Systematic review of health economic studies in cranial neurosurgery

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OBJECTIVE As the cost of health care continues to increase, there is a growing emphasis on evaluating the relative economic value of treatment options to guide resource allocation. The objective of this systematic review was to evaluate the current evidence regarding the cost-effectiveness of cranial neurosurgery procedures.

METHODS The authors performed a systematic review of the literature using PubMed, EMBASE, and the Cochrane Library, focusing on themes of economic evaluation and cranial neurosurgery following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Included studies were publications of cost-effectiveness analysis or cost-utility analysis between 1995 and 2017 in which health utility outcomes in life years (LYs), quality-adjusted life years (QALYs), or disability-adjusted life years (DALYs) were used. Three independent reviewers conducted the study appraisal, data abstraction, and quality assessment, with differences resolved by consensus discussion.

RESULTS In total, 3485 citations were reviewed, with 53 studies meeting the inclusion criteria. Of those, 34 studies were published in the last 5 years. The most common subspecialty focus was cerebrovascular (32%), followed by neuro-oncology (26%) and functional neurosurgery (24%). Twenty-eight (53%) studies, using a willingness to pay threshold of US\$50,000 per QALY or LY, found a specific surgical treatment to be cost-effective. In addition, there were 11 (21%) studies that found a specific surgical option to be economically dominant (both cost saving and having superior outcome), including endovascular thrombectomy for acute ischemic stroke, epilepsy surgery for drug-refractory epilepsy, and endoscopic pituitary tumor resection.

CONCLUSIONS There is an increasing number of cost-effectiveness studies in cranial neurosurgery, especially within the last 5 years. Although there are numerous procedures, such as endovascular thrombectomy for acute ischemic stroke, that have been conclusively proven to be cost-effective, there remain promising interventions in current practice that have yet to meet cost-effectiveness thresholds.

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KEYWORDS neurosurgery; systematic review; economic evaluation; cost-effectiveness

HEALTH care spending in the US accounted for nearly 18% of gross domestic product in 2015, with 4% annual growth over 2008–2013, and this growth is further projected to increase to 5.8% annually (<https://www.cdc.gov/nchs/fastats/health-expenditures.htm>).³¹ Because the cost of health care continues to increase, there is a growing emphasis on assessing the relative economic value of medical treatment options to guide resource allocation. Furthermore, given that an estimated 60% of health

care spending is linked to or impacted by physicians, it is essential that physicians are armed with high-quality scientific evidence on both the treatments' effectiveness and their associated financial cost.⁴

The trend toward value-based medicine is particularly pertinent to the field of neurosurgery, because it remains one of the most expensive areas in medicine while also being the most profitable specialty for hospitals.^{52,67} Whereas economic evaluation of spine surgery has received sig-

ABBREVIATIONS CCEMG = Campbell and Cochrane Economics Methods Group; CEA = carotid endarterectomy; DALY = disability-adjusted life year; EPPI-Centre = Evidence for Policy and Practice Information and Coordinating Centre; ICER = incremental cost-effectiveness ratio; LY = life year; NHS EED = National Health Service Economic Evaluation Database; QALY = quality-adjusted life year; UK = United Kingdom; WTP = willingness to pay.

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nificant attention in the literature over the last 10 years, other subspecialties of neurosurgery have been less scrutinized.^{32,46,67} To our knowledge, this is the first systematic review of cost-effectiveness studies of cranial neurosurgery procedures.

Methods

Search Strategy and Study Selection

This study was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017064708). We performed a systematic review of literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, using 3 databases—PubMed, EMBASE, and the Cochrane Library—to identify all economic evaluation studies of cranial neurosurgery.⁴⁸ We used the National Health Service Economic Evaluation Database (NHS EED) search filter and MeSH terms to identify studies under the theme of economic evaluation and cranial neurosurgery (Table 1).¹⁷ An additional manual search was performed using references from review articles and in Google Scholar, using the same search terms as noted above.

Titles and abstracts were reviewed to identify studies published between January 1, 1995, and May 1, 2017, with a focus on comparative economic evaluation of any cranial neurosurgery procedures. Studies were excluded if they involved nonneurosurgical procedures (i.e., general surgery procedures, orthopedic procedures) or noncranial neurosurgical procedures, including spine surgery. Non-English publication, editorials, technical reports, conference abstracts, errata, book chapters, case reports, or burden-of-illness studies, and study types other than cost-effectiveness analysis or cost-utility analysis were excluded. A secondary review of full texts was done to specifically identify studies that measured health outcomes in life years (LYs), quality-adjusted life years (QALYs), or disability-adjusted life years (DALYs).

Data Extraction, Synthesis, and Analysis

For all included studies, 3 independent reviewers (W.H.A.R., M.M.H.Y., S.M.) extracted the study data using a standardized abstraction form developed a priori. Data fields included the following: author; country; currency year (specific fiscal year used in determining cost value in the study); year of publication; journal of publication; study design (cost-effectiveness analysis, cost-utility analysis); economic evaluation model (Markov model, decision tree model); perspective (health care system, health care payer, society); data source (literature, single-study estimates, hospital database, national database such as Medicare/Medicaid); comparators (treatments being compared); patient population (specific neurological condition of interest); time horizon (duration of time that the cost and health outcome of interest were being evaluated); discount rate (analysis to adjust for changes in cost and health outcome associated with passage of time); health outcome measure (LYs, QALYs, DALYs); sensitivity analysis (1-way, multiway, probabilistic analysis); uncertainty parameters (variables incorporated into the sensitivity analysis); study results (estimated cost and health outcome

TABLE 1. Summary of systematic literature search strategy

Theme	Search Terms
Economic analysis	1. Economics/
	2. exp "costs and cost analysis"/
	3. Economics, dental/
	4. exp economics, hospital/
	5. Economics, Medical/
	6. Economics, Nursing/
	7. Economics, Pharmaceutical/
	8. (economic\$ or cost or costs or costly or costing or price or pricing or pharmaco-economic\$). ti, ab.
	9. (expenditure\$ not energy). ti, ab.
	10. value for money. ti, ab.
	11. budget\$. ti, ab.
	12. or/ 1–11
	13. ((energy or oxygen) adj cost). ti, ab.
	14. (metabolic adj cost). ti, ab.
	15. ((energy or oxygen) adj expenditure). ti, ab.
	16. or/ 13–15
	17. 12 not 16
	18. Letter.pt
	19. Editorial.pt
	20. Historical article.pt
	21. or/ 18–20
	22. 17 not 21
	23. exp Animals/not humans/
	24. 22 not 23
Neurosurgery	1. neurosurgery
	2. neurologic surgery
	3. neurological surgery
	4. neurological procedure

Ab = abstract; adj = adjacent operator; exp = explode subject heading; pt = publication type; ti = title.

