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Review Article

Decision analytic modeling in spinal surgery: a methodologic overview with review of current published literature

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Abstract

BACKGROUND CONTEXT: In recent years, there has been an increase in the number of decision analysis studies in the spine literature. Although there are several published reviews on the different types of decision analysis (cost-effectiveness, cost-benefit, cost-utility), there is limited information in the spine literature regarding the mathematical models used in these studies (decision tree, Markov modeling, Monte Carlo simulation).

PURPOSE: The purpose of this review was to provide an overview of the types of decision analytic models used in spine surgery. A secondary aim was to provide a systematic overview of the most cited studies in the spine literature.

STUDY DESIGN/SETTING: This is a systematic review of the available information from all sources regarding decision analytics and economic modeling in spine surgery.

METHODS: A systematic search of PubMed, Embase, and Cochrane review was performed to identify the most relevant peer-reviewed literature of decision analysis/cost-effectiveness analysis (CEA) models including decisions trees, Markov models, and Monte Carlo simulations. Additionally, CEA models based on investigational drug exemption studies were reviewed in particular detail, as these studies are prime candidates for economic modeling.

RESULTS: The initial review of the literature resulted in 712 abstracts. After two reviewer–assessment of abstract relevance and methodologic quality, 19 studies were selected: 12 with decision tree constructs and 7 with Markov models. Each study was assessed for methodologic quality and a review of the overall results of the model. A generalized overview of the mathematical construction and methodology of each type of model was also performed. Limitations, strengths, and potential applications to spine research were further explored.

CONCLUSIONS: Decision analytic modeling represents a powerful tool both in the assessment of competing treatment options and potentially in the formulation of policy and reimbursement. Our review provides a generalized overview and a conceptual framework to help spine physicians with the construction of these models.

Keywords: Systematic review; Decision analytic models; Cost-effectiveness studies; Markov model; Decison tree; Monte Carlo simulation

Introduction

In an effort to develop better evidence for the interventions we perform, the American Recovery and Reinvestment Act allocated $1.1 billion dollars in 2009 toward the performance of comparative effectiveness research [1]. This type of research allows for the direct comparison of existing health-care interventions to determine which work best for which patients and which result in the greatest benefits and harms. Although the results of such

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research are not currently used unilaterally in coverage decisions in the United States, it is highly likely that we will increasingly follow the example of other countries, like the United Kingdom, where all coverage decisions regarding health-care technology include an economic analysis using complex mathematical modeling to determine whether, and under which circumstances, said technology should be adopted [2].

This paradigm shift toward value-based health care is of particular importance to spine surgeons because there are often multiple treatment options for a given spinal pathology [3]. Accordingly, there has been an increase in the number of economic analyses published in the spine literature over the last several years [4,5]. A recent focus issue dedicated to reviewing the existing literature on the value of spine procedures across a variety of spinal conditions found that although the number of studies that attempted to include an economic analysis had certainly increased, very few studies followed the guidelines of a proper economic analysis [5]. This is most likely because although most spine surgeons are now familiar with terms such as cost-benefit, cost-utility, and cost-effectiveness, relatively few have an understanding of how to properly calculate these parameters [6].

Decision analytic modeling plays an important role in economic analysis in spine surgery because well-designed prospective, randomized cost-effectiveness studies are lacking [7–9]. Decision analysis quantitatively compares different treatment for a given condition, and through modeling, provides a ranking of strategies in terms of cost and effectiveness. Our purpose was to provide the first overview of the different decision analytic models used in spine surgery along with the current literature in spine surgery that uses these models to define comparative effectiveness of different interventions.

Materials and methods

A systematic computerized MEDLINE literature search was performed using PubMed, Cochrane Database of Systematic Reviews, and Embase. The electronic databases were searched from January 1980 to June 2014. Searches were performed from medical subject headings used by the National Library of Medicine. Specifically, medical subject heading terms ‘‘cost-effectiveness analysis,’’ ‘‘decision tree,’’ ‘‘Markov model,’’ and ‘‘spine’’ were used. The initial search resulted in 712 abstracts being identified. Two reviewer–assessments of the abstracts identified 19 articles that represented the spectrum of analytic model construction and spinal pathology. An overview of the types of models can be found in Table 1. A summary of the articles can be found in Tables 2 and 3.

Table 1
Description and overview of the three principle analytic models used in spine surgery

Type of model	Description	Pro’s	Con’s
Decision tree	Represent the sequence of chance events and decisions over time. Probability of each chance event is estimated from data in clinical studies. Each path through the decision tree represents one possible sequence of chance and decision events and is associated with a consequence, which is valued in terms of a utility. Have three kinds of nodes and two kinds of branches.	Simple to understand and interpret. Allows addition of new possible outcomes. Best suited to model interventions to prevent or treat acute/short-term illnesses.	Not well suited to represent recurrent events that repeat over time (chronic diseases).
Markov	It contains a finite number of mutually exclusive and exhaustive health states (Markov states), having time periods (cycles) of uniform length and in which the probability of movement from one to another depends on the current state and remains constant over time. Categorized into different processes based on whether the state transition probabilities are constant over time or not.	Convenient way of modeling prognosis for clinical problems with ongoing risks. We can count medical costs, living costs, health-related quality of life scores, and so forth. We can tailor the results more by individual characteristics or take more complex and numerous events into account.	Patient in a given Markov state can only make a single state transition during a cycle. Difficult to represent all the possible ways of making a transition from one state to another as a single transition probability.
Monte Carlo	This method relies on repeated random sampling to obtain numerical results; typically one runs simulations many times over to obtain the distribution of an unknown probabilistic entity. The model begins by randomly selecting an individual from a hypothetical sample of persons with the disease, then simulating the course of the patient’s disease over his or her expected lifetime.	The method is useful for obtaining numerical solutions to problems that are too complicated to solve analytically. Enables informed decisions in case of uncertainty. Has the advantage of yielding not only average effects but also the measures of the uncertainty around the average.	Requires informed opinion about likelihood of future scenarios and likely range of variables The practical disadvantage is computing time; because tens of thousands of replications are often needed to obtain stable estimates of event probabilities, especially in the presence of infrequent events, even modern computers can be taxed.

