

Cost-effectiveness of surgery for drug-resistant temporal lobe epilepsy in the US

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Abstract

Objective

Surgery is an effective but costly treatment for many patients with drug-resistant temporal lobe epilepsy (DR-TLE). We aim to evaluate whether, in the United States, surgery is cost-effective compared to medical management for patients deemed surgical candidates and whether surgical evaluation is cost-effective for patients with DR-TLE in general.

Methods

We use a semi-Markov model to assess the cost-effectiveness of surgery and surgical evaluation over a lifetime horizon. We use second-order Monte Carlo simulations to conduct probabilistic sensitivity analyses to estimate variation in model output. We adopt both health care and societal perspectives, including direct health care costs (e.g., surgery, antiepileptic drugs) and indirect costs (e.g., lost earnings by patients and care providers.) We compare the incremental cost-effectiveness ratio to societal willingness to pay (~\$100,000 per quality-adjusted life-year [QALY]) to determine whether surgery is cost-effective.

Results

Epilepsy surgery is cost-effective compared to medical management in surgically eligible patients by virtue of being cost-saving (\$328,000 vs \$423,000) and more effective (16.6 vs 13.6 QALY) than medical management in the long run. Surgical evaluation is cost-effective in patients with DR-TLE even if the probability of being deemed a surgical candidate is only 5%. From a societal perspective, surgery becomes cost-effective within 3 years, and 89% of simulations favor surgery over the lifetime horizon.

Conclusion

For surgically eligible patients with DR-TLE, surgery is cost-effective. For patients with DR-TLE in general, referral for surgical evaluation (and possible subsequent surgery) is cost-effective. Patients with DR-TLE should be referred for surgical evaluation without hesitation on cost-effectiveness grounds.

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Glossary

ASM = antiseizure medications; **DR-TLE** = drug-resistant temporal lobe epilepsy; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life-year; **WTP** = willingness to pay.

The clinical effectiveness of surgery in well-selected patients with drug-resistant temporal lobe epilepsy (DR-TLE) has been well established by at least 2 large randomized controlled trials,^{1,2} a major systematic review by the American Academy of Neurology,³ and a model-based comparative effectiveness analysis.⁴ In addition, it has been suggested that successful surgery may reduce some of the costs associated with epilepsy, especially in the long run.⁵ While surgery may be cost-saving for individual patients who achieve seizure freedom after surgery, it has yet to be established that evaluation for surgery is cost-effective for an entire cohort of patients with DR-TLE given that a meaningful proportion of patients will not be offered surgery and a substantial subset of those who receive surgery will not achieve seizure remission. Consequently, practitioners may be hesitant to refer patients for evaluation in light of the substantial upfront cost associated with presurgical testing and the lack of guarantee that the patient will be found eligible for surgery. Early investigation into the cost-effectiveness of epilepsy surgery in the United States was conducted in the 1990s,⁶ but there were important limitations. Data were not available to model long-term outcomes after surgery, necessitating use of expert opinions, and societal costs of the disease were not included. More recent investigations have been conducted in countries with nationalized health care systems,^{7,8} but the cost-analyses are of limited utility in the US health care context.

The objectives of this study are to evaluate the cost-effectiveness of surgery for patients deemed surgical candidates and to further evaluate whether referral for surgical evaluation is cost-effective for patients who may be potential surgical candidates. The target population is adult patients with DR-TLE, and the definitive interventions being compared are surgical resection and continued medical management. We use a model-based analysis with a lifetime time horizon, from both health care and societal perspectives.

When comparing 2 treatment strategies for a disease, we may determine that a given strategy is cost-effective if it meets 1 of the following criteria: (1) the strategy is more effective than the alternative and reduces costs, or (2) the strategy is more effective than the alternative, at a higher cost, which is deemed reasonable. To adjudicate whether the higher cost associated with a treatment strategy is reasonable, it is possible to compare the incremental cost-effectiveness ratio (ICER) for the strategy to the societal willingness to pay (WTP), both of which are expressed as dollars per additional quality-adjusted life year (QALY). A single QALY represents a year of life in perfect health. The ascribing of specific QALY values to individual health states (e.g., having uncontrolled seizures) is

based on patient surveys in which patients are asked to assign utility scores to different states of disease/health. While there is no universal figure for societal WTP, a range should be considered.⁹ In the United States, figures between \$50,000 and \$150,000 per QALY are reasonable.^{10,11}

Methods

Patient population

Our analyses are based on meta-analysis of existing literature concerning adult patients with DR-TLE. Parameter estimates are derived from pooled estimates from multiple component studies with some heterogeneity in the patient characteristics between studies; the results of our model concern adult patients diagnosed with temporal lobe epilepsy who continue to have seizures despite adequate trials of ≥ 2 appropriately selected antiseizure medications (ASM) (i.e., drug resistant). Due to the nature of the component studies on this topic, the model is optimally informative for patients with lesional disease receiving anterior temporal lobectomies. There is variation in the average age of adult patients included in the epilepsy surgery literature from which parameter estimates were extracted for the present study, but a base-case assumption of 35 years (SD 11 years) is reasonable.⁴

Analytic model

A model-based analysis was performed using a Markov decision-analytic model. For the primary analysis (model 1), we aimed to determine whether surgery was cost-effective compared to continued medical management in patients who had been deemed surgical candidates; thus, the baseline assumption was that a patient with DR-TLE had undergone surgical evaluation and had been deemed a candidate for surgery (figure 1A). For the secondary analysis (model 2), we aimed to determine whether it was cost-effective to evaluate patients with DR-TLE for surgery; thus, the baseline assumption was simply that a patient had been diagnosed with DR-TLE (figure 1B).