The list of the NHS EED filters used to identify all economic evaluations in PubMed and EMBASE in the literature search.

of interest, incremental cost-effectiveness ratio [ICER]); and funding source (public, industry support). Each study was categorized by neurosurgical subspecialty based on diagnosis and intervention.

For clarity in study terminology, we defined a cost-effectiveness analysis as a study in which the health outcome in single natural units such as LYs was used, with results reported as monetary unit per LY saved.²⁴ We defined a cost-utility analysis as a study in which multidimensional health outcomes such as QALYs or DALYs were used, with results reported as monetary unit per QALY or DALY gained.²⁴ Cost-effectiveness ratio refers to cost per health outcome (i.e., LY or QALY) for a specific intervention in question. The term ICER refers to the ratio of difference in the cost of the 2 interventions over the difference in health outcomes.

Based on the previously published report by Zygourakis and Kahn, which highlighted significant heterogeneity

of economic evaluation studies in neurosurgery, including study methodology (i.e., simple cost comparison versus full economic evaluation using cost-utility analysis) and primary outcomes measures (QALYs, LYs, DALYs), data analysis was performed in a descriptive manner.⁶⁷ For each study, the reported cost-effectiveness ratio or ICER was converted from their initial value to 2016 US dollars by using the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) (i.e., CCEMG–EPPI-Centre) cost converter.⁵⁵ This online tool was developed based on published research from the CCEMG–EPPI-Centre.⁵⁵ It allows standardized comparison of cost variables in multiple studies by adjusting for differences in currencies and currency year. For studies that failed to report the currency year, the year of publication was used as the surrogate currency year.

The converted cost-effectiveness ratio or ICER was then assessed against a commonly used willingness to pay (WTP) threshold of US\$50,000 per health outcome (i.e., QALYs or LYs).²⁰ The WTP threshold represents a theoretical maximum cost of an intervention that is deemed acceptable by the health care payer in order to achieve a specified health outcome such as QALYs or LYs.²⁰ The specific intervention being studied was deemed dominant over the alternative treatment option if it met the following criteria: 1) less costly and 2) led to improved health out-

come. For studies included in our systematic review that reported sensitivity analysis, we extracted variables that were found to be influential in the reported cost-effectiveness ratio (i.e., cost of procedure, discount rate).

Three independent reviewers performed quality assessment of the studies by using the Drummond checklist for assessing economic evaluations.⁹ This validated questionnaire consists of 10 items that address key requirements of economic studies in health care, with scores of 8 deemed as high quality. Discrepancies in scores were resolved through discussion between the reviewers.

Results

Search Results and Study Characteristics

In total, 3485 citations were reviewed, of which 53 studies met the inclusion criteria (Fig. 1); 64% (34 studies) of these were published in the last 5 years (Fig. 2).^{1–3, 5–8, 10–16, 19, 21, 22, 25–30, 33–43, 45, 47, 49–51, 53, 54, 56–66, 68} The most common subspecialty focuses of these cost-effectiveness studies were cerebrovascular neurosurgery (32%), followed by neurooncology (26%) and functional neurosurgery (24%) (Fig. 3). The preponderance of studies originated in the US (47%), followed by the United Kingdom (UK; 9%) and the Netherlands (9%) (Fig. 4). Twenty-seven studies (51%) did not specify the source of funding. Of the studies that included funding source, 30% were supported by a public

FIG. 1. Flowchart of the systematic search strategy and study selection based on the PRISMA guidelines.

FIG. 2. Bar graph showing economic evaluation studies included in the systematic review based on year of publication.

FIG. 3. Bar graph showing distribution of economic evaluation studies based on subspecialty of neurosurgery. Studies are organized based on the reported cost-effectiveness ratio against the WTP threshold of US\$50,000 per health outcome (i.e., QALY, LY). The specific intervention being studied was deemed dominant over the alternative treatment option if it met the following criteria: 1) less costly and 2) led to improved health outcome. If the cost-effectiveness ratio of the intervention in question was less than US\$50,000 per health outcome, it was categorized as met. If the cost-effectiveness ratio of the intervention in question was more than US\$50,000 per health outcome, it was categorized as unmet. N/A = not applicable.

FIG. 4. Bar graph showing distribution of economic evaluation studies based on location.

source (i.e., Heart & Stroke Foundation, National Institutes of Health), whereas 19% received industry support (i.e., Medtronic, Johnson & Johnson).

Study Findings and Study Quality

Detailed summaries of study results and methodology are included in Tables 2 and 3. Twenty-eight (53%) studies found a specific surgical treatment to be cost-effective by using a WTP threshold of US\$50,000 per health outcome (i.e., QALYs or LYs) (Fig. 3). In addition, there were 11 (21%) studies that found the specific surgical option to be dominant (both cost saving and having superior outcome). Treatments found to be dominant included endovascular thrombectomy for acute ischemic stroke compared to standard medical care; transsphenoidal surgery compared to medical treatment for prolactinoma; intraoperative mapping for low-grade glioma versus standard resection; carotid endarterectomy (CEA) compared to medical therapy for carotid stenosis; endoscopic pituitary tumor resection compared to microscopic tumor resection; and stereotactic radiosurgery compared to open surgery for metastatic brain tumors. Eight studies (15%; 3 neurooncology, 2 cerebrovascular, 2 functional, 1 epilepsy) incorporated indirect cost (i.e., loss of potential income due to illness or treatment morbidity, caregiver's time) as part of their economic evaluation.