Table 2
Summary of decision tree models used in spine surgery

Study	Model	Time horizon	Costs	Outcome measures	Results
Malter et al., Cost-effectiveness of lumbar discectomy	Simple decision analytic model	10 y	USD (1993) Cost sources: Insurance claims found in MESTAT (January 1987 to December 1989) ICD-9 codes Direct cost estimate from Health Maintenance Organization (n=78)	QOL, QALYs gained PRO good, fair, poor, or bad outcomes Time trade-off utility measure (scale of 1, perfect health, to 0, death) asking willingness-to-give up years of life for symptom resolution Patients reporting good or bad surgical outcome in the trial were assumed to have a comparable quality of life	Discectomy appears to be a cost-effective intervention as compared to other procedures for selected patients with defined indications for surgery. QALYs after Rx: Surgical: 8.70 y. Medical: 8.27 y. Difference: 0.43 Base case: $29,190/QALY gained (insurance claims data) $12,020/QALY gained (HMO cost data) Cost of surgery per QALY gained: $29,200 (no discounting) $33,900 with 5% discounting
Angevine et al., Cost-effectiveness of single-level anterior cervical discectomy and fusion for cervical spondylosis (Comparison of three Rx arms: ACDF with allograft alone, autograft alone, and allograft and plating)	Simple decision analytic model for perioperative and 1-y outcomes, and Markov model for health status and reoperations between 1 and 5 y.	5 y	USD (2000) Cost sources: A retrospective analysis of itemized hospital bills from 78 patients (31 underwent single-level ACDF with allograft alone, and 47 had allograft and plating); Hospital charges were converted to approximate costs using specific cost-to-charge ratios from the Institutional Cost Reports. Medicare reimbursements used as a proxy for surgeon's costs, and previously published costing studies were used to estimate costs of complications.	Outcomes were derived from preoperative and postoperative SF-36 scores (converted into utilities using an algorithm base on the Health Utility Index) from a retrospective cohort study QALYs gained	ACDFP offers benefits relative to ACDF with autograft and ACDF with allograft at a cost per QALY similar to that of other commonly provided treatments. Base case: (5 y) ACDF-autograft Cost: $11,230 QALYs: 4.365 ACDF-allograft Cost: $11,290 QALYs: 4.486 ICER: $496/QALY gained (vs. ACDF-autograft) ACDFP Cost: $12,690 QALYs: 4.529 ICER: $32,560/QALY gained (vs. ACDF-allograft)

Carreon et al., Cost-effectiveness of single-level anterior cervical discectomy and fusion 5 y after surgery	Simple decision analytic model	5 y	USD (2012) Cost sources: Direct costs from 2012 Medicare National Average payment Indirect costs as cost per days off of work from the National Average Wage Index for 2010	Neck Disability Index SF-36, PCS, SF-36 MCS, SF-6D Secondary surgical procedures Return to work QALYs gained	At 5-y follow-up, single-level instrumented ACDF is both effective and durable resulting in a favorable cost/QALYs gain as compared with other widely accepted health-care interventions. Base case: Costs per patient for index ACDF: $15,714 Mean QALY gained in each year follow-up: Cumulative 0.88 ICER: 1 y: $104,831/QALY gained 5 y: $23,460/QALY gained (Cost per QALY gained decreased over time)
O'Neill et al., Anterior cervical discectomy and fusion for adjacent segment disease: clinical outcomes and cost-utility of surgical intervention	Simple decision analytic model	2 y	USD (2013) Cost sources: Direct costs from Medicare reimbursements for Diagnosis-Related Groups (DRG) and CPT Codes Indirect costs from standard human capital approach (change in h worked × gross-of-tax wage rate; reported by patients at study entry)	EQ-5D (derived from a retrospective review of 40 patients) Neck Disability Index SF-12 PCS and MCS Zung depression score. QALYs gained	Performing ACDF for adjacent segment disease is both clinically and cost-effective. Base case: 2-y mean surgery cost: $32,616 2-y cumulative QALY gain: 0.54 2-yr ICER $60,526/QALY gained
Qureshi et al., Cost-effectiveness analysis: comparing single-level cervical disk replacement and single-level anterior cervical discectomy and fusion	Simple decision analytic model	20 y	USD (2010) Cost sources: 2010 Medicare reimbursement for COT and DRG	SF-36 scores Neck Disability Index Range of motion Neurologic status QALYs gained Short- and long-term complications Revision rate	At 5 y postoperatively, patients with ACD had significantly higher quality of life and incurred significantly lower societal costs than those receiving other treatments. Total lifetime costs: CDR: $11,987 ACDF: $16,823 Effectiveness: (QALYs) CDR: 3.94 ACDF: 1.92 Cost-effectiveness ratio: ACER CDR: $3,042/QALY ACER ACDF: $8,760/QALY

(*Continued*)

Table 2
(*Continued*)

Study	Model	Time horizon	Costs	Outcome measures	Results
Rasanen et al., Cost-utility analysis of routine neurosurgical spine surgery	Simple decision analytic model	Lifetime	Euros (2003) Cost source: Direct medical costs from Ecomed (a patient administration system)	15-D HRQOL QALY gained	Both cervical and lumbar spine surgery, in addition to relieving pain, lead to statistically significant improvement in many dimensions of health such as moving, sleeping, depression, distress, and sexual activity. Base case: Costs: (95% CI) Cervical: €3,356 Lumbar: €3,493 QALYs: (95% CI) Cervical: 1.21 Lumbar: 2.01 ACER: (upper 95% CI) Cervical: €2,024/QALY gained Lumbar: €1,347/QALY gained
Garrison et al., Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spine fusion: a systematic review	Simple decision analytic model	2 y	British pound (year NR) Cost sources: Cost of initial current Rx (decompression and fusion) from the National Schedule of Reference Costs 2005 Cost of BMP (InductOs 12 mg Implant Kit) from Wyeth	Unpublished SF-36 data Surgical parameters, reoperation, time to return to work, fusion rate QALY gained	At a willingness-to-pay threshold of £30,000 per QALY gained, rhBMP-2 was not found to be a cost-effective option for spinal fusion surgery in this model (with a probability of 6.4% only). Costs: (95% CI) ICBG: £5,410,656 BMP: £7,243,909 Additional QALYs: 11 ICER with rhBMP-2: £120,390/QALY gained
Burnett et al., Cost-effectiveness of current treatment strategies for lumbar spinal stenosis: nonsurgical care, laminectomy, and X-STOP	Simple decision analytic model	2 and 4 y	USD (2008) Cost sources: Direct costs from Medicare DRG and CPT reimbursement rates from 2008	SF-36 HRQOL QALY gained Revision rates, 2-y failure rates, requiring additional surgery	In single-level procedures, laminectomy was more effective but also more costly than X-STOP and conservative treatment. Costs: (per patient) Nonsurgical: $3,453 Laminectomy: $9,349 QALYs: (per patient) Nonsurgical: 0.0660 Laminectomy: 0.1651 ICER: laminectomy versus nonsurgical $59,487/QALY gained

