the underlying population and setting. Evidence on harms is often hard to determine from tightly controlled randomized trials. Observational studies provide another check on whether results observed in trials appear to hold up under more representative settings and populations.

The interpretation of the evidence and the limits of interpretation are important. Equivalence of different treatments for a group of patients on average does not necessarily imply they are equivalent for all individuals. Attempts to explore subgroups for which benefits or harms of specific interventions vary may be needed. Often, however, there is limited evidence to support strong conclusions about the specific benefits of a particular intervention for subgroups.

U.S. Preventive Services Task Force (USPSTF) Reviews

The EPC conducts systematic reviews of the evidence on specific topics in clinical prevention that serve as the scientific basis for USPSTF recommendations. The USPSTF reviews the evidence (including contracted systematic review), estimates the magnitude of benefits and harms for each preventive service, reaches consensus about the net benefit for each preventive service, and issues a recommendation. Recently, the USPSTF used cancer modeling output, in addition to systematic reviews, to update of their cancer screening recommendations for colorectal, breast, and cervical cancers.

NIH Consensus and State-of-the-Science Conference Reviews

These reviews are contracted to provide an evidence-based, unbiased systematic review for upcoming NIH Consensus Development or State-of-the-Science Conference sponsored by the Office of Medical Applications of Research (OMAR). Consensus Development Conferences are typically undertaken when there is a solid body of high-quality evidence (randomized trials, well-designed observational studies) and it is reasonable to expect that the panel will be able to give clinical guidance. State-of-the-Science Conferences are generally utilized in cases where the evidence base is weaker and the sponsoring NIH Institute or Center is seeking the panel's opinion on future research priorities. The role for modeling in these settings is unclear.

Generalist Program Reviews

The EHC program also funds some additional reviews that do not fit into the CER, USPSTF, NIH Consensus and State-of-the-Science review programs. This general topic category can represent a wide array of topics and large range of quality of evidence in the existing published literature on the topic. We would anticipate that the use of models would be relevant to several topics from generalist program reviews.

Appendix F. Model Documentation

Indentification # 1683
Siebert U, Sroczynski G, Aidelsburger P, Rossol S, Wasem J, Manns MP McHutchison JG, Wong DB. Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines. Pharmacoeconomics 2009;27:341–54.

Base-case population
Cohort of men and women aged 20 to 70 years old with (1) mild chronic hepatitis C, (2) moderate chronic hepatitis C, or (3) compensated cirrhosis.

Strategies
1. No antiviral treatment;
2. Interferon -a-2b (3 million units three times per week) plus ribavirin (1,000–1,200 mg/day) for 48 weeks considering treatment discontinuation at week 24, when HCV RNA viral load was detectable;
3. Pegylated interferon-a-2b (1.5 mg/kg weekly) plus weight-based ribavirin (800–1,200 mg/day) for 48 weeks considering treatment discontinuation at week 24, when HCV RNA viral load was detectable;
4. Genotype-specific treatment duration and dosage according to the German guidelines:
    (a) for HCV genotype 2/3, pegylated interferon-a-2b (1.5 mg/kg weekly) plus ribavirin (800 mg/day) for 24 weeks without using stopping rules;
    (b) for HCV genotype 1, pegylated interferon-a-2b (1.5 mg/kg weekly) plus weight based ribavirin (800–1,200 mg/day) for 48 weeks considering early treatment discontinuation after 12 weeks (if detectable HCV RNA and viral load drop <2 log) and 24 weeks (if detectable HCV RNA in early responders with detectable HCV RNA after 12 weeks).

Model type: Markov

Time horizon: Lifetime

Cycle length: 1 year

Outcomes: 20-year risk of compensated and decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, liver-related death, life expectancy, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs)

Probabilistic sensitivity analysis (y/n): Y

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)

Prevalence of mild chronic hepatitis C (Knodell periportal inflammation score of 0–1) (N)
Prevalence of moderate chronic hepatitis C (Knodell periportal inflammation score of 3–10) (N)
Prevalence of compensated cirrhosis (Knodell fibrosis score of 4) (N)
Risk of diuretic-sensitive ascites (R)
Risk of diuretic-refractory ascites (R)
Risk of variceal haemorrhage (N/R)
Risk of hepatic encephalopathy (N/R)
Risk of hepatocellular carcinoma (N/R)
Risk of liver transplantation (N/R)
Risk of decompensated cirrhosis (N/R)

Indentification # 1691
Bendavid E, Wood R, Katzenstein DA, Bayoumi AM, Owens DK. Expanding antiretroviral options in resource-limited settings—a cost-effectiveness analysis. J Acquir Immune Defic Syndr 2009;52:106–13.

Base-case population
Cohort of HIV infected men and women in South Africa who present for care.

Strategies
1. A strategy of 2 antiretroviral regimens consistent with the World Health Organization (WHO) guidelines and with standard practice in many parts of sub-Saharan Africa. {, 2006 #484} The initial regimen included two older nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitors (NNRTI). That was followed by a second-line regimen with a different backbone of NRTIs and a boosted protease inhibitor (bPI).
2. A three-regimen strategy which started with a triple NRTI regimen followed by two regimens similar (though not identical) to the WHO strategy.
3. A three-regimen strategy which started with WHO's 2 regimens followed by a third-line regimen based on a second-generation bPI.

Model type: Microsimulation model

Time horizon: Lifetime

Cycle length: Monthly

Outcomes: Life expectancy and ICERs

Probabilistic sensitivity analysis (y/n): Y

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)
Rate of progression, by CD4 count and RNA load (N)
Monthly probability of developing a severe opportunistic disease (N)
Risk of death by CD4 count (N/R)
Additional risk of death due to an opportunistic disease (N/R)
Percent suppressed at one year (by treatment regimen) (E)
Drop in CD4 count with drug discontinuation (R)
Rise in viral load set point with drug discontinuation (R)
Risk of regimen change or discontinuation due to drug toxicity (R)

Indentification # 1697
Chaudhary MA, Moreno S, Kumar RN, Nocea G, Elbasha E. Cost-effectiveness analysis of raltegravir in treatment-experienced HIV type 1-infected patients in Spain. AIDS Research and Human Retroviruses 2009;25:679–89.

Base-case population
Cohort of Spanish HIV1-infected men and women who have received previous treatment for HIV and were resistant to at least one drug in each of the three classes [nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs)] of ARTs.

Strategies
1. Optimized background therapy alone
2. Raltegravir 400mg bid and optimized background therapy

Model type: Markov model

Time horizon: 50 years

Cycle length: Instantaneous (differential equation-based model)

Outcomes: Primary and recurrent OI cases, Life Years, QALYs, ICERs

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)
Baseline distribution of cohort by CD4 count (N/E)
Incidence of OIs and other AIDS-related complications (N)
Mortality by CD4 count (N) and history of an opportunistic infection (N)
Duration and monthly risk of death by opportunistic infection (N/R)
Monthly probability of progression by CD4 and RNA count stratified by treatment (E)
Percent discontinuing drug regimen (R)

Indentification # 1767
de Kok IM , van Ballegooijen M , Habbema JDF. Cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. J Natl Cancer Inst 2009;101:1083–92.