The majority of the studies (87%) performed a sensitivity analysis to address uncertainties in the data used for their economic analysis, with the most common method being 1-way deterministic sensitivity analysis, followed by probabilistic sensitivity analysis (Table 4). Thirty-eight of 53 studies (72%) reported using 1-way deterministic sensitivity analysis, which considers a wide range of values for

a specific variable within the model (e.g., cost of treatment, patient age, complication rate, discount rate) to assess the effect of individual variables on the overall cost-effectiveness ratio. Twenty-four of 53 studies (45%) reported using probabilistic sensitivity analysis, which determines the probability of the intervention being cost-effective at certain WTP thresholds by randomly varying every input datum. The most common variables tested in sensitivity models were cost (58%), effectiveness of the treatment in question (43%), age (30%), and discount rate (26%).

Of the studies included in our review, 43 (81%) were judged to be high quality (score > 8) on the basis of the Drummond checklist (range 5–10). The most frequent reason for lower score was failure to address the following requirements: 1) adjusting cost and health outcome for differential timing (23%); 2) providing comprehensive descriptions of the competing treatment options (20%); and 3) performing sensitivity analysis for uncertainty parameters in the economic model (14%).

Discussion

To our knowledge, this is the first systematic review to examine and summarize the current body of evidence on the cost-effectiveness of cranial neurosurgery. We identified 53 studies that evaluated a specific operative neurosurgical intervention against an alternative treatment in a cost-effectiveness context. These articles addressed topics in all subspecialties of neurosurgery, including pediatrics, functional, epilepsy, cerebrovascular, general neurosurgery, and neurooncology; however, cerebrovascular, neurooncology, and functional neurosurgery were the most prevalent.

TABLE 2. Summary of the study characteristics including currency year, patient population, and comparators

Authors & Year	Currency Year	Patient Population	Comparators (intervention of interest vs alternative option)	WTP Threshold 2016 (US\$50,000/ QALY or LY)
Alali et al., 2014	2013	Traumatic brain injury	Decompressive craniectomy vs barbiturate coma	Met
Aronsson et al., 2016	2015	Acute ischemic stroke	Endovascular thrombectomy vs standard medical care	Dominant
Bowen et al., 2012	2010	Pediatric epilepsy	Surgery vs medical management	Dominant
Cho et al., 2006	2000–2003	Benign cranial base tumors	GKS vs open surgery	Met
Dams et al., 2016	2013	PD	DBS of STN + medical treatment vs standard medical care	Met
Dams et al., 2013	2010	PD	DBS vs standard medical care	Met
de Kinderen et al., 2015	2013	Pediatric epilepsy	KD vs VNS vs standard medical care	Unmet
Eggington et al., 2014	2011	PD	DBS vs standard medical care	Met
Esteves et al., 2015	2012	HGGs	5-ALA fluorescence–guided surgery vs standard surgery	Met
Fallah et al., 2016	2016	Pediatric epilepsy w/ tuberous sclerosis	Surgical resection vs KD vs VNS vs addition of 3rd AED	Unmet
Gaetani et al., 1998	NR	Intracranial aneurysms	Early vs delayed surgery for ruptured aneurysm	Met
Ganesalingam et al., 2015	2013–2014	Acute ischemic stroke	Endovascular thrombectomy vs standard medical care	Met
Garside et al., 2007	NR	HGGs	Carmustine wafers + surgery + RT vs surgery + RT	Unmet
Garton et al., 2002	2000	Pediatric hydrocephalus	ETV vs shunt placement	Met
Greving et al., 2009	2005	UIAs	Surgery vs endovascular coiling vs observation	Met
Helmers et al., 2012	2010	Pediatric epilepsy	VNS insertion + medical therapy vs standard medical care (pre-VNS insertion)	NA*
Hofmeijer et al., 2013	2009	Middle cerebral artery infarction	Surgical decompression vs standard medical care	Unmet
Jethwa et al., 2016	2013	Prolactinoma	Transsphenoidal surgery vs standard medical care	Dominant
Johnston et al., 1999	1997	UIAs	Surgery vs endovascular coiling vs observation	Met
Jordan et al., 1996	1992	Arteriovenous malformation	Embolization + surgery vs surgery alone	Met
Kallmes et al., 1998	1996	UIAs in nonsurgical candidates	Endovascular coiling vs observation	Met
Kameda et al., 2017	NR	iNPH	Shunt (VP, LP) vs no shunt	Met
Kawamoto et al., 2016	2014	PD	1) DBS vs standard medical care; 2) early DBS vs late DBS	Met
Khan et al., 2012	2010	Carotid artery stenosis	CAS vs CEA	Unmet
King et al., 1995	1992	Asymptomatic UIAs	Surgery vs observation	Met
King et al., 1997	1994	Intractable temporal lobe epilepsy	ATL vs standard medical care	Met
Koffijberg et al., 2011	2005	Ruptured aneurysms	Endovascular coiling or surgery vs observation	Met
Kunz et al., 2016	2015	Acute ischemic stroke	Endovascular thrombectomy vs standard medical care	Met
Langfitt, 1997	1995	Medically intractable epilepsy	ATL vs standard medical care	Met
Leppert et al., 2015	2012	Acute ischemic stroke	Endovascular thrombectomy vs standard medical care	Met
Lobotesis et al., 2016	2014	Acute ischemic stroke	Endovascular thrombectomy vs standard medical care	Dominant
Martino et al., 2013	2011	WHO Grade II glioma	Intraop electrical stimulation mapping for resection vs standard tumor resection	Dominant
McIntosh et al., 2016	2010	PD	DBS vs standard medical care	Unmet
Mehta et al., 1997	NR	Single brain metastases	SRS + RT vs RT alone vs resection + RT	Met
Nussbaum et al., 1996	NR	Stroke	CEA vs observation alone vs aspirin therapy	Dominant
Ooms et al., 2017	NR	Obsessive-compulsive disorder	DBS vs standard medical care	Unmet
Pollock & Ecker, 2005	2000	Trigeminal neuralgia	MVD vs glycerol rhizotomy vs SRS	Met
Porter et al., 1997	1995	Arteriovenous malformation	Surgery vs SRS	Met
Ravikumar et al., 2017	2016	Essential tremor	FUS vs SRS vs DBS	Met
Rudmik et al., 2015	2014	Pituitary adenoma	Endoscopic vs microscopic tumor resection	Dominant
Rutigliano et al., 1995	NR	Single brain metastases	SRS vs resection vs RT alone	Unmet
Shireman et al., 2017	2015	Acute ischemic stroke	Stent retriever thrombectomy vs standard medical care	Dominant