Udeh et al., The 2-y cost-effectiveness of three options to treat lumbar spinal stenosis patients	Simple decision analytic model	2 y	USD (2013) Cost sources: Direct costs from Medicare reimbursement for CPT and DRG for 2013 Indirect costs were not assessed	QALY gained (derived from published literature)	The MILD (minimally invasive lumbar decompression) strategy appears to be the most cost-effective, with ESI the next best alternative, followed by laminectomy surgery. Base case: Costs: MILD: $5,457 ESI: $7,887 Laminectomy: $13,770 QALYs: MILD: 0.12 ESI: 0.19 Laminectomy: 0.11 ACER: MILD: $43,760 ESI: $81,518 Laminectomy: $125,985
Van den Akker et al., Tubular discectomy versus conventional microdiscectomy for the treatment of lumbar disk-related sciatica: cost-utility analysis alongside a double-blind randomized controlled trail	Simple decision analytic model	1 y	Euros converted to USD (2008) Cost sources: Cost diaries, operating room average cost, equipment costs at time of purchase, yearly use and depreciation, and Dutch standards prices (to represent societal costs)	EQ-5D (from RCT data)	Tubular discectomy is unlikely to be cost-effective compared with conventional microdiscectomy. Costs: (mean societal costs) Tubular: $16,858 Conventional: $15,367 QALYs: US EQ-5D: −0.012 Dutch EQ-5D: −0.014 SF-6D: −0.11 VAS: −0.021 ICER Δ$US
Fehlings et al., Is surgery for cervical spondylotic myelopathy cost-effective? A cost-utility analysis based on data from the AOSpine North America prospective CSM study	Simple decision tree	10 y	CAD (2008) Cost sources: Hospital costs from the hospital's case-costing database Physician costs from the Ontario Schedule of Benefits for Physicians Services	SF-6D utility values derived form SF-32v2 scores Neck Disability Index mJOA scale Modified Nurick scale QALY gained	Surgical treatment for CSM is a cost-effective option, with significant improvement in health utilities as measured by the SF-6D. Base case: Total cost: $21,066 Mean discounted gain of QALY: 0.64 over a 10-y period ICER: $32,916/QALY gained

(*Continued*)

Table 2
(Continued)

Study	Model	Time horizon	Costs	Outcome measures	Results
Ackerman et al., Comparison of the costs of nonoperative care to minimally invasive surgery for sacroiliac joint disruption and degenerative sacroiliitis in a United States Medicare population: potential economic implications of a new minimally-invasive technology	Simple decision analytic model	5-y follow-up extrapolated additional 10 y (lifetime perspective)	USD (2012) Cost sources: 2012 Medicare DRG and CPT reimbursements Truven Health MarketScan Premier's perspective Comparative Database	Cost savings based on data for success and potential complications frequency, which was extrapolated to 291,040 Medicare patients	MIS (minimally invasive surgery) SI joint fusion surgery was more cost-effective than nonoperative care over a 5-y time horizon. Base case: Costs: (per patient) MIS: \$48,185 Nonoperative: \$51,543 Δ Cost: \$3,358 savings with MIS per patient Extrapolated Medicare savings: \$660 million for 196,452 beneficiaries

QOL, quality of life; QALY, quality-adjusted life year; ACDF, anterior cervical discectomy and fusion; SF, short form; ICER, incremental cost-effectiveness ratio; CDR, cervical disc arthroplasty; 15-D HRQOL, 15-dimensional health-related quality of life; CI, confidence interval; BMP, bone morphogenetic protein; RCT, randomized controlled trial; VAS, visual analog scale; LBP, low back pain; ICD, International Classification of Diseases; PRO, Patient reported outcomes; Rx, Prescription; HMO, health maintenance organization; ACDFP, anterior cervical discectomy and fusion with plating; MCS, mental composite summary; CPT, current procedural terminology; EQ, EuroQol; COT, cost of treatment; ACER, average cost-effectiveness ratio; ESI, epidural steroid injection; CSM, cervical spondylotic myelopathy; mJOA, modified Japanese Orthopedic Society; SI, sacroiliac.

Results

Types of models and summary of investigations

Although there are several different decision analytic models used in comparative effectiveness research, they all use an analytic methodology that allows for the accounting of events over time. Specifically, decision tree models and Markov models have been used in spinal surgery and will be discussed in the following sections. Monte Carlo simulations, although the most powerful analytic tool, have not been used to model spine care.

Decision tree

The decision tree remains the most common structure for decision models in economic analysis. In the most basic state, the decision tree is an individual's possible outcomes after some medical intervention that is represented by a series of pathways. All possible pathways are shown explicitly in the decision tree. Decision trees are most appropriate for modeling events that occur over a short period of time, or evaluations, which use an intermediate outcome measure [10,11]. Examples from the recent spine literature include studies comparing anterior cervical discectomy and fusion (ACDF) with cervical disc arthroplasty (CDR) [12], operative treatment of cervical spondylotic myelopathy [13], and operative versus nonoperative treatment of degenerative lumbar spinal stenosis and spondylolisthesis [14].

Two critical components of the decision tree are decision nodes and chance nodes [15,16]. The decision node is represented by a square box at the start of the decision tree and represents the decision being addressed by the model. Once a decision has been made between two possible interventions, the individual enters into a range of possible pathways that characterize the effects of the treatment decision. Within the decision tree, this is represented with branching arms of each strategy. At each of these branch points, also known as chance nodes, there exists a probability of following a particular branch in a predetermined proportion that is set by the probability of acquiring that individual outcome [17]. The sum of all the probabilities from each chance node must equal 1. For example, if we know the rate of pseudarthrosis after two-level ACDF to be 10%, the chance node for pseudarthrosis will be represented by a probability of .1, while the fusion branch will be .9 for a cumulative probability of 1. When deciding on what numerical value should represent each probability, Oxman et al. [18] recommend using a value derived from a systematic review or meta-analysis of the given condition. A schematic of a typical decision tree can be seen in Fig. 1.