The model simulates several possible courses of treatment for the patients of interest. The patient could either receive surgery or continue medical management. If surgery is chosen, the patient could have either a permanent major complication (including hemiparesis or disability after surgery), perioperative death, or no major complication. After allocation into 1 of these 3 major categories, patients fall into 1 of 2 pre-specified health states (free or not free of consciousness-impairing seizures) for a series of 1-year cycles until death. Patients could transition between these health states from year to year (Markov modeling). Patients could also die

Figure 1 Diagram of Markov decision-analytic model used for primary analysis (model 1)

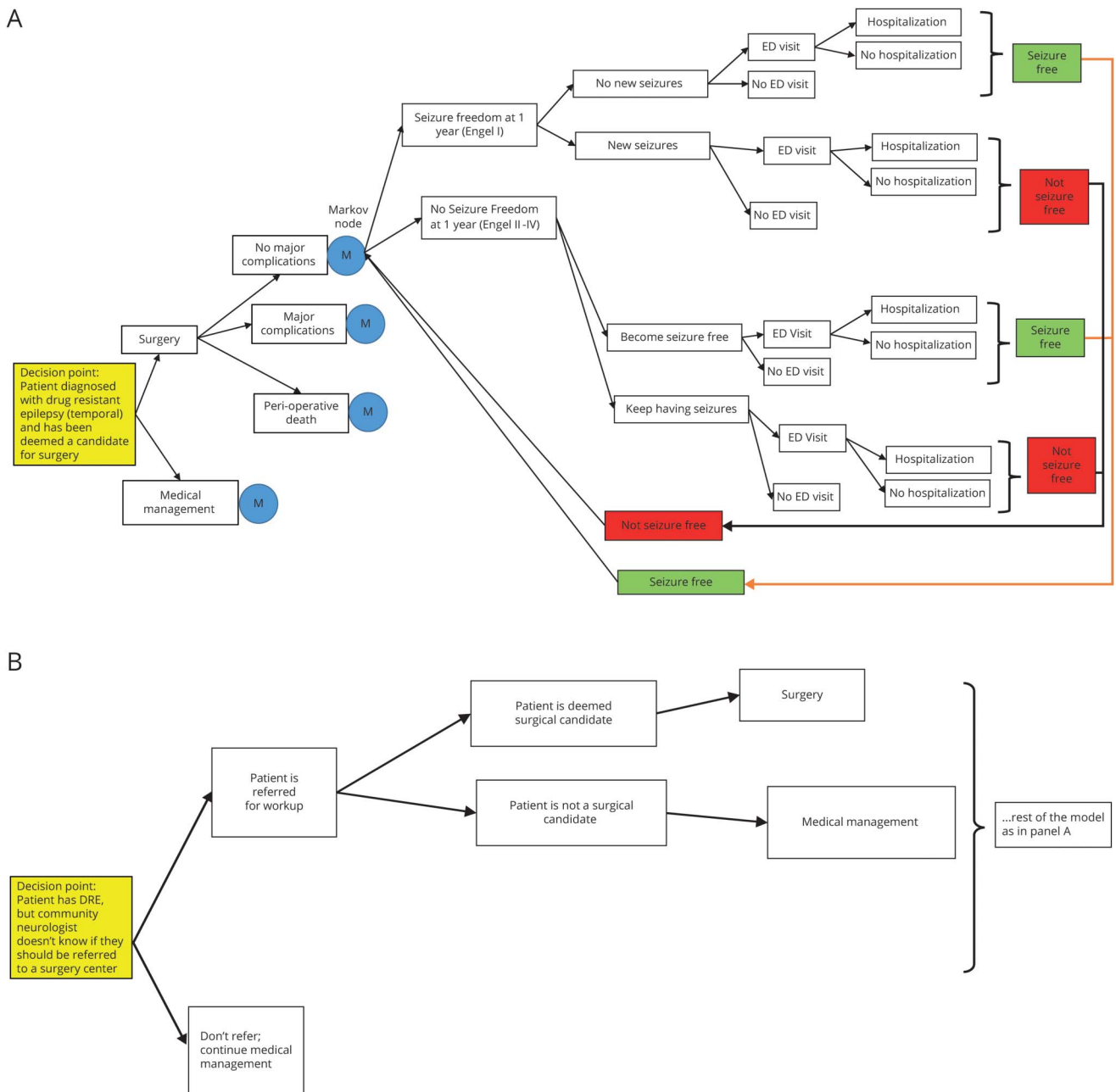


Illustration of the primary and secondary models developed to study cost-effectiveness. (A) Diagram shows the structure of the decision-analytic model used for cost-effectiveness analysis in patients with DR-TLE deemed to be surgical candidates. The M nodes represent Markov nodes that are built into the decision tree, allowing the creation of iterative loops (1-year cycles) during which patients can transition between health states. The 3 health states are seizure-free, having seizures, and dead (not shown). Each branch of the tree is annotated with an average estimate and a probability distribution, allowing probabilistic sensitivity analysis (Monte Carlo simulations). (B) Diagram of the decision-analytic model used for secondary analysis (model 2). The decision-analytic model was restructured as shown in this diagram in order to conduct the secondary analysis (evaluating whether referral for surgical evaluation is a cost-effective strategy). DRE = drug-resistant epilepsy; ED = emergency department.

during each yearly cycle, with a risk of death calculated from the age-adjusted baseline mortality rate and their seizure status. On the basis of their course in the model, patients would also incur costs associated with their care, including 1-time fixed costs such as surgery, as well as iterative yearly costs such as annual outpatient visits. Each branch of the model is annotated with an estimated probability derived from the literature. The reportable outcomes from our model

include life expectancy, quality-adjusted life expectancy, total costs, and ICER.

The outcomes from our model are based on parameter estimates; thus, it is important to quantify the variability in model predictions on the basis of these estimates. We conducted 1-way sensitivity analysis on all variables in the model. Furthermore, we used the Monte Carlo simulation method to

conduct probabilistic sensitivity analysis, which allows us to quantify the variability in the model output produced by simultaneous variation in all model variables. To conduct this type of sensitivity analysis, we used a probability distribution (mean and 95% confidence interval) for each estimated probability in the model. We then simulated cohorts of 10,000 patients (i.e., 10,000 second-order Monte Carlo simulations). The reportable outcomes of this sensitivity analysis include acceptability curves, incremental cost-effectiveness scatters, and proportion of simulations favoring surgery.