Base-case population
Dutch population of young girls at risk for HPV infection, CIN, and cervical cancer.

Strategies
1. Screening
2. Screening + Vaccination for HPV

Model type: Microsimulation model

Time horizon: Lifetime

Cycle length: Not stated

Outcomes: Clinical cases of CIN 2 or 3, screen-detected cancers, disease-specific deaths, life-years, QALY

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): N

Model parameters (N = natural history; E = effectiveness; R = risk)
HPV prevalence (N)
CIN grades 1, 2, and 3 prevalence (N)
Cancer incidence by stage [International Federation of Gynecology and Obstetrics (FIGO) stages IA, IB, and II+] (N)
Relative risk of developing cancer in unscreened compared to screened population (E)
Vaccine efficacy and duration (E)
Cure rate for a screen-detected precancer or cancer (E)

Indentification # 1750
Walensky RP, Wolf LL, Wood R, Fofana MO, Freedberg, KA, Martinson NA, Paltiel AD, Anglaret X, Weinstein MC, Losina E for the CEPAC (Cost-Effectiveness of Preventing AIDS Complications)-International Investigators. When to start antiretroviral therapy in resource-limited settings. Ann Intern Med 2009;151:157–66.

Base-case population
HIV-infected patients in South Africa

Strategies
1. No treatment,
2. ART initiated at a CD4 count less than 0.250 x 10^9 cells/L
3. ART initiated at a CD4 count less than 0.350 x 10^9 cells/L.

Model type: Markov model (state-transition model)

Time horizon: 5-year and lifetime

Cycle length: Monthly

Outcomes: Opportunistic infections, deaths, life-expectancy and ICERs

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): N

Model parameters (N = natural history; **E = effectiveness; R = risk)**
Counts of persons with CD4 count between 0.250 and 0.350 X 10^9 cells/L (N)
Counts of persons living with AIDS, receiving care and receiving ART (N/E)
Baseline CD4 and RNA distribution (N)
Risk of CD4 count decrease by RNA level (N)
Risk of a mild or severe OI by CD4 count (N)
Efficacy of antiretroviral therapy (E)
Efficacy of cotrimoxazole (E)

Indentification # 1721
Zechmeister I, Freiesleben de Blasio B, Garnett G, RaeNeilson A, Siebert U. Cost-effectiveness analysis of human papillomavirus-vaccination programs to prevent cervical cancer in Austria. Vaccine 2009;27:5133–41.

Base-case population
Multiple cohorts of girls (and boys) in Austria

Strategies
1. Screening
2. Vaccination of 12 year old girls + screening
3. Vaccination of 12 year old girls and boys + screening (of women)

Model type: Differential equation/transmission model (for effectiveness measures)

Time horizon: 52 years (2008 to 2060)

Cycle length: Instantaneous/NA

Outcomes: Life years, ICERs

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)
Progression rates from type-specific infection to persistent infection, CIN (1, 2, 3) and cancer (stages 1, 2, 3, 4) (N)
Regression rates from type-specific infection and CIN (N)
Stage specific survival (N)
Hysterectomy rates (N)
Rate of loss of natural immunity (N)
Sexual activity by level and age (N/R)
Average partner change (N)
Transmission rate (by HPV type) (N)
Screening coverage by age (E)
Sensitivity of screening for CIN and cancer (E)
Vaccination coverage (E)
Vaccine efficacy (E)
Vaccine duration (E)

Indentification # 1722
Coupé VMH, de Melker HE, Snijders PJF, Meijer CJLM, Berkhof J. How to screen for cervical cancer after HPV16/18 vaccination in The Netherlands. Vaccine 2009;27:5111–19.

Base-case population
Cohort of 12-year-old girls in the Netherlands

Strategies
1. Vaccination of 12-year-old girls only
2. Screening (with varying intervals, age of first screening and use of cytology and HPV DNA tests) + vaccination

Model type: Markov model

Time horizon: Lifetime

Cycle length: 6 months

Outcomes: CIN 2/3s, cancers, cancer deaths, QALYs, ICERs

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)
HPV incidence (by HPV type) (N)
Regression rates of HPV and CIN (1, 2, 3) (N)
Progression rates of HPV and CIN (1, 2, 3) (N)
Cancer progression rates and symptoms (by FIGO Stage 1or 2+) (N)
Screening coverage (E)
Sensitivity for CIN (1–3) by test type (cytology or HPV) (E)
Vaccine efficacy (E)
Vaccine coverage (E)

Indentification # 1726
Rogoza RM, Westra TA, Ferko N, Tamminga JJ, Drummond MF, Daemen T, Wilschut JC, Postma MJ. Cost-effectiveness of prophylactic vaccination against human papillomavirus 16/18 for the prevention of cervical cancer: Adaptation of an existing cohort model to the situation in the Netherlands. Vaccine 2009;27:4776–83.

Base-case population
Cohort of 12-year-old girls in the Netherlands

Strategies
1. Screening only
2. Vaccination and screening

Model type: Markov

Time horizon: Lifetime

Cycle length: Not stated

Outcomes: HPV infections (both overall and serotype specific), CIN2+ cases, cervical cancer cases, cytologies, health care resource use and life-years lived by the cohort

Probabilistic sensitivity analysis (y/n): Y

Validation (y/n): Not stated

Model parameters (N = natural history; E = effectiveness; R = risk)
NOTE: reader referred to an earlier publication for details of the model used in this analysis
HPV infection and progression rates (by HPV and CIN) (N)
Screening coverage (E)
Screening and follow up test performance (E)
Vaccine efficacy (for vaccine included types and related types) (E)
Duration of vaccine efficacy (E)
Vaccine coverage (E)

Indentification # 1760
Robotin MC, Kansil M, Howard K, George J, Tipper S, Dore GJ, Levy M, Penman AG.
Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than
cancer screening. Journal of Hepatology 2009;50:990–98.

Base-case population
Cohort of 35-year-old Sydney, Australia-based Asian men and women with chronic hepatitis B
(CHB) infection.

Strategies
1. Management based on risk defined by hepatitis B virus DNA and ALT levels
2. Current clinical practice, of limited treatment of CHB and some hepatocellular carcinoma
   (HCC) surveillance, with most patients receiving neither.