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TABLE 2. Summary of the study characteristics including currency year, patient population, and comparators

Authors & Year	Currency Year	Patient Population	Comparators (intervention of interest vs alternative option)	WTP Threshold 2016 (US\$50,000/ QALY or LY)
Sivakanthan et al., 2014	2011	Trigeminal neuralgia	MVD vs SRS vs percutaneous rhizotomy	Met
Slof et al., 2015	NR	WHO Grade IV glioma	5-ALA–induced fluorescence–guided glioma surgery vs standard surgery	Met
Stroupe et al., 2014	2010	PD	DBS of GPI vs DBS of STN	Unmet
Tomaszewski & Hol-loway, 2001	2000	Late-stage PD	DBS vs standard medical care	Unmet
Valledeoriola et al., 2007	NR	PD	DBS of STN vs standard medical care	Unmet
Voigt & Barnett, 2016	2015	HGG where maximal resection not feasible	Brain LITT system vs current treatments (craniotomy w/ or w/o Gliadel wafer)	Met
Vuong et al., 2013	2009	1–2 brain metastases	SRS vs resection	Dominant
Vuong et al., 2012	2007	Brain metastasis	SRS vs resection	Dominant
Wernicke et al., 2016	2008–2010	Brain metastasis	Resection + ¹³¹ Cs intraop brachytherapy vs resection + SRS	Dominant
Zhu et al., 2014	2009	PD	DBS of STN vs standard medical care	Unmet
Zygourakis et al., 2014	2010–2013	Vestibular schwannoma	Surgery vs RT (GKS) vs observation	Unmet

AED = antiepileptic drug; ATL = anterior temporal lobectomy; CAS = carotid artery stenting; DBS = deep brain stimulation; ETV = endoscopic third ventriculostomy; FUS = focused ultrasound; GKS = Gamma Knife surgery; GPI = globus pallidus internus; HGG = high-grade glioma; iNPH = idiopathic normal pressure hydrocephalus; KD = ketogenic diet; LITT = laser interstitial thermal therapy; LP = lumboperitoneal; MVD = microvascular decompression; NA = not applicable; NR = not reported; PD = Parkinson disease; RT = radiation therapy; SRS = stereotactic radiosurgery; STN = subthalamic nucleus; UIA = unruptured intracranial aneurysm; VNS = vagal nerve stimulator; VP = ventriculoperitoneal; 5-ALA = 5-aminolevulinic acid.

The cost-effectiveness ratio of the intervention in question (i.e., cost per health outcome) was compared against the WTP threshold of US\$50,000/QALY or LY.

* Study did not report a cost-effectiveness ratio or ICER, and therefore we were unable to determine whether intervention met the WTP threshold.

The findings of our review reflect a growing emphasis on incorporating economic value within neurosurgical decision making and continuing the growth of economic evaluation research in neurosurgery. A previous nonsystematic review by Zygourakis and Kahn examined 26 economic evaluation studies of neurosurgery published before 2014; however, they found that many were not true cost-effectiveness studies.⁶⁷ In addition, a number of those studies focused on nonoperative practices such as the use of diagnostic imaging for brain injury.²³ In contrast, we found 30 studies focused specifically on operative neurosurgical care that were published between 2013 and 2017. More importantly, 74% of the 53 included studies found that the treatment evaluated was dominant or cost-effective at a WTP threshold of US\$50,000 per health outcome (i.e., QALYs, LYs).

Eleven studies (21%) found that a treatment was economically dominant compared to the alternative considered. Three of these studies highlighted the cost-effectiveness benefit of endovascular thrombectomy for acute ischemic stroke,^{2,40,56} and reflect the recent advances from multiple clinical trials, such as the ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) trial, which show a significant increase in the number of functionally independent patients after endovascular thrombectomy.¹⁸ A similar long-term economic benefit of reduced stroke-related disability was reported by Nussbaum et al., who found CEA dominant over medical management in patients with symptomatic carotid

stenosis.⁴⁵ The impact of improved long-term patient outcome in cost-effectiveness analysis was also demonstrated in surgical management for medically intractable epilepsy, awake craniotomy for low-grade glioma resection, and pituitary tumor resection.^{3,25,41,53} In these studies, higher direct costs often related to cost of surgery were compensated by long-term benefits and lower follow-up costs.^{3,25,41,53} In contrast, 3 studies evaluating the cost-effectiveness of metastatic brain tumor treatment, for which life expectancy remains more limited, found that options with lower procedural cost and lower postoperative morbidity were dominant. These included stereotactic radiosurgery and intraoperative brachytherapy.^{63–65}

Compared with the findings of Zygourakis and Kahn in their earlier review of the literature, certain subspecialties of neurosurgery, particularly cerebrovascular and neurooncology, have contributed a significant number of cost-effectiveness studies (31/53 studies in our review), particularly within the last 5 years.⁶⁷ However, other subspecialties (epilepsy, neuro-critical care, and pediatrics) remain poorly represented in the health economics literature, with only a few published studies. We view this as a call-to-arms and an opportunity to conduct health economic studies examining treatments within these particular subspecialties.

Limitations of the Study

The literature we identified was unfortunately too het-

TABLE 3. Summary of the economic analysis (data source, time horizon, cost, perspective, primary outcome) and study results