Data

Clinical parameters

Clinical parameters used in the model are shown in table 1. A strong comparative effectiveness analysis on this topic has been published,⁴ and clinical parameters have been derived using extensive literature review and meta-analytic methods (random-effects model); we were able to use many of their clinical parameters for our model.^{1,12–30} Thus, the parameter estimates in our model represent the pooled and appropriately weighted averages of several component trials and case series. We were not aware of previously published reports on the frequency of emergency department visits and hospitalizations in this patient population and thus analyzed use data from the Cleveland Clinic for these parameters. The normal distribution was used to model clinical parameter estimates, except when doing so produced implausible probability estimates (i.e., probability <0% or >100%). In the latter cases, the beta distribution was used.

Mortality tables

We used the latest mortality tables available from the US Census Bureau. The risk of mortality for a patient in our model in a given year is equal to the age-adjusted risk of death multiplied by a standardized mortality ratio, which is determined by the patient's seizure status (table 1).

Preference-based utility (quality of life) scores

We use previously reported preference-based utility scores from patients surveyed at the Columbia University Medical Center using the standard gamble approach⁴ (table 1). Estimates were modeled with uniform distributions.

Health care costs

We used a bottom-up costing strategy to estimate costs of care whereby costs were modeled by creating standardized packages of care including all the component health care services that patients typically receive in their course. We developed care packages for surgical evaluation, surgery, medical management, emergency department visits, and hospitalization. The individual services included in each package are shown in table 2. There is poor standardization in cost-effectiveness literature for the question of which type of costs (hospital costs vs public payer reimbursement vs charges) should be used for analysis in the United States. Panel guidelines support the general recommendation of using costs that reflect

the monetary cost to society, but a universal methodologic approach is not apparent.⁹ We recognize the merits of using public payer reimbursements, so we have included estimates based on Centers for Medicare & Medicaid data in table 2. These estimates were generated with the method described by Flowers et al.³¹ There are important limitations to using these data in the present study. First, only a subset of patients with epilepsy are Medicare recipients. Second, when we compared Medicare reimbursements to the true costs of services at our center, there were clear disparities. This observation is in line with the well-documented phenomenon that Medicare reimbursement often covers only a fraction of the cost of providing services at hospitals. For the model analysis, we used internal patient-level costs for each service provided. While these service costs cannot be published for proprietary reasons, they carry significant benefits over using publicly available reimbursement estimates. First, they are payer insensitive and represent the real cost to the hospital of providing a given service, as opposed to the charges assessed to a payer or the postnegotiation reimbursement. Second, this method allows a robust estimation of costs for a given service that does not vary with peculiarities of coding and billing methods across individual centers. Finally, the costs of services used in the model are considerably higher than the Centers for Medicare & Medicaid estimated reimbursements. Thus, our choice of using internal costs favors the medical treatment arm in the analysis. Costs are modeled with gamma distributions.

Drug costs

There is no standard drug therapy for epilepsy, and patients with drug-resistant epilepsy are placed on an extremely wide range of drug regimens, which significantly complicates the task of modeling baseline drug costs. To overcome this issue, we manually reviewed electronic medical records of 100 randomly selected drug-resistant patients who received care at our center in the last decade (Appendix figure 1A, available in Dryad, doi.org/10.5061/dryad.kpr4xh1m). We use drug costs from the Federal Supply Schedule with appropriate adjustment (1.21 adjustment factor), as recommended by the Health Economics Resource Center.³² These amounts represent the cost of drugs to the health care system, not out-of-pocket costs to patients (which are highly variable). Analysis of drug costs of the medical regimens from our patient sample showed a significantly right-skewed distribution with a mean value of \$21,772/y and SD of \$19,144/y (Appendix figure 1B).

We recognize that the question of when to discontinue medications in seizure-free surgical patients is an ongoing area of debate, and no broadly adopted consensus guidelines are yet available.^{33–35} Previously published estimates of ASM use after epilepsy surgery show that at least 62% of patients have some kind of postoperative reduction in ASM use, and ≈21% have discontinuation.³⁶ In our model, patients who are seizure-free after surgery continue to take medications for 2 years after surgery, after which they are transitioned to monotherapy (levetiracetam 1,000 mg) as long as they remain

Table 1 Clinical parameters

Variable	Probabilities, %	Reference
Becoming seizure-free during first year		
Medical management	8 (0–16)	1
Surgery	71.9 (69.5–74.3)	1, 10–21 ^a
Seizure relapse if seizure-free at end of year 1		
Medical management	25.4 (10.9–46.2)	22
Surgery	5.6 (2.9–8.3) for years 1–5, 4.2 (1.6–6.8) for all subsequent years	1, 12, 16, 21, 23 ^a
Seizure remission if not seizure-free at end of year		
Medical management (years 1–5)	4.7 (3–7) for years 1–5, 1.6 (1–2.3) for all subsequent years	22
Surgery (years 1–5)	5.9 (0.9–11) for years 1–5, 2 (0.2–7.2) for all subsequent years	11, 12 ^a
Surgical complications		
Surgical mortality (temporal)	0.3 (0–7.5)	3
Permanent complication (temporal)	4 (2–6)	
Standardized mortality ratios		
Seizure-free	1.1 (0.6–1.9)	24, 25 ^a
Not seizure-free (after surgery)	5.6 (3.5–9.1)	
Not seizure-free (after medical management)	5.4 (4–7.4)	26–28 ^a
Rate of emergency department visits		
Patients with seizures, medical arm	0.9 (0.6–1.3)	Internal data
Patients without seizures, medical arm	0.4 (0.1–0.6)	
Patients with seizures, surgical arm	0.7 (0.4–1)	
Patients without seizures, surgical arm	0.1 (0–0.22)	
Percentage of patients admitted to the hospital from the emergency department	11 (7.9–13.7)	
Patient reported quality of life (utility) scores (standard gamble method)		
Seizure-free	4	
Medical	0.96 (0.84–1)	
Surgery, no major complication	0.97 (0.87–1)	
Surgery, major complication	0.77 (0.32–1)	
Not seizure-free		
Medical	0.75 (0.38–1)	
Surgery, no major complication	0.78 (0.41–1)	
Surgery, major complication	0.66 (0.19–1)	

Clinical parameters used for the model-based analysis. All probabilities are listed as mean (95% confidence interval).

