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Evidence-Based Medicine in Otolaryngology, Part XI: Modeling and Analysis to Support Decisions

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Abstract

Objective. To provide a resource to educate clinical decision makers about the analyses and models that can be employed to support data-driven choices.

Data Sources. Published studies and literature regarding decision analysis, decision trees, and models used to support clinical decisions.

Review Methods. Decision models provide insights into the evidence and its implications for those who make choices about clinical care and resource allocation. Decision models are designed to further our understanding and allow exploration of the common problems that we face, with parameters derived from the best available evidence. Analysis of these models demonstrates critical insights and uncertainties surrounding key problems via a readily interpretable yet quantitative format. This 11th installment of the Evidence-Based Medicine in Otolaryngology series thus provides a step-by-step introduction to decision models, their typical framework, and favored approaches to inform data-driven practice for patient-level decisions, as well as comparative assessments of proposed health interventions for larger populations.

Conclusions. Information to support decisions may arise from tools such as decision trees, Markov models, microsimulation models, and dynamic transmission models. These data can help guide choices about competing or alternative approaches to health care.

Implications for Practice. Methods have been developed to support decisions based on data. Understanding the related techniques may help promote an evidence-based approach to clinical management and policy.

Keywords

decision analysis, decision sciences, comparative effectiveness, decision tree, Markov model, microsimulation, dynamic transmission model, evidence-based medicine

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Decision models have influenced clinical management, including the use of transoral robotic surgery (TORS) for oropharyngeal cancer and timing of tracheostomy.[1-6] These models can also support discussions with patients about the comparative benefits and harms of possible treatment strategies. These analytic tools provide these insights by demonstrating key potential choices, their related probabilities, health outcomes data, and cost expenditures, based on best available evidence. In doing so, these models support the selection of optimal clinical choices.[7,8] Their inherently structured framework promotes a systematic evaluation of options (ie, diagnostic tests, preventative measures, and treatment interventions) and their downstream ramifications, while accounting for varying patient types, health care settings, and inherent uncertainty.[7,9] Decision models also help predict health outcomes and guide resource allocation related to diagnosis and spread of infections.[7,8] Understanding such models serves clinicians, as we face a continuous stream of complex decisions through a data-driven approach. It is thus beneficial for high-level decision makers who guide broad-scale practice, as well as clinicians and other stakeholders, to understand procedural approaches to decisions in clinical care. Thus, in this installment of the Evidence-Based Medicine in Otolaryngology series,[10] we discuss decision models used in medical decision making, including their parameters, analyses, and reporting.[7,11]

Design of a Decision Model: Overview of Concepts

Decision models are designed to provide insight into clinical problems and incorporate possible prognoses, outcomes, and uncertainties associated with known options.[12-16] One well-

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Table 1. PROACTIVE Approach to Decision Making.[a]

PROACTIVE	Step	Considerations
Problem	Define the problem	What will happen if I do nothing? Is there a problem?
Reframe	Reframe from multiple perspectives	Consider the perspective of the patient, physician, department, hospital, payer, and society
Objective	Focus on the objective	Consider diagnostic uncertainty, medical effectiveness, psychosocial, micro- and macroeconomics, political, ethical, and philosophical aspects
Alternatives	Consider all relevant alternatives	Wait-and-see, intervention, obtain information
		Different combinations, sequences, and positivity criteria of diagnostic tests
Consequences and chances	Model the consequences and estimate the chances	Model disease and events
		Estimate the corresponding probabilities
		Determine quality-of-life weights
		Determine costs
Trade-offs	Identify and estimate value trade-offs	Immediate vs long-term risk
		Quality of life vs length of life
		Health outcome vs costs
Integrate	Integrate the evidence and values	Qualitatively
		Quantitatively
Value	Optimize expected value	Maximize desirable outcomes
		Minimize undesirable outcomes
Explore and evaluate	Explore assumptions	Evaluate heterogeneity
		Evaluate parameter uncertainty
		Evaluate model structure uncertainty

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defined way to design these models is through the PROACTIVE approach, which is a 9-step process outlined in **Table 1**. It encompasses the following: problem definition, reframe by perspective, objective focus, alternative consideration, consequence modeling, trade-off estimates, integration of evidence, value optimization, and exploration of assumptions.[12,15,17]

Decision models address 2 types of objectives: fundamental objectives and means objectives.[12] Fundamental objectives refer to the final outcome desired by the decision maker; this final outcome often motivates the ultimate decision about the clinical problem. Means objectives represent intermediate goals, which are important but insufficient in isolation to achieve fundamental objectives.[12,18,19] For instance, optimizing access to head and neck cancer therapy is a means to achieve the fundamental objectives of reduced mortality and optimal quality of life.[12] Clearly described objectives are critical when designing models and analyses to support decisions.