Authors & Year	Data Source (i.e., single-study-based estimate, literature)	Time Horizon (i.e., duration of follow-up)	Perspective (i.e., health care system, health care payer, society)		Outcome Metrics (i.e., LYs, QALYs)	Result in Terms of Cost-Effectiveness Ratio
			Cost (i.e., direct vs indirect cost)	Health care payer	QALYs	
Alali et al., 2014	Literature	Lifetime	Direct medical cost	Health care payer	QALYs	ICER of US\$9565/QALY gained for decompressive craniectomy over lifetime compared to barbiturate coma.
Aronsson et al., 2016	Literature	Lifetime	Direct medical cost	Health care payer	QALYs	Endovascular thrombectomy dominates (US\$ -223/QALY gained) for ischemic stroke over lifetime compared to standard care.
Bowen et al., 2012	Literature	20 yrs	Direct medical cost	Health care payer	QALYs	Surgery dominates compared to medical management in patients w/ epilepsy who are deemed surgical candidates (Can\$).
Cho et al., 2006	Wages reported by patient & direct costs from the single hospital center; single-study-based estimate	5 yrs	Direct & indirect cost	Societal	QALYs	US\$3762/QALY for GKS vs US\$8996/QALY for open surgery for skull base tumor of <3 cm in diameter or 30 ml in vol. No ICER calculated.
Dams et al., 2016	Literature	Lifetime	Direct medical cost	Health care payer	QALYs	ICER of €22,710/QALY gained for DBS of STN over lifetime compared to best medical therapy alone.
Dams et al., 2013	Literature; single-center billing record	Lifetime	Direct medical cost	Health care payer	QALYs	ICER of €6677/QALY gained for DBS over lifetime compared to medical therapy.
de Kinderen et al., 2015	Literature; expert meetings	5 yrs	Direct medical cost	Health care payer	QALYs	At 5 yrs, VNS had an ICER of €11,378/QALY gained compared to KD and ICER of €68,489/QALY gained compared to standard medical care.
Eggington et al., 2014	Literature; Department of Health, UK; Medtronic UK price list	5 yrs	Direct medical cost	Health care payer	QALYs	ICER of £20,678/QALY gained for DBS over 5 yrs compared to standard medical management alone.
Esteves et al., 2015	Literature; Portuguese reimbursement list	Lifetime	Direct medical cost	Health care payer	QALYs, LYs	ICER of €6675/LY gained, €9097/QALY gained for 5-ALA over lifetime compared to standard surgery.
Fallah et al., 2016	Literature; AMA; ICD codes; medical expenditure panel survey; AHRQ website	5 yrs	Direct medical cost	Health care payer	QALYs	Of the 4 management strategies, the least costly option was adding a 3rd AED. However, resective surgery led to highest QALY gained, w/ ICER of US\$268,335/QALY gained compared to adding 3rd drug. KD & VNS implantation was dominated by treatment strategy of adding a 3rd AED.
Gaetani et al., 1998	Literature; diagnosis-related group reimbursement	Lifetime	Direct medical cost	Not stated	QALYs	26,639,000/QALY for early (w/in 3 days of rupture) & 27,791,000/QALY for delayed (5 days after rupture) surgical clipping (Italian lira). No significant difference in the incremental cost btwn the 2 treatment strategies. No ICER calculated.
Ganesalingam et al., 2015	Literature	20 yrs	Direct medical cost	Health care payer	QALYs	Mechanical thrombectomy had an ICER of US\$11,651/QALY gained compared to intravenous tPA alone.
Garside et al., 2007	Literature; expert opinion; industry submissions; NHS database	5 yrs	Direct medical cost	Not stated	QALYs	Base case ICER for carmustine wafer with surgery/RT was £54,500/QALY gained compared to surgery/RT. Base case ICER for temozolomide/surgery/RT was £36,000/QALY gained compared to surgery/RT.

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TABLE 3. Summary of the economic analysis (data source, time horizon, cost, perspective, primary outcome) and study results

Authors & Year	Data Source (i.e., single-study–based estimate, literature)	Time Horizon (i.e., duration of follow-up)	Cost (i.e., direct vs indirect cost)	Perspective (i.e., health care system, health care payer, society)	Outcome Metrics (i.e., LYs, QALYs)	Result in Terms of Cost-Effectiveness Ratio
Garton et al., 2002	Single-study–based estimates; BCCH Health Services Study Unit; UMI Health Care System's Clinical Information; Canadian published fee schedule for Medical Services Commission	Median follow-up of 35 mos (max 6 yrs)	Direct medical cost	Health care payer	QALYs, days free of the hydrocephalus treatment	Can\$11–18/day free of hydrocephalus treatment for both ETV & shunt; ICER for shunt was Can\$2153–\$6187/QALY gained compared to ETV.
Greving et al., 2009	Literature	Lifetime	Direct medical cost	Health care payer	QALYs	For rupture rates of 0.3%/yr in 50-yr-old men, ICER was €19,818/QALY for clipping & €18,588/QALY for coiling compared to observation. With rupture rates of 3.5%/yr, ICERs decreased to €940/QALY for clipping & €2194/QALY for coiling compared to observation.
Helmers et al., 2012	Medicaid; literature	From 3 yrs to death, device removal, or Medicaid end date (whichever came first)	Direct medical cost	Health care payer	QALYs	Lifetime QALY gained after VNS insertion was 5.9618 (1- to 11-yr age group), 4.8242 (12- to 17-yr age group). Average quarterly health care costs in the 2 groups were US\$18,437 vs US\$18,839 pre- & post-VNS for 1- to 11-yr group ($p = 0.052$) & US\$14,546 vs US\$19,695 for 12- to 17-yr group total health care costs ($p = 0.002$). Cumulative cost savings of VNS insertion outweigh the cost of VNS insertion after 1–1.5 yrs. No ICER calculated.
Hofmeijer et al., 2013	Dutch manual for cost research & Dutch diagnosis treatment prices; single-study–based estimates	3 yrs & lifetime	Direct medical cost	Societal	QALYs	Decompressive craniectomy group had ICER of €127,000/QALY gained in first 3 yrs and €60,000/QALY gained for lifetime compared to medical therapy alone.
Jethwa et al., 2016	Medicare; literature	5 & 10 yrs	Direct medical cost	Health care payer	QALYs	At 5 yrs, microscopic surgery had a cost-effectiveness ratio of US\$2797/QALY, endoscopic surgery US\$3151/QALY compared to medical therapy, which had US\$3901–4380/QALY. At 10 yrs, microsurgery had a cost-effectiveness ratio of US\$1530/QALY, endoscopic US\$1683/QALY. At both time points, the surgical arm dominated the medical arm. No ICER calculated.
Johnston et al., 1999	Literature; case-based estimates from single institution	Lifetime	Direct medical cost	Societal	QALYs	For base case of <10 mm, w/ no symptoms & no previous SAH, both coiling & clipping led to loss in QALYs & higher health care cost. Clipping or coiling in anyone with >10 mm lesion or who was symptomatic was cost-effective, w/ a cost-utility ratio of US\$11,000/QALY to US\$38,000/QALY. No ICER calculated.
Jordan et al., 1996	Literature; estimates from single institution	Not stated	Direct & indirect cost	Societal	QALYs	Combined embolization & resection resulted in a lower cost/QALY at US\$6734/QALY vs US\$9814/QALY for surgery alone. No ICER calculated.