Model type: Markov model

Time horizon: 50 years

Cycle length: Yearly

Outcomes: Cases of HCC averted, deaths averted and QALYs gained

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): Not stated

Model parameters (N = natural history; E = effectiveness; R = risk)
Autoimmune cure (stratified by CHB or cirrhosis; current practice or prevention program) (E)
Develop cirrhosis (stratified by CHB or cirrhosis; current practice or prevention program) (N/E)
RR of cirrhosis with prevention program (stratified by CHB or cirrhosis) (E)
Develop HCC; current practice (stratified by CHB or cirrhosis) (N)
RR of HCC with prevention program (stratified by CHB or cirrhosis) (E)
CHB-related death; current practice (for patients with liver failure or HCC) (N)
RR of CHB-related death with prevention program (for patients with liver failure or HCC) (E)

Indentification # 1665
Rose J, Hawthorn RL, Watts B, Singer ME. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. BMJ 2009;339:b3653.

Base-case population
Cohort of Indian infants at risk of rotavirus infection

Strategies
1. No vaccination
2. Vaccination with live attenuated human rotavirus vaccine (RIX4414)

Model type: Markov model

Time horizon: 5 years

Cycle length: one month

Outcomes: Decrease in rotavirus gastroenteritis episodes (nonsevere and severe), deaths, outpatient visits, and admission to hospital; ICERs

Probabilistic sensitivity analysis (y/n): Y

Validation (y/n): Not stated

Model parameters (N = natural history; E = effectiveness; R = risk)
Risk of first, second, and third infection by age in months (N)
Probability of symptoms and severity of symptoms by infection (N)
Probability of dying from severe infection (N)
Prevalence of strains of proteins present in vaccine (N, E)
Coverage by dose (E)
Efficacy (by prevalence of proteins included in vaccine) (E)
Relative efficacy of vaccine in symptomatic compared to severe infection (E)
Duration of vaccine efficacy (E)
Probability of admission to hospital given nonsevere or severe infection (E)
Probability of outpatient treatment given nonsevere or severe infection (E)
Probability of access to oral rehydration solution at home (E)

Indentification # 1670
Burgos JL, Kahn JG, Strathdee SA, Valencia-Mendoza A, Bautista-Arredondo S, Laniado-Laborin R, Castañeda R, Deiss R, Garfein RS. Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost effective in Mexico. Int J Tuber Lung Dis 2009;13:962–8.

Base-case population
Cohort of Mexican commercial sex workers and IV drug users at high risk of HIV infection and tuberculosis (TB).

Strategies:
1. Screening and treatment for TB
2. No screening for TB; treatment based on clinical diagnosis (assumed).

Model type: Markov model

Time horizon: 20 years

Cycle length: 1 year

Outcomes: Number of latent TB infection cases identified, TB cases averted, TB-related deaths averted, QALYs and ICERs

Probabilistic sensitivity analysis (y/n): N – random walk with samples

Validation (y/n): Not stated

Model parameters (N = natural history; E = effectiveness; R = risk)
Annual risk of LTBI (latent TB infection) (N)
Annual risk of HIV infection (N)
Annual risk of progression from LTBI to active TB (N)
Probability of death from active TB without treatment (N)
Probability of death from other causes (N)
Efficacy of INH (isoniazid) in reducing TB (E)
Increased adherence to INH due to financial incentives (E)
EFficay of INH treatment for LTBI infection (E)
Duration of efficacy against TB reinfection (E)
Probability of INH toxicity (R)
QFT-GIT (QuantiFERON-TB Gold In-Tube) sensitivity and specificity for LTBI (E)
QFT-GIT sensitivity and specificity active TB detection (E)

Indentification # 1688
Colantonioa L, Gómezc JA, Demarteaud N, Standaerte B, Pichón-Rivièrea A, Augustovski F.
Cost-effectiveness analysis of a cervical cancer vaccine in five Latin American countries.
Vaccine 2009;27:5519–29.

Population
Eleven-year-old cohort of girls from at risk of HPV infection and cervical cancer and living in
one of five Latin American countries (Argentina, Brazil, Chile, Mexico, and Peru).

Strategies:
1. Screening only (at different ages to begin screening and intervals)
2. Vaccination at 12 years and screening (at different ages to begin screening and screening
   intervals)

Model type: Markov model

Time horizon: Lifetime

Cycle length: 1 year

Outcomes: Number of cervical cancer cases and deaths, QALYs, ICERs

Probabilistic sensitivity analysis (y/n): N

Validation (y/n): Y

Model parameters (N = natural history; E = effectiveness; R = risk)
Progression and regression rates for HPV and CIN (assumed to be the same for all five countries)
(N)
Population size of 11-year old girls (country specific) (N)
Age-specific oncogenic HPV incidence rates (country specific) (N)
Age-specific mortality rates (country specific) (N)
Age-specific cervical cancer death rates (country specific) (N, E)
Prevalence of HPV 16, 18, 31, and 45 in invasive cervical cancer (country specific) (N)
Regular screening coverage (country specific) (E)
Interval between regular screening (country specific) (E)
Irregular screening coverage (country specific) (E)
Population without screening (country specific) (E)
Age of initiation of screening (country specific) (E)
Sensitivity of Pap smears to detect CIN 1 (country specific) (E)
Sensitivity of Pap smears to detect CIN 2&3 (country specific) (E)
Estimated positive Pap smears (country specific) (E)
CIN 1 and CIN 2/3 detection and efficacy of treatment (country specific) (E)
Five-year cancer cure rate (country specific) (E)
Vaccine effectiveness in preventing oncogenic HPV infection (only HPV 16/18; all four
serotypes) (E)
Duration of vaccine efficacy (E)

Indentification # 1660
Gupta S, Faughnan, Bayoumi AM. Ebolization for pulmonary arteriovenous malformation in hereditary hemorrhagic telangiectasia. A decision analysis. Chest 2009;136:849–58.

Base-case population
40-year-old men with hereditary hemorrhagic telangiectasia (HHT) and an asymptomatic pulmonary arteriovenous malformation (PAVMs) with a 3-mm feeding artery.

Strategies
1. No embolotherapy
2. Embolotherapy only in the event of a PAVM complication (i.e., stroke, transient ischemic attack (TIA), brain abscess, hemothorax, massive hemoptysis)
3. Immediate embolotherapy

Model type: Markov

Time horizon: Lifetime

Cycle length: One month

Outcomes: Life expectancy, quality-adjusted life expectancy, proportion with a major stroke over time

Probabilistic sensitivity analysis (y/n): No

Validation (y/n): No

Model parameters (N = natural history; E = effectiveness; R = risk)

- PAVM complication rates (stroke, TIA, abscess, hemothorax, massive hemoptysis) without embolization (N)
- PAVM complication rates with embolization (E)
- Reperfusion or new growth after embolization (N)
- Major neurologic deficit from stroke/abscess (N)
- Death from PAVM complications (N)
- Embolization complications (death, stroke, pleurisy, deep vein thrombosis, migration of coil) (R)

Indentification # 1669
Rubenstien JH, Waljee AK, Jeter JM, Velayos FS, Ladabaum U, Higgins PDR. Cost effectiveness of ulcerative colitis surveillance in the setting of 5-aminosalicylates. Am J Gastroenerol 2009 (online).