^a The probability estimates are taken from the meta-analysis conducted by Choi and colleagues.⁴ Internal data for emergency department visits are derived from a prospective patient outcomes registry at our center and include visits for both seizure- and non-seizure-related reasons. The risk of death for a patient in a year of the simulation is equal to the age-adjusted risk of death for that patient (based on US Census Bureau data, not shown here) multiplied by the standardized mortality ratio based on the patient's seizure status.

Table 2 Cost estimates

Package	Service	Medicare reimbursement estimates (publicly available data), \$	True cost to large tertiary care hospital
Surgery	EEG (outpatient, no video)	663	Internal data from Cleveland Clinic
	EEG (inpatient, with video, 4.6-d stay in epilepsy monitoring unit)	6,431	
	Brain MRI (rate listed per study, patients receive 3 studies)	503	
	PET-CT	1,395	
	MEG	1,334	
	Neuropsychology (per hour, patients receive ≈12 h)	123	
	Surgical resection	20,054	
	6-mo outpatient follow-up	266	
	Cost of medications for 2 y	See text	
Surgical evaluation	Same as surgical package but not including cost of surgical resection, postsurgical follow-up, or medications	10,449	
Medical management	Outpatient follow-up (rate listed per visit, patients have 2 visits/y)	266	
	Cost of medications (annually)	See text	
Emergency department visit	Baseline emergency department visit cost	697	
	Head CT	267	
	CBC + CMP	19	
	Serum drug levels (per test rate calculated as average for valproate, phenytoin, carbamazepine, lamotrigine, levetiracetam, zonosamide) (rate listed as per test cost, patients receive serum tests for 3 drugs)	15	
	Outpatient follow-up	266	
	Sum	1,264	
Hospitalization	Based on DRG code of seizures, average length of stay 2.6 d	4,774	
Societal costs		Annual cost (\$)	Reference
Reduction in labor market earnings in patients with uncontrolled seizures		23,635	38
Reduction in labor market earnings in patients with controlled seizures		13,342	
Reduction in domestic productivity in patients with uncontrolled seizures		799	
Reduction in domestic productivity in patients with controlled seizures		1,482	
Loss of earnings in a patient, i.e., disabled after surgery		61,858	Current Population Survey 2017, Census Bureau
Lost productivity of care providers		11,678	39

Abbreviations: CBC = complete blood count; CMP = Comprehensive Metabolic Panel; DRG = diagnosis-related group; MEG = magnetoencephalography. Cost estimates for health care services, drugs, and social costs. Service costs are listed as estimates of Medicare reimbursement based on publicly available Centers for Medicare & Medicaid data. However the model used true service costs at the Cleveland Clinic (see Methods for discussion of comparison in costs of service delivery between the data sources). All dollar amounts are in 2019 equivalents.

seizure-free. To ensure that the analysis was robust to variation at this point, we modeled probability of having to continue medications in seizure-free surgical patients as a variable with a wide range (0.2–0.8) and conducted 1-way sensitivity analysis on it (the model recommendations were not sensitive to variation within this range).

Societal costs

Following recommendations, we include a societal reference case including both health care costs and non-health care costs.⁹ This is appropriate because previous studies have suggested that the bulk of costs associated with epilepsy are indirect costs.³⁷ We include 4 major societal costs in our

analyses: reduction in labor market earnings in patients with controlled and uncontrolled seizures, reduction in domestic productivity in patients with controlled and uncontrolled seizures, lost productivity of care providers, and lost earnings of patients disabled after a permanent complication associated with surgery (table 2). Data for the first 3 of these categories are derived from the existing literature and are based on actuarial methods for estimating lost earnings attributable to epilepsy.^{38,39} The estimate of lost earnings in patients disabled after surgery is derived from the Current Population Survey (2017) assuming that patients were earning the median annual income before surgery. All patients are assumed to retire at the age of 65 years.

All cost data are adjusted to 2019 dollar equivalents using the Consumer Price Index for health care from the Bureau of Labor Statistics. We use a standard half-cycle correction for our Markov process. We modeled global discount rate as a variable with a normal distribution (with a mean of 3%) and included this variable in sensitivity analyses.

Data availability

As detailed above, we have used data from published literature to populate the decision-analytic model; the parameter estimates can thus be replicated by referring to the cited literature.

Results

Model validation

While there is no firm consensus on how to assess the validity of cost-effectiveness models,⁴⁰ panel guidelines recommend internal validation (i.e., the model is responsive to chosen parameters) and external validation (i.e., model predictions are comparable to outside observed data that were not used in model construction).⁹

Internal validation

We compared the life expectancy and quality-adjusted life expectancy estimates generated by our model to published estimates⁴ that used similar clinical parameters. Our results are very similar, suggesting that our model is responsive to the parameters we have chosen (Appendix figure 2, A and B, doi.org/10.5061/dryad.kpr4xh1m).

External validation

We compared the survival curves of a simulated cohort in our model with the observed survival curves in a longitudinal study.⁴¹ Comparison shows that the modeled survival curves are virtually identical to observed survival curves in the surgical arm (Appendix figure 3, A and B, doi.org/10.5061/dryad.kpr4xh1m). In the medical arm, however, the survival curves from our model overstate seizure-free survival associated with medical management. This is apparent from the modeled survival curve of medically managed patients wherein the proportion of seizure free patients in the cohort

actually increases over the first 8 years of the simulation before decreasing toward zero (Appendix figure 3B). In reality, the proportion of seizure-free patients decreases as early as the second year of observation.⁴¹ For further verification, we compared our model-generated 5-year and 10-year seizure-free survival estimates after surgery with those in the published literature. Our model estimates 62% and 53% seizure-free survival at 5 and 10 years, respectively. These estimates are well within the ranges expected from the published literature: 5-year seizure-free survival between 50% and 75% and 10-year seizure-free survival between 41% and 66%.⁴²

Primary analysis

Model results

The results of the cost-effectiveness analysis for both models are tabulated in table 3. In interpreting these data, it is important to underscore that the 2 models are informative for 2 conceptually distinct questions. While model 1 answers the question of whether surgery is cost-effective in patients who have already been found to be surgical candidates after extensive evaluation, model 2 answers the question of whether referral for surgical evaluation (with the possibility of subsequent surgery) is cost-effective among patients with a diagnosis of DR-TLE. These data suggest that, among patients who have already been found to be eligible for surgery, surgery is the cost-effective strategy from both the health care and societal perspectives. Among patients diagnosed with DR-TLE who may or may not be surgically eligible, referral for surgical evaluation is the cost-effective strategy from both the health care and societal perspectives. In fact, over the lifetime time horizon for the simulated cohort, these strategies actually become cost-saving in addition to being more clinically effective.