Costs in decision trees may be assigned to events within the tree or at the terminal nodes. Costs are typically labeled as either direct or indirect. Direct costs represent the opportunity costs of formal health-care goods and services such

Table 3
A summary of the Markov models used in spine surgery

Study	Model	Time horizon (y)	Costs	Outcome measures	Results
Kuntz et al., Cost-effectiveness of fusion with and without instrumentation for patients with degenerative spondylolisthesis and spinal stenosis	Markov	10	USD (1997) Cost source: Boston hospital accounting system	Time-trade off from the Beaver Dam Health Outcomes Study (a longitudinal cohort study of health status and health-related quality of life) QALY gained	Laminectomy with non-instrumented fusion was more cost-effective than the laminectomy with instrumented fusion. Base case: Costs: (10-y cumulative) Laminectomy: $21,025 Non-instrumented fusion: $26,965 Instrumented fusion: $35,669 QALYs: (10-y cumulative) Laminectomy: 7.938 Non-instrumented fusion: 8.053 Instrumented fusion: 8.056 ICER: (compared with laminectomy) Instrumented fusion: $56,500/QALY gained
Kim et al., Cost-utility of lumbar decompression with or without fusion for patients with symptomatic degenerative lumbar spondylolisthesis	Markov	10	CAD (2010) Cost source: Author's hospital finance department (based on average cost per prospective cohort cases over 4 y)	SF-6D (from a retrospective cohort and some model probabilities from literature) QALY gained	For a select subgroup of patients, decompression without fusion is significantly more cost-effective than instrumented fusion. Base case: Costs: (10-y cumulative) Decompression: $6,514 Decompression/fusion: $20,797 QALYs: Decompression: 6.263 Decompression/fusion: 6.340 ICER: $185,878/QALY gained
Furlan et al., The combined use of surgery and radiotherapy to treat patients with epidural cord compression due to metastatic disease: a cost-utility analysis	Markov	Lifetime, but <1	USD (2010) Cost sources: Hospital costs from Ontario Case Costing Initiative Physicians costs from Ontario schedule of benefits for physician services Cost of revision spinal procedures Costs per h of operating time Cost per bed day Annual mean gross salary from all employee jobs	Discharge home (based on a single RCT for probabilities and rates of clinical events) QALY gained	Combined use of surgery and radiotherapy for treating patients with MSCC increase the health-care costs but significantly increase the quality of life. It became a cost-effective option when the initial costs within the first 60 d were less than $29,439. Base case: ICER: $250,307/QALY gained

(*Continued*)

Table 3
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Study	Model	Time horizon (y)	Costs	Outcome measures	Results
Virk et al., Cost-effectiveness analysis of graft options in spinal fusion surgery using Markov model	Markov	40	USD (2011) Cost source: Costs associated with clinical visits, surgery, and graft prices	Mortality rates Revision rates Low back pain scores Graft-specific complications QALY values for failed/ successful revision surgery	rhBMP is the most cost-effective option for low lumbar fusion for degenerative spondylolisthesis largely due to the reduced rate of revision surgery. Base case: Costs: (40-y cumulative) Chronic LBP: $0 rhBMP: $45,471 LBG: $48,135 ICBG: $48,158 CCA: $51,239 DBM: $ 48,323 QALYs: (40-y cumulative) Chronic LBP: 8.03 rhBMP: 10.77 LBG: 10.30 ICBG: 10.29 DBM: 10.30 CCA: 9.85 ACER: (graft option vs. living with chronic LBP) rhBMP: $16,595/QALY LBG: $21,204 QALY ICBG: $21,308 QALY DBM: $21,287 QALY CCA: $28,153 QALY
Koenig et al., How does accounting for worker productivity affect the measured cost-effectiveness of lumbar discectomy?	Markov	4 and 8	USD (2009) Cost sources: Direct medical costs (from Medicare claims data, adjusted to account for differences in private payer and Medicare payment levels) Worker's earnings (from National Health Interview Survey)	Direct measure from Functional Limitation Index score (as reported by SPORT) Indirect measure from missed workdays QALY gained	Increased workers earnings resulting from the disk herniation surgery may offset the increased medical costs associated with surgery; making surgery a highly cost-effective treatment option. Estimated annual earnings: With surgery: $47,619 Nonsurgical Rx: $45,694 Cost of surgery/QALY gained: $52,416 to $35,146, using a 4-y time horizon $27,359 to $4186, using an 8-y time horizon

(*Continued*)

Table 3
(*Continued*)

Study	Model	Time horizon (y)	Costs	Outcome measures	Results
Ament et al., Cost-effectiveness of cervical total disc replacement versus fusion for the treatment of two-level symptomatic degenerative disc disease	Markov	2	USD (year NR) Cost sources: DRG codes from institutional billing data (applying 2012 Medicare reimbursement rates) Costs of complications and return to work data	Neck Disability Index Visual analog scale SF-6D used to transform 12-item Short-Form Health Survey in to health utilities (data derived from an RCT that followed 330 patients for 2 y) QALY gained	CTDR appears to be a highly cost-effective surgical modality compared with ACDF for a two-level cervical disc disease. Base case: Costs: CTDR: $4,305,995 ACDF: $4,092,030 QALYs: CTDR: 1.58 ACDF: 1.50 ICER: (CTDR vs. ACDF at 2 y) $24,594/QALY gained
McAnany et al., The 5-y cost-effectiveness of anterior cervical discectomy and fusion and cervical disc replacement: a Markov analysis	Markov	5	USD (2010) Cost sources: Physicians costs from 2010 Medicare reimbursement (fixed at 140%) Hospital costs from the Nationwide Inpatient Sample	SF-36 at baseline and 5 y (from the treatment arms of the ProDisc-C trial) QALY gained	CDR was found to be the dominant strategy because it was more cost-effective at 5 y than ACDF. Base case: Costs: (5-y cumulative) CDR: $102,274 ACDF: $,119,814 QALYs: CDR: 2.84 ACDF: 2.81 ICER: (CDR vs. ACDF) −$557,849?QALY gained

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; SF, short form; RCT, randomized controlled trial; LBP, low back pain; ACDF, anterior cervical discectomy and fusion; CDR, cervical disc arthroplasty; MSCC. metastatic spinal cord compression; ACER, average cost-effectiveness ratio; SPORT, Spine Patient Outcomes Research Trial; NR, not reported.

as hospital, physician, and nursing home care, and drugs. It is often more difficult to define what exactly represents an indirect cost. Indirect costs in general are unintended costs that occur as a result of an action. Most often in surgical decision models, the indirect costs are represented as time lost from work and the cost that is incurred to the patient and society as a result of this action. An example of the importance of indirect costs can be seen in the article by Fehlings et al. [13] created a simple decision tree to model the operative treatment of symptomatic cervical spondylotic myelopathy. The authors reported a total cost of $21,066 and a quality-adjusted life year (QALY) gain of 0.64 over 10 years with operative intervention. The incremental cost-effectiveness ratio (ICER) was calculated to be $32,916/QALY, demonstrating an acceptable cost-effectiveness given a willingness-to-pay threshold of $50,000/QALY. Indirect costs were not included as part of the analysis, which may artificially inflate the ICER of the operative arm, potentially underestimating the cost-effectiveness of surgical treatment.