Once objectives are identified, with outcomes to avoid or achieve,[9,12,17,20] the issue is approached from the perspective of affected parties.[12,20] This range of perspectives helps shape the fundamental questions posed and the decision model structure. The model then incorporates a range of reasonable alternatives for the clinical problem of interest; these alternatives are typically considered in 3 categories: (1) wait and see/do nothing/active surveillance, (2) intervention to treat now, or (3) obtain further information before deciding (eg, diagnostic testing).[12] The alternatives included in the model are determined by the nature of the decision faced,[9] and each alternative is associated with a sequence of possible downstream consequences related to key results.[12,21] The strongest evidence available is used to identify relevant probabilities, objective outcomes, quality-of-life effects, and costs to inform the model.[22,23] Analysts consult widely with subject experts and stakeholders to ensure that models accurately represent disease processes and observed outcomes.[9] Analysts also clearly specify any and all assumptions made to ensure reader comprehension and study reproducibility.[11]

The model is then developed to support an analysis, which integrates the benefits and harms of alternative strategies, to help determine the optimal choice and explore points of uncertainty.[12,24] Each potential choice for each population of interest has associated health effects and costs, each of which is delineated in the designed model. The sum of the costs and health effects associated with each possible decision is then determined, thus providing an estimate of the resources required and clinical benefits provided for selected strategies over a specified time frame.

Models can then support a comparative assessment of the incremental benefits, risks, and costs of alternatives to the standard of care. In doing so, they can also be used to establish trade-offs between the resource consumption and

Table 2. Types of Decision Models and Analyses Used in Medical Decision Making.[11,44]

Approach	Description	Uses	Limitations
Balance sheet	Table of potential events and consequences of a clinical decision	Simple overview of consequences of strategies to inform decision making or guide future decision analysis model	Unable to combine different outcomes of decisions Inability to present the relative importance of outcomes for each strategy
Decision tree	Schematic representation of the question of interest and the possible consequences that occur in each strategy	Simulate simple clinical questions over a short time horizon	Challenging to model recurring events and risk that is ongoing over time Cannot model events that can occur with uncertain timing
State transition	Conceptualize collectively exhaustive, mutually exclusive health states and the transitions among these states	Clinical situations that can be described in terms of the conditions that individuals can be in ("states"), how they can move among such states ("transitions"), and how likely such moves are ("transition probabilities")	Do not capture interactions Transitions may occur only at specified time intervals
	Markov cohort model: simulate a cohort of patients that transition between health states	Simple state transition model of homogenous population in limited number of health states	Memory-less model State explosion can make models unmanageable or prone to error
	Microsimulation model: simulate individual movements between health states	Analyze individual clinical pathways that take into consideration past events and variations in individual characteristics within a heterogenous population	Computationally intensive Require simulations of 1000 to 1,000,000 individuals to obtain stable outcome measures
Dynamic transmission	Models capable of simulating transition probabilities that depend on the states of other individuals	Simulate individual interactions with other individuals or with other aspects of the model	Computationally intensive State explosion can make models unmanageable and prone to error

clinical benefits of a new strategy. Analysis of the model can determine a preferred strategy based on the highest health effects, lowest costs, least number of adverse events, or another predetermined outcome.[7] Decision models thus incorporate sequences of prognoses, outcomes, and potential uncertainties, which may be associated with a range of alternative decisions, while incorporating associated risks, benefits, and potential costs.[12-16] Additional concepts related to comparative analyses and their clinical application are presented in a previous installment of this series.[25]

Types of Decision Models

Different types of decision models can be used to evaluate clinical questions. A summary of different types of models is presented in **Table 2**, and each is described in turn. The choice of model is related to the decision question and the outcomes of interest to the analyst and stakeholders.