Figure 2 shows how the ICER changes over time for both models. This method of data representation allows us to answer the question of how long a given strategy would have to be adapted before it became cost-effective for the simulated cohort. For patients who are surgically eligible, surgery becomes cost effective within 3 to 4 years (depending on whether we consider the societal or health care perspective.) For patients diagnosed with DR-TLE, referral for surgical evaluation becomes a cost-effective strategy for the cohort within 5 to 7 years. Notably, both these strategies become cost-effective more rapidly when we adopt a societal perspective, which is consistent with the significant societal costs associated with uncontrolled seizures.

Probabilistic sensitivity analysis

Figure 3 shows the incremental cost-effectiveness scatters produced when 10,000 second-order Monte Carlo simulations of the models were generated from societal and health care perspectives. Each dot in the scatter represents a separate simulation; whenever a dot falls to the right of (i.e., below) the WTP line, the model recommends surgery. When the simulations are run until cohort death (i.e., lifetime time horizon),

Table 3 Results of decision-analytic model

	Strategy	Cost, thousands USD, discounted	Difference in costs, discounted USD	Effectiveness, discounted QALYs	Difference in effectiveness, discounted QALYs	ICER, \$/QALY	Winning strategy
Model 1: is surgery cost-effective in patients deemed surgically eligible?							
Health care perspective	Medical	423	95	13.6	- 3	-31,667	Surgery
	Surgery	328		16.6			
Societal perspective	Medical	1,007	184	13.6	- 3	-61,333	Surgery
	Surgery	822		16.6			
Model 2: is referral for surgery cost-effective in patients with DR-TLE?							
Health care perspective	Continue medical management	408	15	14.5	- 0.9	-16,667	Refer for surgical evaluation
	Refer for surgical evaluation	423		13.6			
Societal perspective	Continue medical management	682	3	14.6	- 0.9	-3,333	Refer for surgical evaluation
	Refer for surgical evaluation	685		13.7			

Abbreviations: DR-TLE = drug-resistant epilepsy of the temporal lobe; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; USD = US dollars.

Estimates of costs and effectiveness generated by the model from different analytical perspectives. Results for model 1 (which answers the question, "Is surgery cost-effective among surgically eligible patients?") and model 2 (which answers the question, "Is surgical-evaluation cost-effective in patients with DR-TLE?") are shown separately. By convention, differences in effectiveness are calculated as follows: (effectiveness of medical arm) – (effectiveness of surgical arm). Thus, a negative value in the Difference in Effectiveness column indicates that surgery is more effective. Similarly, a negative value in the ICER column indicates that surgery/surgical referral is cost-effective.

84% of simulations recommend surgery among surgically eligible patients from the health care perspective, and 89% of simulations recommend surgery from the societal perspective. Among patients with DR-TLE who have not yet received surgical evaluation, 80% of simulations favored referral from the health care perspective, and 78% favored referral from the societal perspective. Figure 4 shows acceptability curves that demonstrate variation in the proportion of simulations that recommend surgery at different thresholds of WTP. These data demonstrate that surgery and referral for surgical evaluation would be cost-effective strategies across a wide range of WTP thresholds.

One-way sensitivity analysis

All variables included in the model were subjected to sensitivity analysis. The model was sensitive to 1-way variation for 5 variables. Surgery would not be cost-effective if any of these 5 conditions were met:

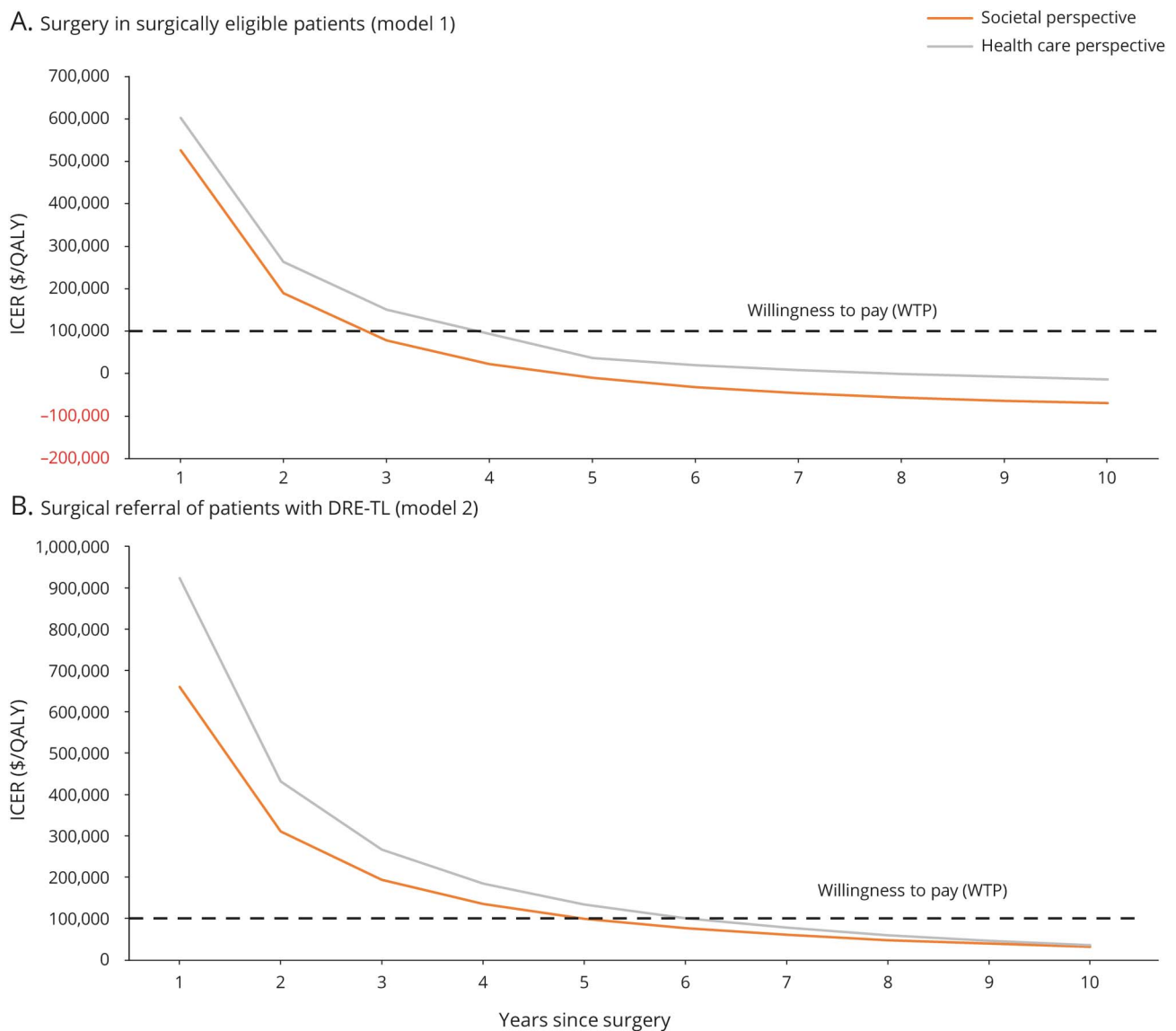
1. The true probability of initial seizure freedom after surgery was <21% (data-derived estimate used in model is 71.9%)
2. The true probability of relapse after initial surgical success was >27% (data-derived estimate used in model is 5.6%)
3. The patient's age was >97 years
4. The cost of surgery was >5 times our estimated cost
5. The true proportion of patients who were found to be eligible for surgery after initial surgical referral was <5% (at our center, the proportion of referred patients who are found to be surgically eligible is between 20% and 40%)