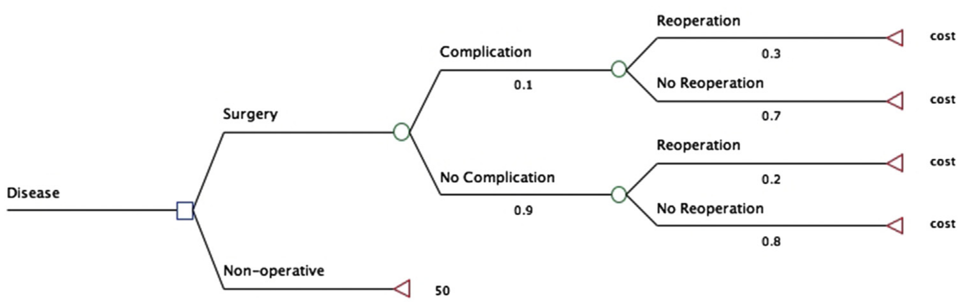

Fig. 1. Schematic representation of a generic decision tree demonstrating decision nodes, chance nodes, and terminal nodes.

The total cost of an intervention is then determined by the summation of all the costs for each unique pathway in the relevant area of the tree. The determination of the appropriate costs in a decision tree represents one of the critical components to ensure integrity in the model. There are number of ways to regenerate costs data including: large insurance databases, Medicare/Medicaid databases, individual hospital costs and charges, or large multicenter aggregated mean costs. Malter et al. [19] in 1996 published the first cost-utility study in spine surgery comparing surgical discectomy versus nonoperative treatment of herniated lumbar discs. The authors used a simple decision analytic model with a 10-year time horizon. Costs were denominated in 1993 dollars derived from the insurance claims found in MEDSTAT from January 1987 through December 1989. The authors found that surgical treatment of herniated lumbar discs was a cost-effective option at $12,000/QALY gained. In contrast, Angevine et al. [6] constructed a simple decision analytic model from the societal perspective for perioperative and 1-year outcomes after ACDF. Costs were determined from itemized hospital bills from 78 patients, with Medicare reimbursements used as a proxy for surgeon's costs. An example of using Medicare database to generate cost data can be seen in the study by Carreon et al. [20] Costs were derived from 2012 Medicare National Average Payment. Indirect costs were calculated as cost per days off of work and were derived from the National Average Wage Index for 2010. Several other authors have used the Medicare database to generate direct costs data [14,21,22].

Outcomes of the tree are represented by terminal nodes, and can be life, death, or any other state of health and disease [23,24]. Decision analysis has incorporated the use of utilities, or patient preferences to reflect the fact that certain health states are preferred over others [24–29]. Utility values range from 0 to 1, with 0 representing death and 1 representing perfect health. Realistically, no patient is likely to achieve perfect health after a given intervention. Angevine et al. [6] in their study reported a postoperative utility value of 1 after ACDF. This likely over represents the true health benefit to the patient. In addition, the best sources of utility values can be found in randomized controlled trials (RCTs) with large patient samples, which likely represent the true spectrum of disease disutility and benefit derived from treatment of the general population. However, several studies have used inferior methods for deriving utility values. For example, Qureshi et al. [12] and Udeh et al. [30] both used expert opinion to estimate utility in their respective studies. This introduces a significant amount of bias into the model and further necessitates the use of a sensitivity analysis to validate that input variables in the model.

Quality-adjusted life years use utility scores to report on the absolute gain or loss of life in response to having undergone an intervention [31,32]. In comparing two competing strategies, the difference in QALYs saved or lost may be calculated. At each terminal node, the difference in cost can be calculated and weighed against the probability of the outcome. For each outcome, the cost and effectiveness can be calculated.

In constructing a true decision tree model, it is important to have an experimental group and control group; or simply a new method of treatment that can be compared with a gold standard. This allows for a meaningful analysis to be performed determining the true cost-effectiveness of a procedure. Carreon et al. [20] constructed a simple decision analytic model to analyze the 5-year cost-utility of ACDF in patients enrolled in the Bryan and Prestige cervical disc arthroplasty. The authors were able to demonstrate a decreasing cost per QALY gained over time. The 5-year ICER was $23,460/QALY. However, to generate a true ICER, it is necessary to have a comparison group as part of the analysis, and in this study, the authors did not include a comparison group.

Once the decision tree is constructed and all outcomes and variables associated with the chance nodes are defined, the formal analysis may be performed. The analysis proceeds from right to left or from terminal node to decision node. This ''roll-back'' weights each possible outcome by the probability of obtaining that outcome [33]. These weighted values are then summed at the chance node that led to a particular outcome. The process repeats from right to left, with each successive value at a chance node being multiplied by the probability of getting to the chance node, and again summed with the other weighted values at the next most proximal chance node. At the most proximal chance nodes, there will be a single value representing each arm or strategy modeled in the tree. In the case of a cost-effectiveness analysis, the optimal strategy will be represented in cost ($) per QALY. These results represent the initial assumptions of the model and are referred to as the base case.

After the base case analysis is performed, it is necessary to perform a sensitivity analysis to validate the assumptions made in the model and define threshold values over which a strategy is cost-effective [34]. Varying the baseline values of each variable allows for testing the strength of the conclusion of the analysis [16]. If small changes in a variable cause the conclusion of the analysis to change, the model is determined to be sensitive to that variable. Another important aspect of the sensitivity analysis is the identification of variables that warrant further analysis. Van den Akker et al. [35] compared traditional open microdiscectomy with tubular discectomy using a cost-utility analysis with a simple analytic decision model. From the societal perspective, a nonsignificant difference of US $1,491 (95% confidence interval, −1,335 to 4,318) in favor of conventional microdiscectomy was found; however, the authors did not perform a sensitivity analysis as part of the study.