Balance Sheets

A balance sheet is the most basic form of decision model and focuses on providing a visual digest of the health and economic outcomes related to a clinical decision.[26] Balance sheets summarize important attributes of a clinical question, including consequences, probabilities, and value outcomes of the decision problem, while comparing options for alternative interventions.[17] The balance sheet in **Table 3** illustrates the potential consequences of treatment for uncomplicated acute otitis media in older children. The trade-offs of treatment include the risk of adverse effects associated with antibiotic therapy and the risk of developing antibiotic-resistant bacteria due to antibiotic overuse.[12,27] Withholding antibiotics, we anticipate that the risk of antibiotic resistance is practically zero.[27-29] Symptom resolution at 48 hours is estimated at 35% with amoxicillin-clavulanate therapy and 28% without it.[30] Children with acute otitis media experience reduced quality of life, whether managed with watchful waiting or antibiotics, although the duration of those symptoms may differ among individuals, according to management choice and individual variance within each population.[29,31] Cross-tabulation of results is performed to summarize the objective evidence and value estimates for the proposed options.

A balance sheet provides a succinct overview of the events and consequences of a clinical decision. It can be used to help structure a more complex decision analysis

Table 3. Balance Sheet for Treatment Options of Watchful Waiting vs Antibiotic Therapy for a Patient With Uncomplicated Acute Otitis Media.[a]

	Watchful waiting	Antibiotic therapy
Adverse effects of antibiotic therapy	No adverse effects of antibiotic therapy	Adverse effects of antibiotic therapy Development of drug-resistant bacteria
Morbidity due to infection	Reduced quality of life with acute otitis media—duration according to the natural history of acute disease	Reduced quality of life with acute otitis media—possible decreased duration of acute symptoms,[30,31] particularly if the infection is bacterial and responsive to the given antibiotic in children with applicable age and severity of illness
Costs of treatment	Avoid costs of antibiotic therapy	Costs of antibiotic therapy

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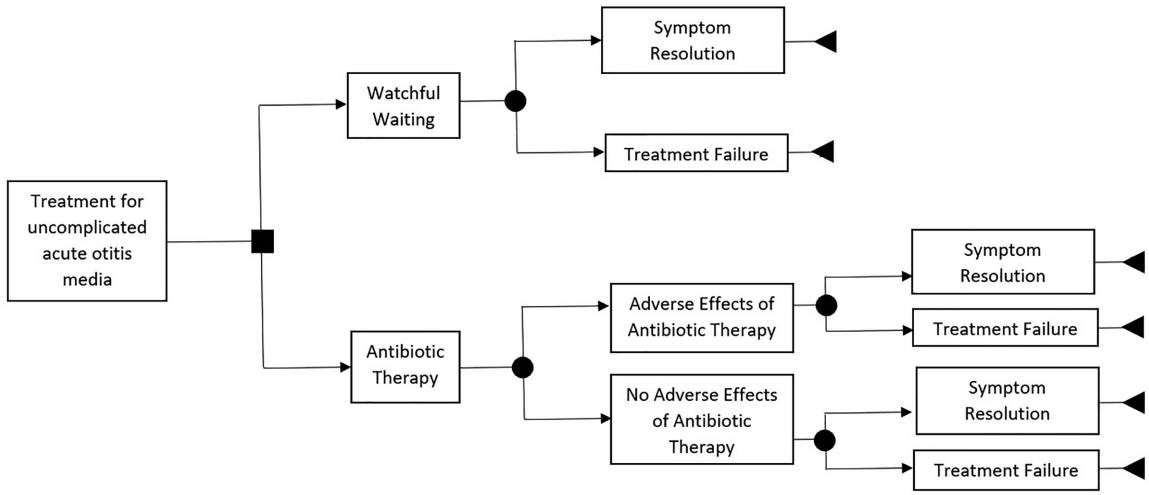

Figure 1. This decision tree compares antibiotic therapy and watchful waiting for uncomplicated acute otitis media.

model if the optimal strategy is not apparent from the sheet. Balance sheets are limited in their capacity to combine different component possibilities into a single pathway or strategy. They are also limited in their ability to present the relative importance of outcomes for each strategy. Instead, users must evaluate and draw conclusions based on their personal weightings of the costs, benefits, and harms presented for each strategy.[26]