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TABLE 3. Summary of the economic analysis (data source, time horizon, cost, perspective, primary outcome) and study results

Authors & Year	Data Source (i.e., single-study–based estimate, literature)	Time Horizon (i.e., duration of follow-up)	Perspective (i.e., health care system, health care payer, society)		Outcome Metrics (i.e., LYs, QALYs)	Result in Terms of Cost-Effectiveness Ratio
			Cost (i.e., direct vs indirect cost)	Societal	QALYs	
Kallmes et al., 1998	AMA CPT codes; literature	Lifetime	Direct medical cost	Societal	QALYs	ICER of US\$23,000/QALY gained for unclippable lesions in a cohort of patients who underwent embolization compared to observation. ICER of US\$19,000/QALY gained for patients not medical candidates for open surgery who underwent embolization compared to observation.
Kameda et al., 2017	Diagnosis-procedure combination code data in Japan; literature	2 yrs	Direct medical cost	Not stated	QALYs	Based on the SINPHONI & SINPHONI-2 study results, ICER for shunting is US\$29,934/QALY gained (VP) & US\$58,346/QALY gained (LP) compared to medical management. After 2 yrs, ICER reduced to US\$8563/QALY gained (VP) & US\$15,713/QALY gained (LP).
Kawamoto et al., 2016	Literature; single-institution estimates	10 yrs	Direct medical cost	Health care payer	QALYs	Base case scenario, ICER of DBS was US\$25,600/QALY gained compared to medical treatment alone. Cost-effectiveness ratio of early-stage DBS was US\$70,200/QALY compared to the intermediate stage, w/ US\$25,600/QALY & late-stage treatment, w/ US\$27,200/QALY.
Khan et al., 2012	Nationwide Inpatient Sample dataset; literature	4 yrs	Direct medical cost	Not stated	QALYs	ICER for CAS was US\$229,429/QALY gained compared to CEA.
King et al., 1995	Medicare; literature	Lifetime	Direct medical cost	Societal	QALYs	Base case for elective surgery had ICER of US\$24,200/QALY gained compared to expectant management.
King et al., 1997	Medicare; single-institution estimates	Lifetime	Direct and indirect cost	Societal	QALYs	ICER for ATL in patients w/ temporal lobe epilepsy is US\$27,200/QALY gained compared to best medical management.
Koffijberg et al., 2011	Literature	Lifetime	Direct medical cost	Not stated	QALYs	ICER for surgical treatment of ruptured aneurysm was below the threshold of €50,000/QALY gained for women ages 70–79 yrs and men ages 70–74 yrs admitted in good condition <4 days after rupture. In the base group, aneurysm occlusion had an ICER of €247/QALY gained.
Kunz et al., 2016	Literature; Medicare	30 yrs	Direct medical cost	Health care payer	QALYs	For the base case, endovascular thrombectomy had an ICER of US\$3096/QALY gained compared to standard care alone. In patients w/ an ASPECTS of 9–10 or time from symptom onset >300 min, endovascular therapy was dominant over standard care. In patients w/ an ASPECTS of 0–5 or M ₂ occlusion, ICER was <US\$30,000/QALY gained.
Langfitt, 1997	Literature	Lifetime	Direct medical cost	Health care system	QALYs	ATL has an ICER of US\$15,581/QALY gained compared to best medical therapy.
Leppert et al., 2015	Literature	Lifetime	Direct medical cost	Health care payer	QALYs	Intraarterial therapy has an ICER of US\$14,137/QALY gained compared to standard care.
Lobotesis et al., 2016	Literature	Lifetime	Direct medical cost	Health care system	QALYs	Stent retriever w/ tPA was dominant over tPA alone, w/ net monetary benefit of £79,402 over patient's lifetime.

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TABLE 3. Summary of the economic analysis (data source, time horizon, cost, perspective, primary outcome) and study results

Authors & Year	Data Source (i.e., single-study-based estimate, literature)	Time Horizon (i.e., duration of follow-up)	Perspective (i.e., health care system, health care payer, society)		Outcome Metrics (i.e., LYs, QALYs)	Result in Terms of Cost-Effectiveness Ratio
			Cost (i.e., direct vs indirect cost)	Health care system		
Martino et al., 2013	Single-study-based estimates	Lifetime	Direct & indirect cost	Societal & health care system	QALYs	Early direct cost of intraop mapping arm was higher than standard arm (US\$38,662 vs US\$32,116). However, by 6 mos, the total cost of intraop mapping group was lower due to more patients returning to work. Accounting for health utility outcome, the intraop mapping group had US\$12,222/QALY vs US\$31,927/QALY for standard tumor resection group ($p < 0.05$). Intraop mapping was dominant, w/ savings of US\$16,298/QALY gained compared to standard surgery.
McIntosh et al., 2016	Literature	12 mos, 5 & 10 yrs	Direct & indirect cost	Societal & health care system	QALYs	At 1 yr, DBS had an ICER of £468,528/QALY gained compared to medical therapy. For extrapolation to 5 yrs: ICER improved to £45,180/QALY gained, & at 10 yrs ICER was £70,537/QALY gained. The extrapolation is dependent on the assumptions of a 10-yr life span for electrode, surgical QALY gain around 30%, & annual medical therapy cost increases by 30%.
Mehta et al., 1997	Literature	Not stated	Direct medical cost	Health care system	QALYs, LYs	Cost-effectiveness ratio for RT alone: US\$16,250/LY; SRS + RT: US\$13,729/LY; surgery + RT: US\$27,523/LY. ICER for SRS + RT compared to RT alone was US\$12,289/LY gained. Cost-utility ratio for RT alone: US\$32,500/QALY; SRS + RT: US\$15,102/QALY; surgery + RT: US\$31,454/QALY. ICER for SRS + RT was US\$10,753/QALY gained compared to RT.
Nussbaum et al., 1996	Literature & single-study-based estimates	Lifetime	Direct medical cost	Health care system	Quality-adjusted life expectancy	Average lifetime cost of observation after stroke was estimated to be US\$26,535 per patient compared to US\$24,069 per patient for aspirin therapy & US\$23,538 for CEA. CEA produced a cost saving of US\$5730 over the cost of observation & US\$3264 over the cost of aspirin therapy. Quality-adjusted life expectancy was extended to 13.8 mos compared to observation & 11.2 mos compared to aspirin therapy.
Ooms et al., 2017	Single-study-based estimates	4 yrs	Direct & indirect cost	Societal	QALYs	DBS has an ICER of €141,446/QALY gained compared to medical therapy.
Pollock & Ecker, 2005	Single-study-based estimates	20.6 mos (follow-up period—they did not state time horizon)	Direct medical cost	Health care system	Quality-adjusted pain-free yr	Cost per quality-adjusted pain-free yr was US\$6342, US\$8174, & US\$8269 for glycerol rhizotomy, MVD, & SRS, respectively. No ICER calculated.
Porter et al., 1997	Literature; estimates from multiple hospitals	Lifetime	Direct & indirect cost	Societal	QALYs	Surgical management had an ICER of Can\$7100/QALY gained compared to SRS.
Ravikumar et al., 2017	Literature; Medicare	Not stated	Direct medical cost	Societal	QALYs	FUS led to highest utility value while being the 2nd-least costly option. It dominated against DBS. ICER of DBS was US\$483,599/QALY gained compared to SRS. ICER of FUS was US\$7435/QALY gained compared to SRS.
Rudmik et al., 2015	Literature	25 yrs	Direct medical cost	Health care payer	QALYs	Endoscopic approach was dominant over microscopic approach. Cost for endoscopic approach was US\$17,244; produced a total of 24.3 QALYs. The microscopic approach cost a total of US\$23,756; produced 24.2 QALYs.