Base-case population
35-year-old men with a 10-year history of ulcerative pancolitis that is quiescent.

Strategies
1. No 5-Aminosalicylates (5-ASAs) or surveillance
2. Surveillance without 5-ASA at intervals of 1–10 years (10 strategies)
3. Surveillance with 5-ASA at intervals of 1–10 years (10 strategies)
4. 5-ASA alone

Model type: Markov

Time horizon: Until age 90 or death

Cycle length: One year

Outcomes: QALYs

Probabilistic sensitivity analysis (y/n): Yes

Validation (y/n): No

Model parameters (N = natural history; E = effectiveness; R = risk)

- Rate of ulcerative colitis flare requiring colectomy (N)
- Colorectal cancer incidence (N)
- Progression from dysplasia to cancer (N)
- Latency of cancer until symptomatic presentation (N)
- Risk ratio of cancer with 5-ASA vs. no 5-ASA (E)
- Cancer at presentation (metastatic, local, other) (N)
- Relative risk of metastatic with surveillance vs. no surveillance (R)
- Test characteristics of colonoscopy (E)
- Complications of colectomy and colonoscopy (morbidity/mortality) (R)

Indentification # 1693
PubMed ID: 19436120
Amemiya S, Takao H. Computed tomographic coronary angiography for diagnosing stable coronary artery disease: a cost-utility and cost-effectiveness analysis. Circulation Journal 2009;73(7):1263–70.

Base-case population
60-year-old men at risk for stable coronary artery disease (CAD) (pretest risk assumed to be 50 percent), with history of chest pain, but without a definitive diagnosis of CAD.

Strategies
1. No examination and no treatment.
2. Medication; all patients receive medication for CAD, but undergo neither computed tomography coronary angiography (CTCA) nor conventional coronary angiography (CAG), thus not being revascularized until a cardiac event occurs.
3. Routine coronary angiography followed by optimal treatment for patients with CAD including elective revascularization. All patients with left main disease require revascularization. For other vessel diseases, 14.5 percent were modeled to subsequently undergo elective revascularization within the first year, referring to the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (crossover rate in the first year).
4. CTCA; all patients undergo CTCA, and those with a positive test result receive medication for CAD, some of whom go on to elective revascularization. If revascularization is planned, the patient will have coronary angiography for further evaluation as a workup study; 12 percent of CTCA-positive patients were also modeled to have CAG, but not revascularization. Patients with a negative result receive no specific treatment.

Model type: Markov

Time horizon: Lifetime

Cycle length: One year (implied)

Outcomes: QALYs

Probabilistic sensitivity analysis: Yes

Validation: Not stated

Model parameters

- Prevalence of CAD (N)
- CAD-specific mortality, by extent of disease (N)
- Risk reduction with by medication (E)
- Risk reduction by revascularization, by extent of disease (E)
- Relief of angina, by type of treatment (E)

- Risk of nonfatal myocardial infarction, by disease and treatment (N/E)
- Risk of revascularization, by extent of disease and treatment (N/E)
- Complications of coronary angiography (R)
- Diagnostic performance of CTCA (E)

Indentification # 1727
Park SM, Kim SY, Earle CC, Jeong SY, Yun YH. What is the most cost-effective strategy to screen for second primary colorectal cancers in male cancer survivors in Korea? World J Gastroenterol 2009;15:3153–60.

Base-case population
50-year-old Korean male colorectal cancer survivors, one year after the index cancer diagnosis.

Strategies
1. No screening
2. Annual fecal occult blood test (FOBT)
3. FOBT every 2 years
4. Sigmoidoscopy every 5 years
5. Double contrast barium enema every 5 years
6. Colonoscopy every 10 years
7. Colonoscopy every 5 years
8. Colonoscopy every 3 years

Model type: Markov

Time horizon: Lifetime

Cycle length: One year (implied)

Outcomes: Life expectancy

Probabilistic sensitivity analysis: No

Validation: Not stated

Model parameters

- Prevalence of polyps at age 50 (N)
- Polyp incidence in cancer survivors (N)
- Percent of cancers arising from polyps (N)
- Relative risk of colorectal cancer in cancer survivors compared with the general population (N)
- Dwell time in colorectal cancer early stages (N)
- Percent of cancers detected in early stages without screening (N)
- Survival for index cancer (N)
- Survival for second primary colorectal cancer, by stage (early/late) (N)
- Test performance of colorectal cancer screening tests (E)
- Adherence to colorectal cancer screening (E)
- Complications of colonoscopy/polypectomy, sigmoidoscopy, and barium enema (R)

Indentification # 1735
PubMed ID: 19539109
Xie F, Blackhouse G, Assasi N, Campbell K, Levin M, Bowen J, Tarride JE, Pi D, Goeree R. Results of a model analysis to estimate cost utility and value of information for intravenous immunoglobulin in Canadian adults with chronic immune thrombocytopenic purpura. Clinical Therapeutics 2009;31:1082–91.

Base-case population
Adults with persistent chronic immune thrombocytopenic purpura (ITP) at age 35 years and a body weight of 70 kg, presenting with platelet counts <20,000/μL and no active bleeding.

Strategies
1. Intravenous immunoglobulin (IVIg) at a dose of 1 g/kg of body weight per day in an outpatient setting for 2 consecutive days (according to Canadian guidelines).
2. Oral prednisone at a dose of 1 mg/kg of body weight per day for a month (according to published studies).

Model type: Markov

Time horizon: Lifetime

Cycle length: One year

Outcomes: QALYs

Probabilistic sensitivity analysis: Yes

Validation: Not stated

Model parameters

- Initial response to prednisone – considered usual care (N)
- Initial response to IVIg (E)
- First-year relapse after initial prednisone (N)
- First-year relapse after initial response to IVIg (E)
- Splenectomy after treatment of prednisone (N)
- Initial response to splenectomy (N)
- Long-term relapse with IVIg and prednosone (N)
- Long-term relapse after splenectomy (N)
- Death in refractory ITP (N)

Indentification # 1749
Morton RL, Howard K, Webster AC, Wong G, Craig JC. The cost-effectiveness of induction immunosuppression in kidney transplantation. Nephrol Dial Transplant 2009;24: 2258–69.

Base-case population
46-year-old cohort of kidney transplant patients.