Decision Trees

A decision tree is a visual representation of outcomes and consequences of different management options with each alternative represented in a branching, treelike structure.[9,12,32,33] The initial line of a decision tree is labeled with the population or problem of interest, as illustrated in **Figure 1**, which demonstrates an example with otitis media. Squares denote decision nodes where 1 treatment strategy must be chosen. Alternative strategies for management and their consequences are represented by separate branches in the tree. Chance nodes are depicted by a circle with a branch and indicate points where $\geq$2 possible events may occur.[12] Several sequences of chance nodes may be needed to describe the scope of a problem within the analysis.[12,14] Decision trees also contain terminal nodes, which represent subsequent prognosis or death for given combinations of patient characteristics and events. These terminal nodes are represented with a triangle and are assigned a value to determine the final outcome of the decision tree, such as crude life expectancy or quality-adjusted life expectancy.[14]

A decision tree can simulate simple clinical questions over a short time horizon. Decision trees are limited in their ability to model recurring events, risk that is ongoing over time, or events that can occur with uncertain timing.[7,14] Analysts may make the assumption that events occur at the average time associated with a known event rate. An example of decision tree usage is provided by Sun et al,[34] who evaluated the use of multiple strategies for acute otitis media using a decision tree. The analysis suggested that watchful waiting was the preferred strategy, resulting in improved health outcomes and cost savings.

State Transition Models

State transition models analyze the decision problem in terms of the stages of the disease process, or ''health states,'' the transitions between health states, and the probability of transitioning between health states.[11,20] State transition models require analysts to identify mutually exclusive and collectively exhaustive health states of a disease, the duration of time spent in each health state, and the value of each health state.[33,35] These models are best suited for decision questions that require time-dependent parameters (eg, probability of recurrent cancer after treatment), time to an event (eg, disease-free survival), or repeated events (eg, second episode of acute otitis media).[11] These complex models can assess either a closed cohort of individuals and transition the population of interest at specified time intervals or a dynamic population (eg, the US adult population).[11] State transition models can be divided into (1) cohort, or ''Markov,'' models and (2) individual-based, or ''microsimulation,'' models.[11,13,36]

Markov (Cohort) Models. Markov models can incorporate changes in risk over time or recurring events. These models are particularly useful when the timing of events is critical for a research question.[11,14,32] Analysts can extrapolate results to the future and analyze long-term outcomes and prognosis.[11] These models assume that patients in a cohort are always in one of a finite number of health states referred to as Markov states.[11,14,37] A state transition diagram can be used to depict the model structure, where each state is represented by a circle and arrows connecting 2 different states, which indicate permissible transitions (**Figure 2**).[14] Arrows leading from a state to itself indicate that patients may remain in that state in consecutive cycles.[14] The starting cohort should be homogenous with respect to demographic and clinical characteristics, which affect the transition probabilities or state values.[11] The entire cohort is then distributed across states each cycle.[11] Markov cycles are divided into equal time increments over a specified time horizon, which must be sufficiently long enough to capture the health effects and costs relevant to the decision question.[9,11,14] A cost or health outcome value can be applied per cycle to a health state or a transition. Aggregating all the state and transition values over the model's cycles estimates the model's total cost and health outcomes.[37]

During each cycle, a patient may make a transition from within and among states. Only 1 transition occurs during each patient's cycle.[14] The exact timing of that single transition during the cycle is not known. A half-cycle correction is made to assign half of the value of each state, as though the transition occurs halfway through the cycle on average. This approach ensures that expected values are neither overestimated by transitions occurring at the end of each cycle nor underestimated by transitions occurring only at the start of each cycle.[7,11,35] Disease incidence, prevalence, prognosis, and time-dependent complications can be modeled with a Markov model to provide an accurate simulation of a disease process over time.[7] For example, radiation therapy for laryngeal cancer carries a risk of secondary malignancy. However, time to development of a secondary cancer will have a significant impact on perceived quality of life following treatment.[11,38]