For practical reasons, the analysis performed using a decision tree must be restricted to a finite time frame, which is often referred to as the time horizon of the analysis [36]. Aside from death, the outcomes chosen to be represented by the terminal nodes may not represent true final outcomes but may represent the convenient stopping points for the scope of the analysis. Furthermore, there is no explicit time variable in a decision tree, and those elements of an economic analysis that are time dependent may be difficult to model. A practical example of this limitation can be seen when trying to adjust survival duration for health-related quality of life in cost-utility analysis. Similarly, O'Neill et al. [37] performed a cost-utility analysis to model secondary ACDF due to adjacent segment disease. The authors calculated a 2-year cost of $32,616 and a cumulative QALY gain of 0.54 with the 2-year ICER being $60,526/QALY. A lack of treatment group limits any meaningful interpretation of the calculated ICER.

A second limitation of decision trees is that they can become very complex when attempting to model complicated long-term prognoses [38]. When modeling complex chronic diseases, new risks may present themselves for future time periods. To appropriately model these events requires a series of chance nodes and branches for particular time periods. This causes the model to become onerous in size with multiple mutually exclusive pathways. As noted by Tom and Schulman [36], a decision tree with few branches and a time period of 1 year can have hundreds of branches when analyzed over 5 or 10 years. Rasanen et al. [39] performed a cost-utility analysis with a lifetime horizon for patients with cervical or lumbar radiculopathy with utilities based on the 15-dimensional health-related quality of life questionnaire before and 3 months after surgery. The ability to model lifetime benefit with utilities generated at 3 months after surgery represents a significant limitation and is likely underpowered to truly demonstrate a lifetime benefit.

Markov models

The limitations experienced with decision trees led to the application and development of Markov models for use in health-care economic modeling. In 1983, Beck and Pauker [40] first described the use of Markov models for determining prognosis in medical applications. Markov models, also known as state transition models, allocate members of a population into one of several categories, or health states. Time elapses explicitly with a Markov model, with the probability of a patient occupying a particular health state assessed over a series of discrete time periods, or cycles [41]. Transitions between the health states occur from one state to another over these discrete cycles, which are most commonly set to 1 year. Through simulation, the number of members of the population passing through each state at each point in time can be estimated. The process of moving between states occurs until a patient enters an absorbable, or end state, such as death. Each state in the model is assigned a utility, and the relative contribution of this utility to the overall prognosis is determined by the length of time that the individual spends in the state [42].

In general, there are two broad classes of Markov models: Markov chains and Markov processes [43]. Markov chains are defined by constant transition probabilities. Markov processes are defined as having time-dependent transition probabilities. Markov processes are best used when the time horizon of interest is short. Markov chains are more commonly used for chronic disease states, or those with a long time horizon. Additionally, Markov models allow for variation of the time horizon to compare the treatment effects at different time points. For example, Koenig et al. [44] used a Markov model to assess the impact of disc herniation surgery on workers' earnings and missed workdays and how accounting for this effect influences the cost-effectiveness of surgery. Two separate time horizons were used: 4 and 8 years. More fully accounting for the effects of disc herniation surgery on productivity reduced the cost of surgery per QALY from $52,416 to $35,146 using a 4-year time horizon and from $27,359 to $4,186 using an 8-year time horizon.

Another example of how time horizon can impact the result of a model can be seen in the study by Virk et al. [45]. The authors constructed a Markov model to assess five different graft options used in the fusion of degenerative lumbar spondylolisthesis. The graft options included: recombinant human bone morphongenetic protein 2 (rhBMP-2), iliac crest bone graft (ICBG), local bone graft (LBG), demineralized bone matrix (DBM) with local bone, and corticocancellous allograft chips (CCA). Costs were denominated in 2011 US dollars. Outcomes included mortality and revision rates, QALY values for successful/failed revision surgery, and graft-specific complications. In the base case, the incremental cost-effective ratio for each graft option when compared with living with chronic back pain was $21,308/QALY for ICBG, $16,595/QALY for rhBMP, $21,204/QALY for LBG, $21,287/QALY for DBM, and $28,153/QALY for CCA. Therefore, the most cost-effective graft option in the base case was rhBMP. A major criticism of the study was a lack a horizon with respect to revision rates. After 6 years, the authors assumed in their model that revision rates would fall to zero. This likely under represents the true revision rate over the 40-year time horizon of the model. This would directly impact the associated cost per QALY.

Construction of a Markov model generally begins with defining the health states that will represent the clinical scenario of interest [46]. These states consist of a well state, a death state, and various states of disease. These can be seen schematically in Fig. 2. Additionally, Fig. 3 represents a Markov model as it would be constructed in decision software. These states are represented as circles or ovals within the simulation. The allowable transitions among the heath states are then added and are represented as arrows between the various states [16]. Arrows may be bidirectional, which indicate that an individual can transition back and forth between that health state. Unidirectional arrows lead to absorbable states that cannot be left once entered. It is important that the probabilities of each health state are derived from consistent sources such as a systematic literature

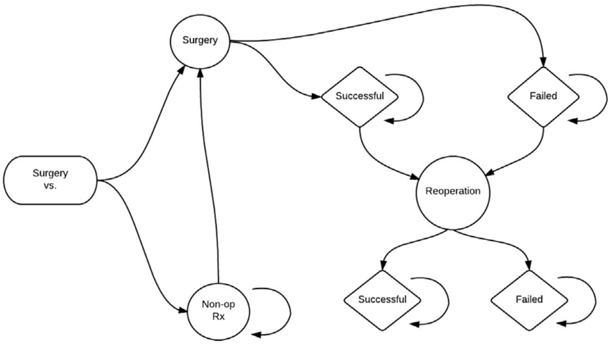

Fig. 2. Conceptual representation of a generic Markov model.

review or pooled data from a multicenter RCT. For example, Kuntz et al. [47] created a cost-utility Markov model to assess the treatment of degenerative lumbar spondylolisthesis and stenosis with laminectomy without fusion, laminectomy with non-instrumented fusion, and laminectomy with instrumented fusion. However, the probabilities were derived from different literature sources and were not associated with the cost source, thereby introducing uncertainty into the model.

Transition probabilities are derived from a review of the literature. Typically, a systematic review or meta-analysis is performed, which allows for the generation of high-quality data. Kim et al. [48] presented their Markov model for the treatment of degenerative lumbar spondylolisthesis treated with decompression alone or with instrumented fusion. The authors used transition probabilities that were derived from the existing literature wither performing a formal systematic review to capture the breadth of the existing literature. Unlike transition probabilities in a simple analytic decision tree, the probabilities in a Markov analysis may be allowed to vary over time.