Strategies

1. No induction, which was a triple immunosuppression regimen of a calcineurin inhibitor (tacrolimus or cyclosporine), with an antiproliferative agent (mycophenolate mofetil) and a steroid (prednisolone)
2. Induction with interleukin-2 receptor antagonists (IL2Ra) using a standard basiliximab dosing regimen of 2 ×20 mg on day 0 and day 4
3. Induction with polyclonal antibody induction using all contemporary formulations of anti-thymocyte or antilymphocyte depleting antibodies, derived from rabbit or horse at a dose of 2–5 mg/kg for 7 days

Model type: Markov

Time horizon: 20 years

Cycle length: 1 year

Outcomes: Life years, QALYs

Probabilistic sensitivity analysis: No

Validation: Not stated

Model parameters

- Surgical complications and probability of CAN (N)
- Graph loss due to other causes (N)
- Recurrence of primary disease (N)
- Subsequent transplant (N)
- Delayed graft function with subsequent transplant (N)
- Mortality, by year of transplant and dialysis status (N)
- Probability of functioning transplant, by intervention (N/E)
- Probability of delayed graph function, by intervention (N/E)
- Probability of acute rejection, by intervention (N/E)
- Probability of steroid-resistant acute rejection, by intervention (N/E)
- Probability of graph loss post acute rejection, by intervention (N/E)
- Probability of CMV infection the first year post transplant, by intervention (N/R)
- Probability of malignancy the first year post transplant, by intervention (N/R)

Indentification # 1764
PubMed ID: 19249771
Nguyen GC, Frick KD, Dassopoulos T. Medical decision analysis for the management of unifocal, flat, low-grade dysplasia in ulcerative colitis. Gastrointestinal Endoscopy 2009;69(7):1299–1310.

Base-case population
45-year-old individuals with ulcerative colitis for 10 years who are newly diagnosed with unifocal, flat low-grade dysplasia (LGD) on initial surveillance colonoscopy.

Strategies

1. Immediate (within 6 months of initial diagnosis of LGD) colectomy with 2-stage ileal pouch anal anastomosis (IPAA)
2. Enhanced surveillance (repeated colonoscopy at 3, 6, and 12 months, and then annually). Detection of LGD, high-grade displasia, or cancer during secondary surveillance prompts immediate referral for colectomy.

Model type: Markov

Time horizon: Lifetime

Cycle length: Three months

Outcomes: QALYs

Probabilistic sensitivity analysis: Yes

Validation: Face validity checks

Model parameters

- Risk of synchronous cancer (N)
- Incidence of LGD from no dysplasia (N)
- Incidence of advance neoplasia, from LGD or from no dysplasia (N)
- Distribution of advanced neoplasia (LGD or cancer) (N)
- Distribution of cancer stage (N)
- Cancer-specific mortality, by stage (N)
- Diagnostic performance of colonoscopy (E)
- No risk of cancer with colectomy (E)
- Complications of IPAA (R)
- Supportive care requirements for IPAA, by type and year (R)

Indentification # 1774
Cowie MR, Marshall D, Drummond M, Ferko N, Maschio M, Ekman M, de Roy L, Heidbuchel H, Verboven Y, Braunschweig F, Linde C, Boriani G. Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: results of Markov modelling in a European population. Europace 2009;11:716–26.

Base-case population
45-year-old patients with chronic heart failure in New York Heart Association class II or III, or prior myocardial infarction with or without heart failure with ulcerative colitis for 10 years who are newly diagnosed with unifocal, flat LGD on initial surveillance colonoscopy.

Strategies

1. Prophylactic implantable cardioverter defibrillator (ICD)
2. No ICD (conventional therapy)

Model type: Markov

Time horizon: Lifetime

Cycle length: 1 month

Outcomes: Life years, QALYs

Probabilistic sensitivity analysis: Yes

Validation: Yes

Model parameters

- Mortality risks (sudden death, heart failure, other cardiac, non-cardiac) (N/E)
- Initial implant operative death probability (R)
- One-month probability of ICD complications (inappropriate shocks) (R)
- Probability of discontinuing ICD after inappropriate shocks (R)
- Probability of lead replacement (R)
- Probability of lead infection, initial and replacement (R)
- Probability of lead dislodgement, initial and replacement (R)

Indentification # 1790
PubMed ID: 19502849
Neuman HB, Elkin EB, Guillem JG, Paty PB, Weiser MR, Wong WD, Temple LK. Treatment for patients with rectal cancer and a clinical complete response to neoadjuvant therapy: a decision analysis. Dis Colon Rectum 2009;52(5):863-71.

Base-case population
65-year-old men, medically fit to undergo major surgery, without distant metastases, with stages I to III rectal cancer who have a clinical complete response 8 to 12 weeks after completion of neoadjuvant (i.e., preoperative) chemoradiotherapy.

Strategies
1. Surgical resection
2. Observation

Model type: Markov

Time horizon: Lifetime

Cycle length: One month

Outcomes: Life years, QALYs

Probabilistic sensitivity analysis: Yes

Validation: Yes

Model parameters
- Likelihood of pathologic complete response if clinical complete response (N)
- Risk of relapse if pathologic complete response and observation alone (N)
- Risk of relapse if pathologic partial response and observation alone (N)
- Risk of relapse if pathologic complete response and surgery (E)
- Risk of relapse if pathologic partial response and surgery (E)
- Percent of recurrences that are distant, by pathologic response and treatment (N/E)
- Percent receiving salvage surgery for local recurrence, by treatment (N/R)
- Survival after local recurrence, by salvage surgery status (N)
- Survival after metastatic disease (N)
- Surgical mortality for index and salvage surgeries (R)

Indentification # 1794
Ehler L, Overvad K, Sorensen J, Christensen S, Bech M, Kjolby M. Analysis of cost effectiveness of screening Danish men aged 65 for abdominal aortic aneurysm. BMJ 2009;338:b2243.

Base-case population
Cohort of men aged 65 invited (or not invited) for ultrasound screening in the Danish health care system.

Strategies
1. No screening program
2. Ultrasound screening; refer large (≥5.5 cm) aneurysms for vascular surgical assessment, and rescan regularly if the aneurysm was small (3-4.4 cm) or medium sized (4.5-5.4)

Model type: Markov

Time horizon: Lifetime

Cycle length: One year

Outcomes: QALYs

Probabilistic sensitivity analysis: Yes

Validation: Yes

Model parameters

- Prevalence of abdominal aortic aneurysm ≥3 cm (N)
- Distribution of size of abdominal aortic aneurysm (N)
- Annual risk of rupture, by size (N)
- Growth rate per year (small to medium; medium to large) (N)
- Screening participation rate (E)
- Proportion of patients with large abdominal aortic aneurysm who are eligible for surgery (E)
- Mortality from elective or emergency surgery (R/N)
- Proportion of ruptures where patient reaches hospital alive (N)
- Ad hoc diagnosis of abdominal aortic aneurysm (N)

Indentification # 1801
Nuijten M, Andress DL, Marx SE, Sterz R. Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: a US perspective. Curr Med Res Opin 2009;25(5):1221-34.

Base-case population
Cohort of chronic kidney disease patients.