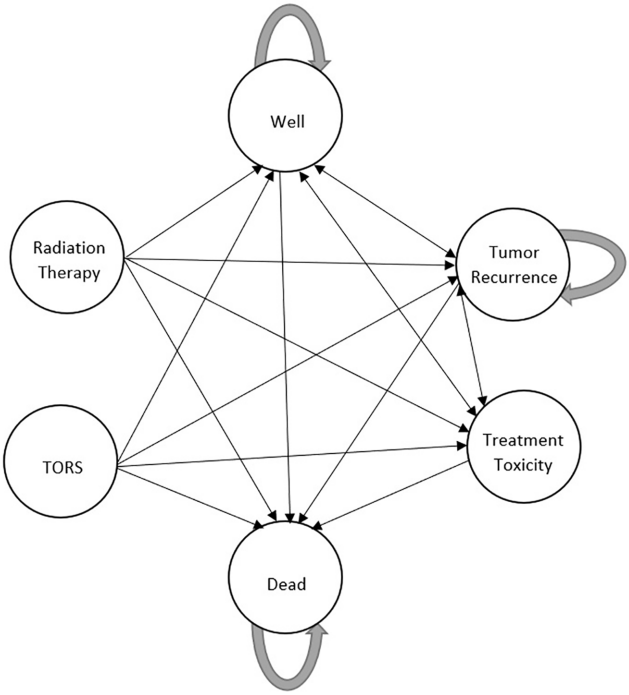

Figure 2. Overview of a simple state transition diagram. Patients can transition from 2 possible treatment strategies ("radiation therapy" or "transoral robotic surgery [TORS]") to specified downstream health states until they reach the absorbing state ("dead").

Transitions are restricted in Markov models to reflect plausible, real-world events. States within the model may be categorized as absorbing, active, or temporary. For example, a person who is in the ''dead'' state cannot make a transition to any other state. ''Dead'' is thus an absorbing state, as represented diagrammatically by a single arrow directed into the ''dead'' state and leading back to itself.[13,14] Active states are those from which a person can either stay for consecutive cycles or transition to other health states. In contrast to the ''dead'' state, a person treated for laryngeal cancer in the ''well'' state may make a transition to the ''tumor recurrence'' state or the ''dead'' state or stay in the same state for consecutive cycles. Temporary states represent discrete events with only short-term effects, and patients in these states can only transition to other states and not to themselves. For example, the patient treated for laryngeal cancer may experience treatment toxicity, such as airway obstruction.[39] The final analysis of the model yields the average number of cycles, or amount of time, spent in each state.[14]

Markov models are simple to develop, debug, and communicate if the number of states is not too large.[11] The primary disadvantage of the Markovian model is the underlying assumption that the status of an individual in any state is solely dependent on the features of that state and completely independent of past states.[9,11,14] Memory of previous health

states can be addressed in a Markov model by creating states that include history. However, this can greatly increase the number of states, resulting in ''state explosion,'' or very large, unmanageable models that are prone to error.[11,40] An example of a Markov decision model is seen in a comparison of outcomes following insertion of short-term grommet tympanostomy tubes, intermediate-type tubes, and long-term tympanostomy tubes. In this hypothetical cohort of 3000 children, patients could transition between states until they had a normal or healed tympanic membrane, myringoplasty with successful closure, or a perforated membrane state over 6 years.[41] The model demonstrated that intermediate-type tubes combined a balance of a lower perforation rate than permanent tympanostomy tubes and a longer period of ventilation than grommet tubes.

Microsimulation (Individual-Based) Models. Individual-based models are synonymous with Monte Carlo simulations, which reflect individual, simulated patients moving from cycle to cycle one at a time, based on their transition probabilities. The transition probabilities for each transition during each cycle are realized as random events—that is, determined by a computer-generated random number between 0 and 1 that can be correlated with the probability of a transition conditional on the current state. For an individual in the ''well'' state, for instance, a number <0.1 is associated with the probability to transition to ''death''; a number from 0.1 to 0.4 is associated with a transition to ''tumor recurrence''; and a number >0.4 is associated with the probability of remaining in the ''well'' state. Each random number is drawn like playing a lottery or a casino game, hence the name Monte Carlo simulation (named after the famous casinos of Monte Carlo).[12] Microsimulation models overcome the limitations of cohort models by analyzing individual clinical pathways that account for the impact of past events on future outcomes, as well as variations in patient characteristics within a heterogenous population.[20,37] This approach allows analysts to address costs and health outcome values that are attributed to an individual's characteristics (ie, physical, sociodemographic, and geographic features).[42]