In the Markov model, costs are typically assessed each cycle according to the state that the individual occupies. Total costs for each alternative are derived by multiplying the costs associated with each health state experienced by the patient and then summing across all health states experienced by the patient. Utility values or other measures of health outcomes can be attached to each health state model, thereby allowing a relative ranking of severity for each health state. Quality-adjusted life years are calculated by multiplying the quality of life weights associated with each

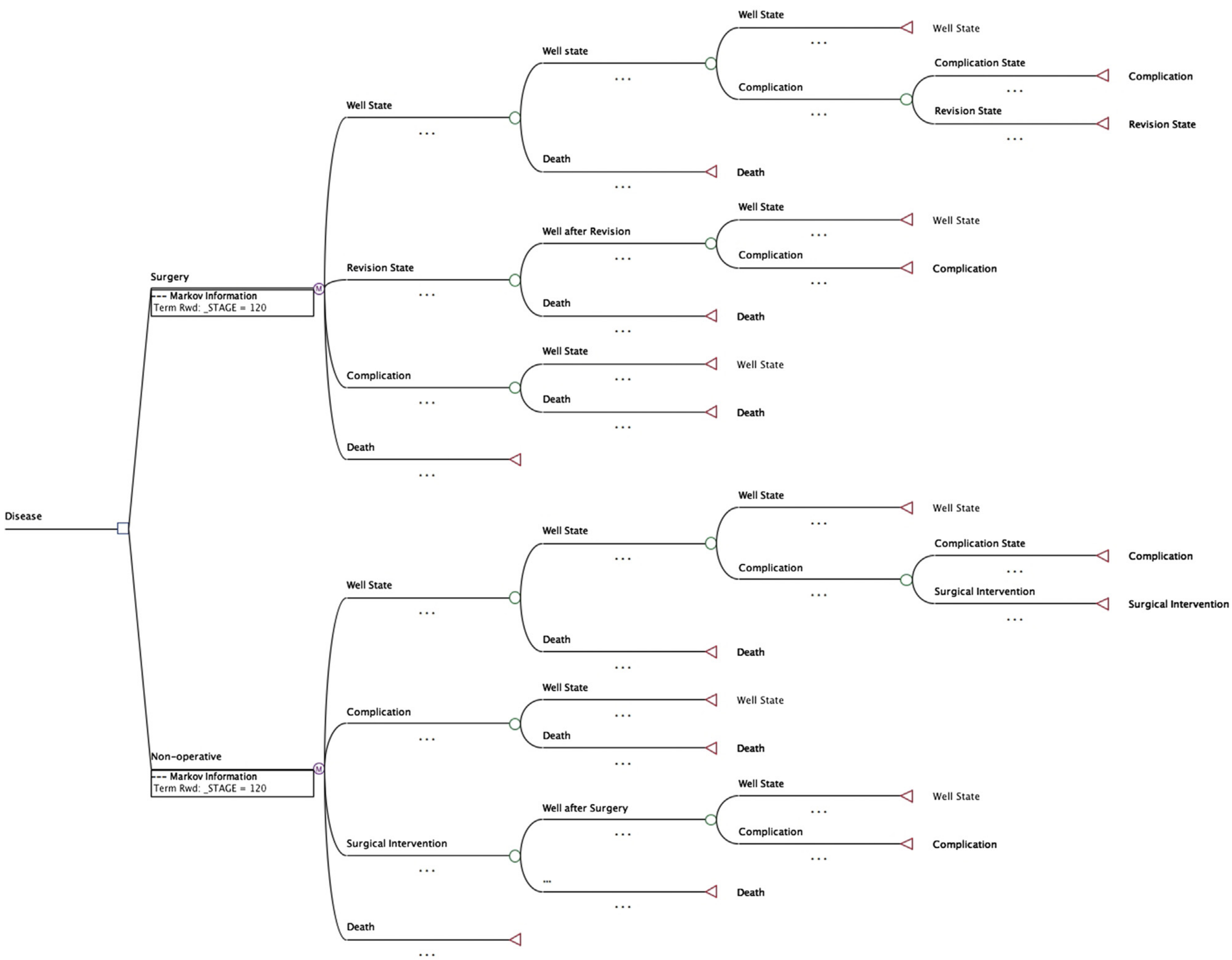

Fig. 3. Schematic representation of a generic Markov model demonstrating the discrete Markov states, chance nodes, and terminal nodes.

health state by the time spent in each health state, and then summing across all states that are experienced in the model [10]. Similar to the decision tree model, it is paramount that the assignment of outcomes be based on disease-specific evidence. A major criticism of the Markov model constructed by Furlan et al. [49] studying the effects of operative versus radiotherapy for the treatment of neoplastic epidural spinal cord compression was the lack of disease-specific outcomes values used within the model.

There are three evaluation methods for evaluating Markov models: fundamental matrix solution, Markov cohort simulation, and the individual Monte Carlo simulation [41]. The fundamental matrix solution was the original technique described by Beck and Pauker [40], although it has now been largely replaced for medical applications of decision analysis. The Markov cohort simulation remains the most commonly used technique for the analysis of Markov processes in the medical literature [41]. The simulation considers a hypothetical cohort of patients beginning the process distributed among the heath states of the model. For each cycle of the model, fractions of the cohort are allowed to move among the states as defined by the transition probabilities. This ultimately results in a new distribution of the cohort among the various states for the subsequent cycle. As the model progresses, more of the cohort transitions into the absorbable state until only a fraction of the cohort remains alive. The cumulative cost and cumulative utility are then able to be calculated.

For both decision trees and standard analyses of Markov models, the usual approach is to follow cohorts through particular states at various points in the model [50]. The Monte Carlo simulation uses an alternative approach as it allows the model to follow individual patients [51,52]. The values for each variable are randomly picked from a predefined distribution of possibilities. Using a Monte Carlo simulation allows for the result of the simulation to represent a sample of the population and all possible outcomes in the model [52]. The model is then run through multiple cycles, with each cycle using a different set of values for each variable. The use of distributions allows certain values to be chosen more frequently than others. Each patient begins in the well state, and at the end of each cycle, a random number generator is used together with the transition probabilities to determine in which state the patient will begin the next cycle. The patient is given credit for each cycle not in the dead state, and each state may be adjusted for quality of life. When the patient enters the dead state, the simulation is stopped. After a large number of trials, a range of expected values and the range of outcomes are expressed in the form of a density function.

Two examples of recent Markov models looking at the relative cost-effectiveness of ACDF and CDR are examples of more robust models published within the spine literature. The utilities in each study are derived from large multicenter RCTs, appropriate sensitivity analyses are performed, and robust cost accounting is provided.