Strategies
1. Treatment with paricalcitol for secondary hyperparathyroidism
2. Treatment with calcitriol

Model type: Markov

Time horizon: Lifetime

Cycle length: One year

Outcomes: QALYs

Probabilistic sensitivity analysis: Yes

Validation: Yes

Model parameters

- Transitions among chronic kidney disease health states, defined according to the Kidney Dialysis Outcomes Quality Initiative (N)
- Risk of developing proteinuria, by disease stage (N)
- Type of treatment started (hemodialysis, peritoneal dialysis, transplantation) for patients progressing to worst stage (N)
- Risk of hospitalization (N)
- Risk of death, by stage and hospitalization (N)
- Absolute reduction in progression of disease with treatment (E)

Indentification # 1985
Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med 2009;150:73-83.

Base-case population
Cohort of 69 year-old men newly diagnosed with nonvalvular atrial fibrillation and no contraindications to warfarin therapy.

Strategies
1. Standard induction of warfarin therapy.
2. Test for CYP2C9*2 and CYP2C9*3 alleles and the A haplotype of VKORC1 and, if present, initiate warfarin therapy at lower dose as calculated by a pharmacogenetic-based algorithm.

Model type: Markov

Time horizon: Lifetime

Cycle length: One month

Outcomes: QALYs

**Probabilistic sensitivity analysis**: Yes

Validation: Yes

Model parameters

- Allele frequency (N)
- Relative hazard of major bleeding events in variants vs. wild-type alleles during initiation phase (E/R)
- Days with subtherapeutic INR (international normalized ratio) (E)
- Relative hazard of major bleeding events during initiation vs. maintenance (R)
- Relative hazard of major bleeding events with pharmacogenetic-guided dosing (E)
- Delayed start time for therapy (R)
- Rate of thromboembolism, by treatment (N/E)
- Prognosis of thromboembolism (death, disability, recovery) (N)
- Rate of bleeding event (untreated), by location of event (N)
- Rate of bleeding event (treated), by location of event (R)
- Prognosis of major bleeding, by type and treatment (death, disability, recovery) (N/R)

Appendix G. Search Strategy for Best Practices Papers

Figure G1. Literature flow diagram
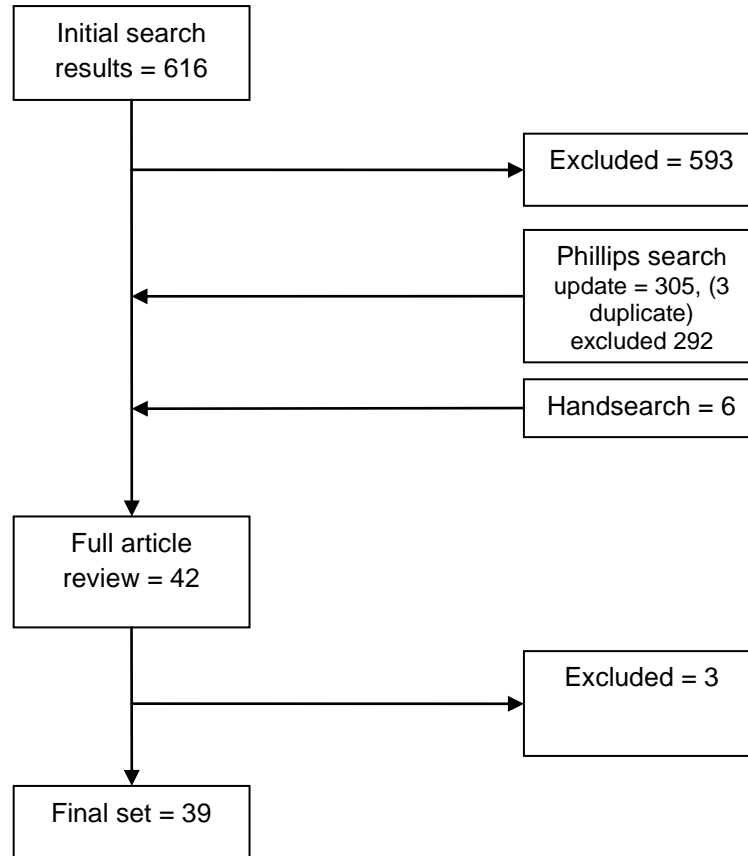
A search performed in October 2010, with the search string provided below, yielded 334 articles. An updated search run on March 3 yielded an additional 282 articles.

Search Term	# articles
1 decision analytic model$.mp.	681
2 decision model$.mp.	909
3 simulation model$.m	3,523
4 markov model$.mp.	3,135
5 state transition model$.mp.	149
6 markov cohort model$.mp.	15
7 1 or 2 or 3 or 4 or 5 or 6	8,253
8 guideline$.mp.	180,168
9 best practice$.mp.	4,970
10 good practice$.mp.	1,535
11 guidance.mp.	38,596
12 8 or 9 or 10 or 11	219,108
13 7 and 12	334

We also updated the search used in the Philips et al. (2004) review using the following search strategy:

1. (checklist? or check list? or standards or standardi?ation or peer
review$ or rules or correct$ or bias or fundamentals or recommend$
or best or strength$ or weakness$ or quality or qualities or validity or
guideline? or validation or checkpoint?).ti.   286,767
. (properly or critically appraise or problems or limitations or
rating scale? or framework$ or protocol? or audit or principles
or methodolog$).ti.   17,5148
3. (validate or validation or evaluating or properties or guidance or
integrity or evaluation or pros or cons).ti.   429,234
4. (decision adj (tree or triage or data or analytic or analysis)).ti.   1,516
5. *"models, economic"/ or *"models, econometric"/   2,467
6. (*"decision support techniques"/ or *"data interpretation, statistical"/
or *"decision theory"/ or *"models, statistical"/ or *"likelihood
functions"/ or *"linear models"/ or *"logistic models"/
or *"proportional hazards models"/) and *"costs and cost analysis"/   14
7 ((economic? or pharmacoeconomic? or decision? or cost? or costing?)
and model$).ti.   2,789
8 (markov or crystal ball).ti.   1,522
9 *"markov chain"/   1,089
10 ((markov model$ or economic model$ or mathematical model$ or
cost$ model$ or pharmacoeconomic model$ or decision model$) adj2
(checklist? or check list? or standards or standardi?ation or peer review$
or rules or critiquing or criteria or good or bad or correct$ or bias or
fundamentals or recommend$ or best or strength$ or weakness$ or quality
or qualities or validity or guideline? or validation or checkpoint?)).ab.   137
11 ((markov model$ or economic model$ or mathematical model$ or
cost$ model$ or pharmacoeconomic model$ or decision model$) adj2
(properly or critically appraise or problems or limitations or rating scale$
or good practice$ or framework$ or protocol$ or audit or principles
or methodolog$)).ab.   102
12 ((markov model$ or economic model$ or mathematical model$ or
cost$ model$ or pharmacoeconomic model$ or decision model$) adj2
(validate or validation or evaluating or properties or guidance or integrity
or avoiding bias or evaluation or pros or cons)).ab.   97
13 ((decision tree or decision triage or decision data or decision
analytic$ or decision analysis or crystal ball) adj2 (checklist? or
check list? or standard$ or peer review$ or rules or critiquing or
criteria or good or bad or correct$ or bias or fundamentals or recommend$
or best or strength$ or weakness$ or quality or qualities or validity or
guideline? or validation or checkpoint?)).ab.   99
14 ((decision tree or decision triage or decision data or decision
analytic$ or decision analysis or crystal ball) adj2 (properly or critically
appraise or problems or limitations or rating scale$ or framework$ or

protocol$ or audit or principles or methodolog$)).ab. 117

15 ((decision tree or decision triage or decision data or decision
analytic$ or decision analysis or crystal ball) adj2 (validate or
validation or evaluating or properties or guidance or integrity or
evaluation or pros or cons)).ab. 30