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TABLE 3. Summary of the economic analysis (data source, time horizon, cost, perspective, primary outcome) and study results

Authors & Year	Data Source (i.e., single-study-based estimate, literature)	Time Horizon (i.e., duration of follow-up)	Cost (i.e., direct vs indirect cost)	Perspective (i.e., health care system, health care payer, society)	Outcome Metrics (i.e., LYs, QALYs)	Result in Terms of Cost-Effectiveness Ratio
Rutigliano et al., 1995	Literature; Medicare	Not stated	Direct medical cost	Societal	LYs	Cost-effectiveness ratio of surgery was US\$32,149/LY vs US\$24,811/LY for SRS. Compared to RT alone, SRS had an ICER of US\$40,648/LY gained, vs US\$52,384/LY gained for surgery.
Shireman et al., 2017	Literature; single-center-based estimates	Lifetime	Direct medical cost	Health care system	QALYs	Stent retriever w/ tPA was dominant over tPA alone over lifetime, w/ net savings of US\$22,203 & higher QALYs.
Sivakanthan et al., 2014	Literature; Medicare	10 yrs	Direct medical cost	Not stated	QALYs	Costs per QALY were US\$4931, US\$7767, & US\$601 for MVD, SRS, & percutaneous rhizotomy, respectively. No ICER calculated.
Slof et al., 2015	Literature	Not stated	Direct medical cost	Not stated	QALYs	ICER of 5-ALA-guided surgery is €9021/QALY gained compared to that of conventional white-light surgery group.
Stroupe et al., 2014	Single-study-based estimates	3 yrs	Direct medical cost	Societal & health care system	QALYs	Provider costs were similar btwn patients undergoing DBS to GPi & STN (GPi: US\$138,044 vs STN: US\$131,822). Societal costs were also similar (GPi: US\$171,061 vs STN: US\$167,706). Patients undergoing DBS to GPi had nonsignificantly higher QALYs (GPi: 1.214 vs STN: 1.153). The ICER of GPi stimulation was US\$54,129/QALY gained compared to STN.
Tomaszewski & Holloway, 2001	Literature; Medicare/single-center estimates	Lifetime	Direct medical cost	Societal	QALYs	DBS had an ICER of US\$49,000/QALY gained compared to best medical care.
Valdeorola et al., 2007	Single-study-based estimates	1 yr	Direct medical cost	Not stated	QALYs	DBS had an ICER of €34,389/QALY gained compared to best medical management.
Voigt & Barnett, 2016	Literature; Medicare	Lifetime	Direct medical cost	Societal	LYs	LITT had an ICER of US\$29,340/LY gained vs current treatments (craniotomy/tumor resection w/ or w/o Gliadel wafer or biopsy). LITT led to longest overall survival.
Vuong et al., 2013	Single-study-based estimates; German reimbursement codes	Lifetime	Direct medical cost	Health care payer	LYs	SRS is dominant over resection at a savings of €1683, & increased LYs of 0.45.
Vuong et al., 2012	Single-study-based estimates	Lifetime	Direct & indirect cost	Societal	LYs	Cost per LY gained was higher for resection than for SRS (US\$2811/LY vs US\$2309/LY) due to the significantly higher indirect cost associated w/ resection.
Wernicke et al., 2016	Single-study-based estimates	Not stated	Direct medical cost	Not stated	QALYs	Surgery + ¹³¹ Cs therapy was dominant over surgery + SRS, w/ savings of US\$13,758.
Zhu et al., 2014	Single-study-based estimates	2 yrs	Direct medical cost	Health care system	QALYs, UPDRS Part III	DBS had an ICER of US\$123,110/QALY gained in 1st yr, & US\$62,846/QALY gained in 2nd yr compared to medical treatment.
Zygourakis et al., 2014	Literature; estimates from single institution	Lifetime	Direct medical cost	Health care system	QALYs	Surgery was the most expensive option but provided the highest QALY. RT was the least costly option. Compared to observation, RT is dominant. Surgery had an ICER of US\$137,747/QALY gained compared to RT.

AHRQ = Agency for Health Care Research and Quality; AMA = American Medical Association; ASPECTS = Alberta Stroke Program Early CT score; BCCH = British Columbia Children's Hospital; Can\$ = Canadian dollar; CPT = Current Procedural Terminology; max = maximum; SAH = subarachnoid hemorrhage; SINPHONI = SINPHONI-2 = Study of INPH on Neurological Improvement trial; tPA = tissue plasminogen activator; UMI = University of Michigan; UPDRS = Unified Parkinson's Disease Rating Scale.