Microsimulations use the same model framework as a Markov cohort model but send 1 hypothetical individual through the model at a time. The model uses variables to track patient characteristics, risk factors, disease progression, and events over time, thus incorporating memory into the model.[11,14,33,43] Individual-level data are then aggregated to provide population-level estimates for this simulated population. An applied example of a microsimulation state transition model is seen in a simulated cohort of individuals aged >62 years with early-stage oropharyngeal squamous cell carcinoma[1]; in this model, individuals entered the study just before decisions were made between standard radiation therapy and TORS. Accounting for age-dependent downstream outcomes, the model found that TORS could be a cost-effective alternative to radiation therapy for these patients. Microsimulation models are computationally intensive, and analysts must simulate 1000 to 1,000,000 individuals to obtain stable values for the outcomes of interest.[11]

Dynamic Transmission Models. Dynamic transmission models are methodologically and conceptually comparable to microsimulation models.[42] The defining feature of dynamic transmission models is their ability to model individual-level relationships that have an impact on results.[9,42] Dynamic transmission models simulate individual interactions with other individuals (eg, transmission of disease from infected to uninfected) or with other aspects of the model (eg, allocation of limited organs to individuals on a waiting list).[9,44] This property allows the model to simulate the changing number of infected individuals over time, in contrast to static state transition models that assume a constant risk of infection.[44] To delineate this type of model, consider the population impact of vaccination for human papillomavirus (HPV)–related infections. A related investigation could classify individuals as ''susceptible to infection,'' ''vaccinated,'' ''HPV infected,'' ''developed HPV-related disease,'' ''recovered from HPV-related disease,'' or ''dead.'' The study model could then simulate vaccine efficacy, virus transmission, and the burden of HPV-related disease, accounting for indirect effects of vaccination through herd immunity.[45-47] Although dynamic transmission models are valuable in their ability to reproduce direct and indirect effects of treatment strategies, these models can be analytically complex and are prone to state explosion.[9,44]

Decision Uncertainty

In the absence of perfect information, decisions to adopt health care interventions based on models are subject to uncertainty. Uncertainty in decision modeling can arise from the underlying data, the type or structure of a decision model, and the validity of the results for intended populations.[1,12,48-50] It is important for analysts to unambiguously describe their decision methods and assumptions, to be cognizant of the influence of uncertainty and heterogeneity in decision models, and to understand the role of sensitivity analyses.[12] The model structure should be determined by the problem of interest and not constrained by data availability or quality.[9]

Sources of Uncertainty and Heterogeneity

Model uncertainty may be described as first- or second-order uncertainty. Individual patient simulations introduce stochastic uncertainty, or so-called first-order uncertainty, which encompasses the randomness of natural events due to chance.[51-53] Identical individuals with the same outcome probabilities can still experience the effects of a disease or intervention differently, just as a fair coin toss can lead to heads in one instance and tails in another. Stochastic uncertainty can be evaluated with microsimulations, which simulate individuals one by one through the model. Tracker variables record the accumulated quality-adjusted life years (QALYs) and costs, along the individual's path. Microsimulations allow analysts to account for the influence of random patient events on

subsequent outcomes.[52] Parameter, or second-order, uncertainty refers to the standard error associated with an input parameter.[51] Parameters are best presented with point estimates and a measure of variance. Analysts should adopt standard statistical practices, such as 95% CIs or plausible evidence-based ranges, and justify their selection.[20]

Variability in the expected payoffs of treatment strategies can result from individual-level heterogeneity, including age, sex, ethnicity, or disease-risk profile within the population of interest, which can influence the measured outcomes.[51,54] For example, a decision model assessing the role of chemotherapy for locally advanced head and neck cancers would incorporate the improved survival in women as compared with men observed in clinical trials.[55]

Sensitivity Analyses

Sensitivity analyses determine the impact of key drivers of a decision outcome and the optimal strategy for different patient subgroups and settings, and they explore heterogeneity in treatment effects, costs, and utilities.[12,51] Sensitivity analyses can be deterministic or probabilistic. Deterministic analyses evaluate the sensitivity of the model results to selected parameter values. Analysts may select a 1-, 2-, or n-way approach to vary input parameters to examine the effect on the model outcomes. One-way sensitivity analyses explore the influence of parameters, where the value of 1 parameter point estimate is varied across a defensible range while the other parameters remain constant.[12,52,54] For example, in a model simulating management of early-stage oropharyngeal squamous cell carcinoma with TORS as compared with radiation therapy, the cost-effectiveness of TORS was found to be sensitive to the age of cancer diagnosis. That is, TORS was found to be a cost-effective strategy, at an incremental cost-effectiveness ratio of $57,380 per QALY gained, when the age of diagnosis was decreased, suggesting that TORS may yield the greatest value for younger patients.[1,50]