16 ((economic evaluation? or economic analysis or economic
stud$ or economic submission?) and guideline$).ti. 47

17 or/10-15 558

18 or/4-9 7,805

19 or/1-3 849,212

20 19 and 18 813

21 16 or 17 or 20 1,389

22 limit 21 to yr="2003-2006" 351

23 limit 22 to english language 326

24 limit 21 to (english language and yr="2007-Current") 308

Appendix H. Focus Group Instructions

Focus Group Instructions
Conducted by François Sainfort, Ph.D., May 16–17, 2010
HILTON ATLANTA, 255 Courtland St. NE, Atlanta, GA 30303

Participants:
- Alan Brennan
- Andy Briggs
- Peter Neumann
- Mark Sculpher

Background: The overarching goal of this project is to provide guidance to determine when incorporating a decision-analytic and/or simulation model alongside a systemic review would be of added value for decision making purposes. Currently, Evidence-based Practice Centers (EPCs) review and synthesize scientific literature on a particular topic in the form of evidence reports and technology assessments to assist public and private organizations in developing strategies that improve quality of health care and decision making.

However, often there is not enough evidence to fully address the questions that are relevant for decisionmakers. Or, there may be enough evidence on several components to the decision (e.g., diagnostic test characteristics, test risks, risk and effectiveness of treating disease) but no studies that evaluate the relevant clinical strategies that incorporate all of these components and are most important for decision making purposes. In such situations, a decision or simulation model can add value to the systematic review.

Focus Group: The goal of this focus group is to gather modeling experts to elicit, characterize, and qualify best practices in decision and simulation modeling in the context outlined above. Elements to be discussed and addressed include:
- model formulation and characterization,
- model development and construction,
- handling and presentation of modeling assumptions,
- definition and presentation of parameters,
- outcomes to incorporate into the model,
- model analysis,
- model testing, validation, and
- model implementation, including results presentation and communication.

Materials attached in preparation for focus group:
Preliminary Findings – Experience with, and Attitude Toward, Decision and Simulation Modeling
Selection of three articles on best practices in decision and simulation modeling:
1. Braithwaite et al., 2007. Incorporating Quality of Evidence into Decision Analytic Modeling, Annals of Internal Medicine, 146:133–41.
2. Cooper et al., 2007. Use of Evidence in Economic Decision Models: Practical Issues and Methodological Challenges, Health Economics, 16:1277–86.
3. Philips et al., 2006. Good Practice Guidelines for Decision-Analytic Modeling in Health Technology Assessment, Pharmacoeconomics, 24(4):355–71.

Appendix I. Summary of Preliminary Findings Provided to Focus Group Participants

<u>Preliminary Findings – Summary of Key Points</u>
Experience with, and Attitude toward, Decision and Simulation Modeling
Evidence-Based Practice Centers Key Informants
Compiled by François Sainfort and Sean Gregory

Telephone interviews with 20 Evidence-based Practice Centers (EPC) key informants were conducted between December 2009 and March 2010.

Key points from these interviews include:

Attitudes Toward Modeling and Appropriateness of Modeling in Systematic Reviews
- Interviewees with modeling experience unanimously held positive attitudes toward modeling with respect to its benefit for EPC projects and much of the course of Agency for Healthcare Research and Quality work.
- All reported that modeling was an important set of techniques and strategies that were applicable to the work they were engaged in, and were generally supportive of incorporating these techniques into their work.
- Some interviewees seemed to struggle with whether the development of a model is within or beyond the scope of a systematic review of the literature.
- Several interviewees were supportive of including models in systematic reviews and felt it was a natural extension of the purpose and intent of the models.

Research Questions and Contexts Best Suited for Decision Modeling and Simulation
- Models are well-suited to address gaps in the literature and to synthesize literature from differing sources and contexts into a single representation of the empirical evidence.
- In many cases there are studies that demonstrate quantitative findings for intermediate effects; but studies of the long-term or terminal effects are underway, inconclusive or not feasible to conduct.
- The comparison of testing, prevention, and diagnostic strategies was also noted as a primary area in which modeling can be of great benefit.
- Most remarked that the comparison of strategies and the establishment of net benefit, that is benefit less harms, can only be determined through the use of a decision model.
- More generally, models are well suited for research questions which have a high degree of uncertainty in assumptions or input parameters; or situations in which there is a great amount of discordance between estimates in empirical studies.
- In many cases, large randomized controlled trials or observational studies have not focused on specific subpopulations. These are situations in which modeling can be used to simulate findings where subpopulation characteristics are believed to impact or change conclusions for a specific subpopulation.
- There is great interest in the benefits modeling can bring to determining the value of information and specification of research priorities and directions.

Definitions of Decision Models and Simulations

- Most converged on a general definition of decision modeling and simulation as the mathematical representation of a decision (or series of decisions) based upon empirical input parameters, supported by a specified framework or mechanism (e.g., a particular representation of the natural history of a disease), and subject to a set of identifiable assumptions.
- While the majority reported a similar definition of a model, there was greater disparity in the ability to differentiate between modeling and the domain of traditional statistics.
- Some drew distinct lines between any statistics used for "inference" and the set of techniques used in decision analysis.
- Others made more specific comments, such as decision models begin with Bayesian statistics and meta-regression and extend to the techniques more commonly employed in decision models, such as Markov modeling and simulation techniques.
- There was high agreement for the general definition, but the distinctions among techniques seemed to represent the interviewees' experiences with particular techniques in particular situations.