McAnany et al. [53] published a Markov model comparing single-level ACDF and CDR. A 5-year time horizon was selected. Costs were denominated in 2010 dollars. Physician costs were based on a fixed percentage of 140% of 2010 Medicare reimbursement. Hospital costs were determined from the Nationwide Inpatient Sample. Utilities were derived from responses to health state surveys (Short Form 36) at baseline and 5 years from the treatment arms of the ProDisc-C trial. Incremental cost-effectiveness ratios were used to compare treatments. Cervical disc arthroplasty generated a total 5-year cost of $102,274, whereas ACDF resulted in a 5-year cost of $119,814. Cervical disc arthroplasty resulted in a generation of 2.84 QALYs, whereas ACDF resulted in 2.81. The ICER was −$557,849/QALY gained. Cervical disc arthroplasty remained the dominant strategy below a cost of $20,486. Anterior cervical discectomy and fusion was found to be a cost-effective strategy below a cost of $18,607. Cervical disc arthroplasty was the dominant strategy when the utility value was above 0.713. Cervical disc arthroplasty remained the dominant strategy assuming an annual complication rate less than 4.37%.

Ament et al. [54] constructed a similar model, although the authors were interested in looking at two-level ACDF versus two-level CDR. Data were derived from an RCT that followed up 330 patients over 24 months. Health states were constructed based on the stratification of the Neck Disability Index and a visual analog scale. Data from the 12-item Short-Form Health Survey questionnaires were transformed into utilities values using the Short Form-6D mapping algorithm. Costs were calculated by extracting diagnosis-related group codes from institutional billing data and then applying 2012 Medicare reimbursement rates. Cervical disc replacement (CDR) had an average of 1.58 QALYs after 24 months compared with 1.50 QALYs for ACDF recipients. Cervical total disc replacement was associated with $2,139 greater average cost. The ICER of CDR compared with ACDF was $24,594 per QALY at 2 years. Despite varying input parameters in the sensitivity analysis, the ICER value stays below the threshold of $50,000 per QALY in most scenarios (range, −$58,194 to $147,862 per QALY).

As described previously, Markov models provide a robust solution for the modeling of the natural history of chronic disease processes. However, Markov models are not without limitations. Inherent within a Markov model is a restriction that is known as the Markovian assumption or the Markov property [15]. In general, the Markov property holds that the behavior of the process subsequent to any cycle depends only on its description in that cycle. The process has no memory of past events, and the current state of health in that cycle is the only parameter used to predict state transition probabilities. This assumption is often violated in real-world health-care management, as physicians will use past information to dictate treatment decision-making. Another limitation of Markov models is the requirement to operate with cycles of fixed length [15]. This limitation can be overcome with the use of Monte Carlo simulation, where a patient may remain in a given state for variable amount of time.

Discussion

Medical economic modeling represents the paradigm shift toward value-based health care. The use of these models is increasing within the literature. Although policy decisions are not directly mandated from the results of these studies in the United States, there is a belief supported by Raftery [2] that decision economic modeling in the United States will follow other countries such as the United Kingdom whereby all coverage decisions regarding health-care technology must include an economic analysis using complex mathematical modeling to determine its relative cost and benefit. Within spine surgery, we are at the forefront of emerging technology, both from instrumentation and orthobiologics standpoints, and the individual surgeons' decision and utilization patterns will come under increasing scrutiny moving forward.

This review article has provided a general overview of the types of models that are frequently used with the spine literature. For the most part, the majority of studies have been simple decision trees. In recent years, there has been an increasing utilization of the more powerful Markov model, which allows for greater flexibility in modeling chronic disease processes. Common to both decision trees and Markov models are several important aspects: utility values derived from high-quality studies such as RCTs; transition probabilities derived from systematic review of the literature; and costs data that are reproducible and takes into account both direct and indirect costs.

Of the 19 studies reviewed in this article, there was considerable variability in the methodology used to generate all the values used to populate the model. Several studies excluded reporting the results of a sensitivity analysis. The sensitivity allows for one to validate the input variable across a reasonable spectrum to determine threshold values whereby which cost, effectiveness, and transitions can likely be found. An inability to report the results of a sensitivity analysis can impact both the reproducibility and integrity of the results of a model.

There was also considerable variation in the methods used to derive costs in the models. For instance, McAnany et al. [53] used the Nationwide Inpatient Sample and a multiple of Medicare to regenerate direct costs in their Markov model comparing single-level ACDF with CDR. The authors did not include an accounting of indirect costs. In contrast, Ament et al. [54] produced cost data based on diagnosis-related group codes form institutional billing data applying 2012 Medicare reimbursement rates while also including the costs associated with complications and the time to return to work. The inclusion of indirect costs allows for a more accurate accounting of the true costs that can be expected over the lifetime of the model. In general, most studies use Medicare reimbursement information. This is likely directly related to the relative ease in obtaining this information. Individual hospital or practitioner cost data may not be as reliable given substantial local and regional variation in charges and reimbursements. Furthermore, cost-to-charge- ratios vary by hospital and provide another source of potential confounding.

Appropriate transition probabilities are the third key component to creating a successful economic model. Transitions between health states (Markov model) or the probability of success versus complication (decision tree) are the principle drivers of the model as these numbers determine how an individual patient would travel through the model. Incorrect probabilities could lead to a patient spending too much time in a particular health state (Markov model) or inappropriately moving into the wrong node within a decision tree. To ensure that these probabilities are as accurate as possible, it is often necessary to perform a systematic review of the literature. As noted by Edwards et al. [4], no one's study captures all the data that are required to make a best care decision. It is through the pooling of the existing evidence-based literature that one can provide the support for a choice within an economic model.

Looking to the future, the use of microsimulation techniques, such as Monte Carlo simulation, will allow authors to use an alternative approach by following individual patients. The values for each variable within the simulation are randomly picked from a predefined distribution of possibilities. Using a Monte Carlo simulation allows for the result of the simulation to represent a sample of the population and all possible outcomes in the model. In other words, instead of specifying exact values for each property, we can specify approximate values within some ranges and let the simulation search through possibilities. After thousands of cycles, a distribution of values is obtained allowing one to understand the range and most plausible distribution of values.

Conclusions

There is a growing body of literature within the field of spine, using the mathematical modeling techniques described in this review. These decision analytic models represent powerful tools both in the assortment of competing treatment options and potentially in the formulation of policy and reimbursement. It remains important that investigators using these techniques adhere to the strict guidelines set forth by Gold et al. [55] regarding the proper use of cost-effectiveness studies.

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