Simultaneous changes in selected variables may be evaluated through 2- and n-way sensitivity analyses.[12,52] In a 2-way sensitivity analysis, the effect of simultaneous changes in 2 variable values is evaluated, while all remaining variables are held constant. In an n-way sensitivity analysis, multiple variable values are varied at the same time to permit evaluation of the results in different settings, for different patients, and for best- and worst-case scenarios. In best- and worst-case scenarios, combinations of plausible assumptions are selected to explore their effect on outcomes. For example, an analysis of a smoking cessation program for patients with oral cavity cancer could compare the best-case scenario (eg, high patient compliance, >50% government financial support, and low probability of withdrawal symptoms) with the worst-case scenario (eg, low patient compliance, <50% government financial support, and high probability of withdrawal symptoms) to determine the impact of these key parameters on health outcomes and costs.[12,20,56] When there is very little or no information on a parameter, analysts should reflect the uncertainty in the parameter through a broad range of possible estimates. A parameter should not be excluded from a sensitivity analysis on the grounds that there is insufficient information; instead, it should be an opportunity to explore the influence of an unknown variable on outcomes to help lay the foundation for future research.[20] Deterministic sensitivity analyses are simple statistical analyses but limited in their ability to present the likelihood of the occurrence of each scenario.

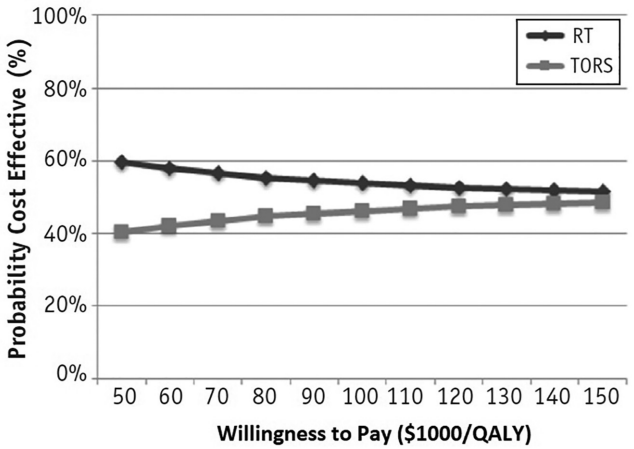

Figure 3. Example of a cost-effectiveness acceptability curve derived from the probabilistic sensitivity analysis, representing the probability that a treatment option is cost-effective for the willingness to pay per quality-adjusted life year (QALY) gained. RT, radiation therapy; TORS, transoral robotic surgery.

Probabilistic sensitivity analyses address uncertainty in estimated input parameters and model results by evaluating the probability distribution of every input parameter that has inherent uncertainty at once. The model calculates results each time with a different set of random values from probability distributions that approximate the distribution of each input parameter. It also presents the probability of a strategy being cost-effective, or of acceptable value for money, at a given willingness-to-pay (WTP) threshold.[33,40,48,52,57] The WTP threshold is a country-specific reference that denotes the maximum amount that an individual would be willing to pay to gain an additional QALY.[50,58,59] **Figure 3** presents an example of a cost-effectiveness acceptability curve, which allows decision makers to estimate their maximum WTP (ie, the maximum acceptability) for a QALY.[60] In this example of management of early-stage oropharyngeal squamous cell carcinoma with TORS as compared with radiation therapy, radiation therapy was determined to be cost-effective in 54% of iterations at a WTP threshold of $100,000 per QALY gained. Conversely, the probability that TORS was cost-effective at this WTP threshold was 46%.[1]