Notably, the sensitivity analysis did not show that the model recommendation was sensitive to 1-way variation in the probability of having to continue medications in seizure-free surgical patients. Even if only 20% of seizure-free surgical patients were able to discontinue medications (with no other reductions in ASM use in postsurgical patients), the ICER was below societal WTP.

Discussion

Our reference case results suggest that surgery is both cost-saving and more effective in the long run for surgically eligible

Figure 2 ICER vs time plot for surgery and referral for surgery



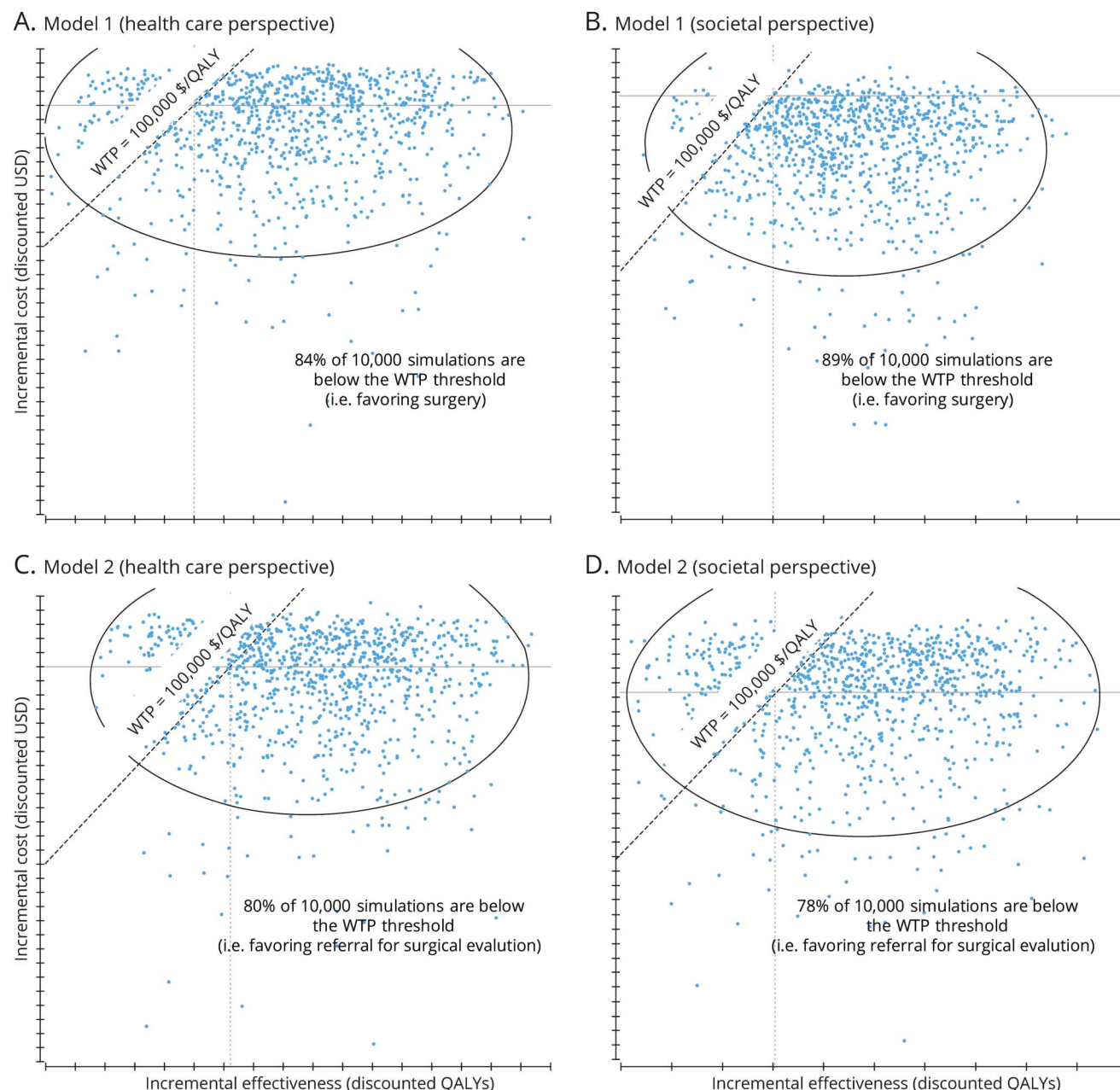
(A) Curves show how the incremental cost-effectiveness ratio (ICER) varies with time from surgery in patients found eligible for surgery. (B) Curves show how the ICER varies with time from surgical referral (and possible subsequent surgery) in patients with drug-resistance temporal lobe epilepsy (DR-TLE). Results of the analysis from the societal (orange) and health care (gray) perspective are shown. Negative values of ICER occur when surgery becomes cost-saving compared to medical management. QALY = quality-adjusted life-year.