Evaluation of a Model and of Model Outputs

- The evaluation of a model or the determination of the quality of a model had high agreement among the group "with experience."
- Albeit qualitative, the majority reported that their opinion as to the "quality and expertise" of the actual modeler who developed the decision model weighed heavily on their overall and initial assessment of the model.
- Most identified the lack of defined standards and methods as a major problem in the evaluation of models, and again hoped that this initiative would bring about some initial draft evaluation standards.
- When pressed for the mechanics of their evaluation of a model, most reported that they routinely inspected the quality and reliability of the input parameters, a determination of the reasonableness of the assumptions, and, if available, an evaluation of the structure of the model.
- All interviewees described the need for standardization of model outputs, as an important factor in the acceptance of models, but also in the practical usage of the models across research questions and policy issues.
- Interviewees with the most extensive reported experience also discussed the need for standardization of the presentation of model results in addition to the outcome metrics reported.

Models and Simulations Results as a Form of "Evidence"

- Interviewees with modeling experience stated that the outputs from a model that are included in a systematic review are indeed evidence, and should be considered as such.
- The rigor of the systematic review methodology ensured high quality parameter inputs to these models, as well as sensitivity analyses and model assumptions, that were consistent with the state of the science according to the literature.
- Interviewees did make statements that this evidence was "manufactured" or "model-produced" evidence, possibly indicating the need to categorize it as a different type of evidence.

- Interviewees did not believe that the current evidence grading methodologies addressed the issues that model and simulation evidence present to a reviewer.
- Interviewees without experience with models and simulation pointed to this lack of evidence standards as the principal reason to exclude any modeling studies from systematic reviews.
- Several reported that even if standards existed, the incorporation of models as evidence was beyond the scope of systematic reviews, which are charged with the compilation of all the available empirical evidence, and thus by definition exclude "modeled" or "simulated" data.
- Those without experience explicitly stated that models and simulations were not on the same "continuum of evidence" as other studies and sources and, in fact, represented a very different data source, the merging of which with traditional evidence, created a number of issues.

Appendix J. General Interview Outline – Modelers and USPSTF Members

1. Evaluate the strengths and weaknesses of current approaches to conducting a simultaneous systematic review and modeling exercise.

2. Evaluate stakeholder perceived needs and whether needs were met.

3. Make recommendations for the process of conducting future similar projects.

4. Evaluate the "lessons learned" from the colorectal, breast, and cervical cancer modeling projects alongside systematic reviews.

5. Evaluate their impact on U.S. Preventive Services Task Force decisionmaking.

Appendix K. Verbatim Quotes from Interviews of Modelers and USPSTF Members, by Theme

Modality

Quote
"The EPC systematic reviewers and the modelers must be joined throughout the process. This was the process issue in the colon cancer study."
"Multiple modeling groups working on the same project is ideal. There is tremendous value in the process, and the comparisons of the outcomes is essential."
"Comparative modeling is a best practice. Multiple modeling groups should be employed in order to develop the best outputs. This allows for sensitivity analyses on the structural assumptions between models."
"CISNET is a "model" for such collaboration…independent development of models prior to collaboration and comparisons."
"The structure of CISNET gives the models produced credibility and validity."
"Multiple modeling groups, same inputs, seeking to address the same problem in multiple ways."
"Simultaneous development of the evidence report and the modeling effort."
"Systematic review and meta-analysis should be conducted and completed first."
"Simultaneously developing models and the reviews is suboptimal, leads to differences in parameters and assumptions."

Communication

Quote
"Most important opportunity is to improve the communication with respect to the models."
"Efforts should focus on increasing the understandability of models and the results."
"Most of the model documentation and appendices are incomprehensible."
"Seek to "tune: the comprehension to the science writer at Washington Post or NY Times. If this can be accomplished, then others can be used to communicate to a wider audience of MDs and patients…those that need to use the information on a daily basis."
"Modelers should go through a communications / media training course in order to elevate their skills in communicating with popular media".
"Use of multiple modeling groups is critical…this creates "convergent validity" of the outcome, assuming that the models converge on the same outcomes using the same inputs. The structure of the model is less important in the same inputs produce the same outcomes."

Modeling Literacy

Quote
"A short manual for the TF would be helpful. Make recommendations about when modeling would be helpful."
"Decision analysis 101 for the users/consumers is critical and should be included in every presentation to the TF, since many members rotate between projects."
"How can we increase the capacity for modelers?"

Process / Recommendations for Future Projects

Quote
"The TF should specify the questions they want answered and how to parameterize/specify the model and analysis."
"Specifying the tables and figures a priori helps frame the question and direct the modeling efforts to ensure that the outputs are what the TF needs to make recommendations."
"TF was very specific with respect to the issues/questions they wanted the modeling effort to address."
"Very helpful when the TF can be very specific about what they are asking for."
"Collaboration with the policy makers in order to develop a better set of outputs to inform decisions and recommendations."
"Models need to assist the TF in the primary goals. Assess the certainty of the NET benefit. Determine the magnitude of net benefits."
"Models should be directed to the key questions that the TF needs to make and that models are well-suited to handle…Strategies concerning the start and stop age for screening and the interval for screening."
"Colon cancer – represented the worst process but the best outcome. Breast cancer – best process and worst outcome. Cervical cancer was least problematic. The groups need to jointly inform and determine the inputs of the model. Dialogue between groups is critical."
"Strong leadership from USPSTF lead assured alignment among the modeling and SR teams."
"An iterative process should be used with the modeling groups and the interactions with the USPSTF. This improves the confidence and belief in the model and the results from the TF perspective."
"Value of information modeling should be used to prioritize research spending."
"Interaction with modelers and systematic review was essential to build quality models. Models are best suited to fill in gaps in the evidence, determine the value of information and address the 'future'."
"We should focus on interpreting the data and results versus spending time trying to create understanding about the modeling or models."
"Efforts should focus on creating parity among cancers, specifically the quantification of benefits, decreasing morbidity, mortality of increasing QALY-saved."
"Develop a consistent approach in the development and quantification of harms (e.g. unnecessary biopsies, false positive rates)."
"Consistency in the quantification of benefits lends itself to the TF goals of assessing the magnitude of benefits for recommendation."

Appendix L. Excluded Studies

1. Summaries for patients. The cost effectiveness of screening the U.S. blood supply for West Nile virus. Annals of Internal Medicine 2005 Oct 4;143(7):44. **Cost only**

2. Summaries for patients. The cost effectiveness of strategies to prevent type 2 diabetes. Annals of Internal Medicine 2005 Mar 1;142(5):28. *Cost only*

3. Summaries for patients. Cost effectiveness of a vaccine to prevent herpes zoster (shingles) in older adults. Annals of Internal Medicine 2006 Sep 5;145(5):14. *Cost only*

4. Summaries for patients. The cost effectiveness of preventive strategies for breast and ovarian cancer for women with BRCA1 or BRCA2 mutations. Annals of Internal Medicine 2006 Mar 21;144(6):40. *Cost only*

5. Summaries for patients. The cost effectiveness of aspirin, statins, or both drugs in the primary prevention of heart disease. Annals of Internal Medicine 2006 Mar 7;144(5):29. *Cost only*

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