Model Calibration and Validation

Models are based on scientific knowledge of diseases supported by empirical evidence. Gaps in knowledge are bridged by assumptions surrounding model uncertainties. It is important to explore the consistency of the model's predicted probability to approximate the actual event

probability. Calibration is a useful tool when multiple sources of data exist or when no observed data are available to inform model parameters.[12,33,61,62] Calibration examines which set of estimates of model parameters results in model outputs that are most consistent with available observed outcome data.[12,61] For example, a model evaluating a screening test to detect HPV type 16 in saliva should be able to produce a population prevalence for HPV type 16 that is consistent with the available literature.[61,63] One or more calibration targets are established for particular disease end points and the unknown parameters are varied to ensure good model fit.[12,64,65] Multiple methods exist for assessing the degree of agreement among model predictions against the calibration target by means of visual or qualitative assessments and goodness-of-fit mathematical functions.[12,61,65,66]

Validation is a vital step in judging model accuracy in making relevant predictions. The face validity of a model refers to the extent to which a model and its predictions correspond to expert consensus and observed data. Model internal validity addresses whether the model's components behave as intended and the model has been implemented correctly. Model structure and outcomes can be compared with other available models through cross-validation to determine the extent to which different models calculate similar results. External validation compares disease outcomes at specific time points in the disease course to the published literature.[67] Ideally, this should be performed through an independent validation process where the model inputs are compared with empirical data that were not used to construct the model.[12] Validation is (1) dependent if the same data set is used for estimating and validating the model or (2) partially dependent if the source was used to build or calibrate part of a model but that part by itself does not wholly determine the outcome to be validated.[67] One of the advantages of a decision model is its ability to forecast events beyond the short time frame of randomized clinical trials.[12,50]

Value of Information Analyses

The cost of uncertainty in the setting of resource constraints in health care lends an added dimension to economic evaluations.[68,69] Value of information analysis is a quantitative means of valuing the expected gain from reducing uncertainty and can be used to guide future research endeavors.[68,70,71] Value of information analyses are based on the presumption that the decision to adopt and reimburse a strategy stems from currently available information, which is shrouded in uncertainty.[68,70] As long as there is parameter uncertainty, there will always be a chance for an inadvertently suboptimal decision. This parameter uncertainty can be decreased by supporting the collection of further evidence, which in turn may avoid reimbursement of suboptimal interventions and promote better use of limited public resources.[52] However, performing further research to establish more accurate parameter estimates in a decision model may not be justified, particularly if there is an opportunity cost of not pursuing alternative research options.[70,72]

The expected value of perfect information (EVPI) estimates the total value of future research that could simultaneously eliminate all parameter uncertainty involved in choosing a strategy.[52,70] The EVPI is equal to the net benefit of the optimal strategy given perfect information minus the net benefit of the strategy that would be adopted given current information, averaged over all model iterations.[70] That is, the value of information analysis informs decision makers how large the cost of a wrong decision is and the maximum that policy makers should pay for further research on model parameters to lower the uncertainty in the decision-making process.[51,73,74] If the cost of obtaining further information (eg, through a costly randomized clinical trial) exceeds the EVPI, there is little economic justification for proceeding with that particular research.[75]

Limitations

While decision analysis has many benefits, it still has constraints inherent to translation of real-world scenarios into mathematical models.[7,13,15] Disease processes are often more complex than models are able to simulate.[7,15] As such, lack of data for probabilities and utilities can be a substantial challenge in model-based decision making.[15] Models are reliant on assumptions and tools such as calibration to bridge the knowledge gaps. Furthermore, ethical, legal, and political considerations affect decision making in health care, but humanistic psychology can be difficult to incorporate into mathematical models.[50] It is important for the outcomes of decision models to be framed to an appropriate audience and setting to bear relevance.

Conclusion

Decision models are powerful tools to guide health care resource allocation decision making in the setting of competing or alternative strategies. These models support the integration of evidence and understanding of trade-offs of multiple strategies in clinical decisions, thereby providing a framework for discussion in a structured, hierarchical format. As models representative of complex health care scenarios, uncertainties around the true values of model input parameters can be challenged to evaluate the robustness of model assumptions and predictions through sensitivity analyses, calibration, and validation processes.

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Author Contributions

Lisa Caulley, contributed to the design of the work, drafted the work, revised it critically for important intellectual content; provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Myriam G. Hunink**, contributed to the design of the work, reviewed the work, revised it critically for important intellectual content; provided final approval of the version to be published, and agreed to be

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Gregory W. Randolph**, contributed to the concept and plan for the work, assessment of relevant information for the work, provided important intellectual content and final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Jennifer J. Shin**, conception of the work and substantial contributions to the work, drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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