patients and that referral for surgical evaluation is cost-effective for patients with a diagnosis of DR-TLE. The recommendation for surgery can be made from both the health care perspective and the societal perspective, although it is notable that surgery becomes cost-effective at a faster rate when viewed from a societal perspective. Referral for surgical evaluation is likely to be cost-effective even if there is only a small ($\approx 5\%$) probability that the patient is a surgical candidate. A key clinical implication of our study is that a strong cost-effectiveness argument favors referral of patients with DR-TLE for surgical evaluation. It is important to recognize that this is the same recommendation made by previously reported decision-analytic tools that made recommendations on the basis of clinical effectiveness alone.⁴³ Taken together,

these studies show a concordant recommendation for referral based on both clinical and cost-effectiveness grounds.

Previous work has repeatedly demonstrated that epilepsy surgery is likely underused across the world, including in developed nations,^{44–46} and this trend has been slow to change despite consensus recommendations and guidelines.⁴⁷ There are multiple reasons that community practitioners may be hesitant to refer patients for surgical evaluation, including a lack of familiarity with the safety profile of the procedure and the chances of postoperative success and a misunderstanding of the evidence-based definition of drug resistance.⁴⁸ The vast majority of neurologists ($>75\%$) also cite a lack of health care resources as a major barrier for surgical evaluation.⁴⁸ It is not

Figure 3 Results of probabilistic sensitivity analysis



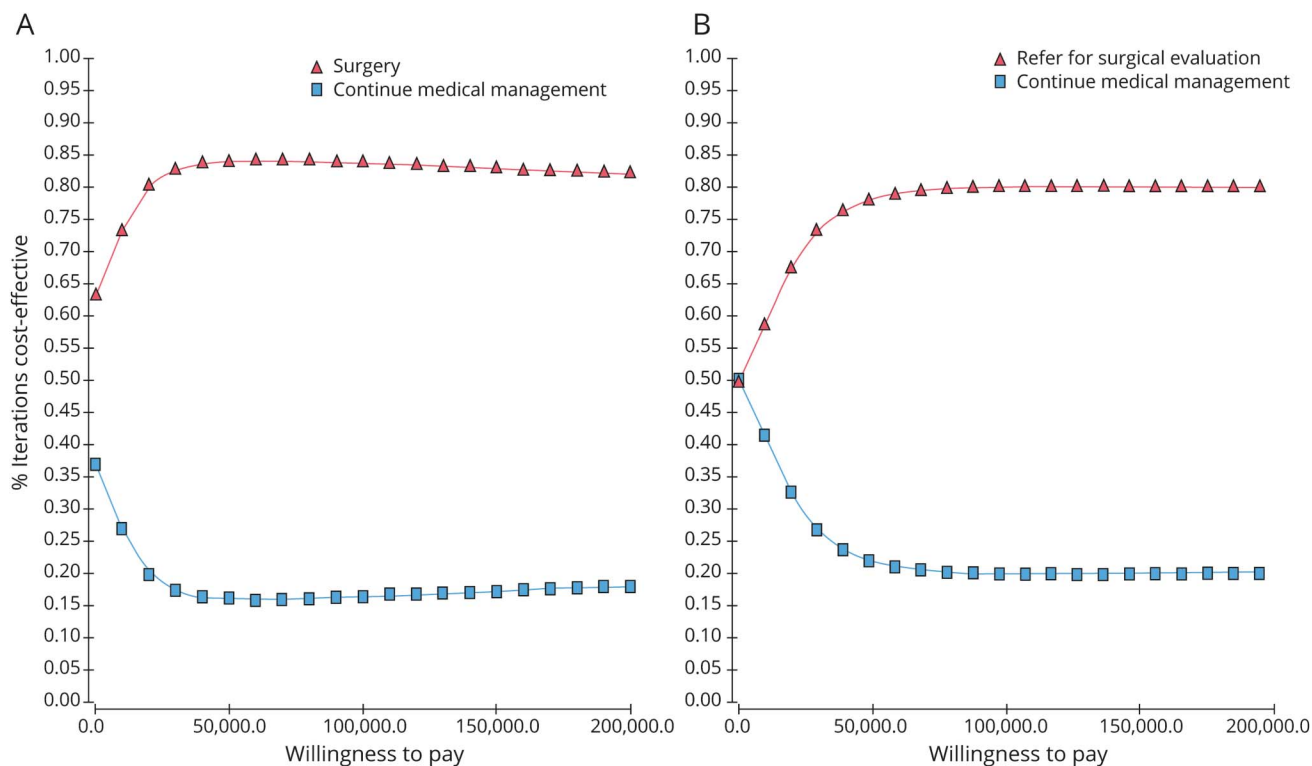
Scatterplots (A–D) show the results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) of the decision-analytic models. Each blue dot represents the results of an individual simulation. Whenever a dot falls to the right of (below) the willingness to pay (WTP) line, the model would find surgery (model 1) or referral for surgical evaluation (model 2) to be cost-effective. QALY = quality-adjusted life-year; USD = US dollars.

uncommon, in our experience, for practitioners to express concern about the potential futility of a costly surgical evaluation for patients with epilepsy who are not offered surgery, expressing regret at the “wasted” health care resources and the inconvenience of extensive workup for the patient. In direct response to this notion, our work suggests that rather than being hesitant to offer surgical evaluation to drug-resistant patients due to substantial upfront cost, we should recognize that a referral-based strategy is the cost-effective one; the upfront cost is absolutely reasonable in patients with even a low chance of being surgical candidates and is likely cost-

saving for patients with high probability of being surgically eligible.

Only a small number of cost-effectiveness studies have been conducted on the topic of epilepsy surgery, only 1 of which, to the best of our knowledge, was in the US health care context. Langfitt⁶ published a study in 1997, far before the majority of outcomes studies in this context had been reported. Langfitt noted at the time that the paucity of data resulted in an inability to model transitions between health states and noted that the use of Markov modeling (as we did here) would allow

Figure 4 Acceptability curves for surgery and referral for surgery strategies



Acceptability curves are generated by running a set of 10,000 simulations for a range of willingness to pay (WTP) and charting the proportion of simulations at each threshold that favor a surgical or medical strategy. For any 1 value of WTP on the horizontal axis, the proportion of simulation recommending surgery and medical management adds up to 1. (A) Acceptability curves for surgery in surgically eligible patients. (B) Acceptability curves for surgical evaluation in patients with drug-resistant epilepsy of the temporal lobe in general.

a better determination of cost-effectiveness in this context. Furthermore, those analyses were limited to a health care perspective, and there was some ambiguity around which health care costs were finally included in the analysis. The result of that analysis was that evaluation for surgery was likely to be both more costly and more effective from the provider perspective. Langfitt noted that “only under the most optimistic assumptions of the model was evaluation associated with long term cost savings.”⁶ Outside of the US context, we are aware of cost-effectiveness studies for epilepsy surgery from France⁷ and Canada,⁸ both of which have nationalized health care systems. It is important to underscore how dramatically different the cost structures are between these earlier studies and the current study (focusing on the US context.) The French study estimated an annual cost of ASM of around \$3,400/y, which is $\approx 88\%$ less than the average cost of drugs estimated in the current study. Similarly, the French study estimated that the total cost of surgery (including full workup, surgical resection, and postoperative care) was around \$14,000. This figure would be insufficient to cover even the surgical evaluation in the US context. Nonetheless, it is worthwhile to note that both the French and Canadian studies found that surgery was a cost-effective strategy; the French study found that surgery became cost-effective after 10 years, and the Canadian study reported (in the pediatric context)

that surgery had an ICER of \$369 per percent reduction in seizures.

We made several assumptions in constructing our model. Perhaps most notably, we assume that resective surgery and continued medical management are the only therapies available for patients with drug-resistant epilepsy. This is not the case; a significant subset of patients may benefit from novel therapeutic modalities such as responsive neuromodulation and laser ablations. The clinical effectiveness of these technologies is still being established, and long-term outcomes data are not yet available and thus were not included in the present work. We also assume that patients can transition between health states (i.e., having seizures vs being seizure-free) only on an annual basis. This is a simplification of the true clinical picture; patients may in reality transition between these health states more frequently. In the same vein, we assume that the annual rate of relapse is consistent over the first 5 years after surgery and then takes on a new value for the rest of the patient’s lifespan. This is again a simplification of the true clinical picture; time-dependent variation in relapse rates is likely to be more complex in real patient cohorts. These simplifying assumptions reflect the metrics used in the limited longitudinal studies available. Our model validation analyses indicate that the outputs of the model closely match

the outcomes observed in real clinical cohorts, suggesting that the assumptions do not limit the usefulness of model outputs.

It is important to recognize that our model has been deliberately designed to have a bias toward continued medical management and that the final recommendation for surgery is made despite this bias. The bias toward medical management exists because (1) we include a higher surgical mortality rate than that seen in the vast majority of centers, (2) the survival curves for medically managed patients in our model show that simulated patients are likely to have longer seizure-free survival than patients in real cohorts, and (3) we assume that patients who suffer major complications and are disabled from surgery were fully employed and earning the median income before surgery (thus inflating the societal costs of surgery).

We have performed both probabilistic and deterministic sensitivity analyses on our model. The probabilistic analyses allow for simultaneous variation in all variables in the model and thus provide a more robust indication of the variation in the model as a whole. Depending on the perspective adopted, 78% to 90% of simulations favored surgery or referral for surgical evaluation. Our deterministic (1-way) sensitivity analysis revealed that extreme variation for 5 variables would meaningfully alter the suggested strategy, including if the initial surgical success rate was <21%, the rate of surgical eligibility was <5%, and the true cost of the surgical package was >5 times our estimated value. The extreme conditions identified in this sensitivity analysis are highly improbable in real patient cohorts.

As with any cost-effectiveness analysis, the predictions made by our model are informative only for the patient population that was studied for estimation of clinical parameters. In this case, the clinical parameters are based on a heterogeneous group of patients who have been diagnosed with pharmacoresistant temporal epilepsy. This includes patients with mesial temporal sclerosis, malformations of cortical development, MRI-negative disease, and others. Our model is based on average clinical parameters for patients with temporal disease and is not able to refine recommendations according to individual patient parameters (lesional vs non-lesional disease, unifocal vs multifocal disease, etc). In terms of scope, we note that our model deals only with patients who do not require invasive EEG monitoring as part of presurgical workup. An increasingly large subset of patients requires invasive investigation before surgery,⁴⁹ and it is possible that the cost-effectiveness of surgical referral and subsequent surgery may be substantively different among those patients. As data on the long-term marginal utility of invasive EEG to guide resection emerge, future studies that specifically look at the cost-effectiveness of these strategies will be particularly meaningful.

In the United States, temporal-lobe epilepsy surgery is cost-effective in patients who have been deemed surgical candidates, and surgical evaluation is cost-effective in pharmacoresistant

patients even if the probability of being a surgical candidate is low ($\approx 5\%$). An important future direction of research should be to develop cost-effectiveness prediction models that can be tailored to individual patient characteristics.

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Shehryar Sheikh, MD, MPH	Cleveland Clinic, OH	Designed and conceptualized study, compiled data, conducted data analysis, drafted manuscript
Michael Kattan, PhD	Cleveland Clinic, OH	Conceptualization of study, advised on data analysis methods, reviewed analysis and manuscript draft
Michael Steinmetz, MD	Cleveland Clinic, OH	Conceptualization of study, reviewed analysis and manuscript draft
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Belinda Udeh, PhD	Cleveland Clinic, OH	Advised on data analysis methods, reviewed analysis and manuscript draft
Lara Jehi, MD	Cleveland Clinic, OH	Designed and conceptualized study, advised on data analysis methods, reviewed analysis and manuscript draft

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