TABLE 4. Summary of sensitivity analysis

Authors & Year	Sensitivity Analysis	Uncertainty Parameters	Impact on Conclusion
Alali et al., 2014	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Age, life expectancy, cost of nursing care, discount rate	Age >65 yrs leads to ICER greater than the threshold of US\$50,000/QALY; all other variables did not lead to ICER crossing the threshold. At the WTP threshold of US\$50,000/QALY, decompressive craniectomy was cost-effective in 78% of cases.
Aronsson et al., 2016	2-way sensitivity analysis, probabilistic sensitivity analysis	Utility decrements, age of simulated patients, cost of adding thrombectomy to standard care, long-term mortality, lifelong time horizon, discount rate, long-term stroke cost	Major changes to all uncertainty parameters did not change ICER to cross the threshold. At the WTP threshold of US\$10,000/QALY, thrombectomy was cost-effective in 100% of cases.
Bowen et al., 2012	1-way sensitivity analysis	Time horizon, discount rate, alternate utility source, assuming treatment effect for children referred to treatment center but who did not have surgery	Changes to uncertainty parameters did not change conclusion of surgery dominating.
Cho et al., 2006	Not done	NA	NA
Dams et al., 2016	1-way sensitivity analysis	Discount rate, age, time until battery exchange, utility improvement, costs of adverse events, costs of battery exchange & surgery, mortality, & reduction rates for motor complications & utilities during the periop phase	Duration of battery exchange had a major effect on ICER, but no single variable exceeded the threshold of €50,000/QALY.
Dams et al., 2013	1-way sensitivity analysis	Starting age, discount rate, time until battery exchange, costs for battery exchange, cost for surgery, cost of adverse events, changes in drug cost, DBS-related mortality, improvement in motor complications, utility improvement, duration of utility improvement, periop utility reduction, shorter time horizons	Model was most sensitive to treatment effect of DBS, effect of time until battery exchange, and discount rate. The cost-effectiveness threshold of €32,000/QALY was not reached in any single parameter.
de Kinderen et al., 2015	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Efficacy of treatment, utility values, costs	At 12 mos, standard care had 100% probability of cost-effectiveness at the threshold of €20,000/QALY. However, at 5 yrs VNS had the highest probability (51%) of being cost-effective at the threshold of €80,000/QALY gained, followed by standard medical care (36%) & KD (14%).
Eggington et al., 2014	1-way sensitivity analysis	Utilities by H & Y class, drug cost per cycle, cost of DBS implantation, cost of hospitalization, DBS infection, DBS battery life, falls per cycle, probability of hospitalization, start age, baseline mortality, off time progression, & H & Y progression	Determining health state utility based on H & Y stage led to significant change in ICER to £84,170/QALY gained. Also, varying drug cycles per arm & cost of DBS increased ICER to >£30,000/QALY gained.
Esteves et al., 2015	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Transition probabilities, costs of each health state, utility values, discount rates	ICER remained <€14,000/QALY gained, €9000/LY gained in all uncertainty states. Probability of 5-ALA cost-effectiveness below the threshold of €20,000 was 99.6% for LYs, & 96% for QALY. Most influential variables were proportion of complete resection in the 5-ALA cohort & probability of death in patient groups.
Fallah et al., 2016	1-way sensitivity analysis	Assumptions: full medical adherence; no adverse events; no major complications or death; 1st-line AEDs are Keppra & valproic acid, 3rd is carbamazepine, 4th is clobazam. Uncertainty parameters: cost of medications, probability of 3rd AED resulting in seizure freedom, utility of seizure-free state, utility of <50% improvement in seizures	At the threshold of US\$100,000/QALY gained, only the treatment option of adding the 3rd AED remained cost-effective in the sensitivity analysis. The most influential variables for ICER were health utility value of refractory seizures & the probability of having seizure freedom from the 3rd AED.
Gaetani et al., 1998	Not done	NA	NA

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TABLE 4. Summary of sensitivity analysis

Authors & Year	Sensitivity Analysis	Uncertainty Parameters	Impact on Conclusion
Ganesalingam et al., 2015	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Health utility, probability parameters, cost	No impact on conclusion at the threshold of US\$30,000/QALY gained. Thrombectomy had 100% probability of being cost-effective at the WTP threshold of US\$33,000/QALY.
Garside et al., 2007	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Median overall survival benefit w/ treatment, median PFS benefit w/ treatment, QOL (utility) for stable disease, QOL (utility) for progressive disease, cost of treatment	Most influential variables were median overall survival, median PFS, QOL utility, & cost of treatment. Carmustine wafer was not under the WTP threshold of £30,000/QALY gained in 89% of cases, and in 15% of cases the carmustine arm was dominated. Similarly, temozolomide did not meet the WTP threshold in 77% of cases. To be below the threshold, the median survival benefit needed to be 22 wks, up from 11 wks.
Garlon et al., 2002	1-way sensitivity analysis	Posthospitalization recovery, costs, discount rates, different rates of ETV success	No impact on conclusion.
Greving et al., 2009	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Utility of awareness of an untreated aneurysm, development of de novo & recurrent aneurysms, clipping- & coiling-related complications, outcome of SAH, mortality	Results were sensitive to utility awareness of aneurysm & treatment-related disability. Increasing surgical risk of death or moderate to severe disability for 70-yr-old patients resulted in increased cost-effectiveness ratio beyond the WTP threshold of €20,000/QALY gained. Presence of vascular disease reduced the cost-effectiveness of treatment from €19,818/QALY to €22,298/QALY in 50-yr-old men, w/ a rupture rate of 0.3%/yr.
Helmers et al., 2012	Multivariate regression analysis	Age, sex, health state, AED, depression, mental retardation, bipolar disorder, anxiety, use of antimicrobials, use of anesthetics, analgesics	Adjusting for confounders did not change the cost analysis comparing average quarterly health care cost before & after VNS insertion.
Hofmeijer et al., 2013	Probabilistic sensitivity analysis	Not specified	Sensitivity analysis w/ the threshold of €80,000/QALY showed that 98% of cases of decompressive craniectomy were not cost-effective. Admissions to a rehabilitation unit & long-term nursing home were the most important drivers for cost.
Jethwa et al., 2016	1-way & 2-way sensitivity analysis, probabilistic sensitivity analysis	Surgical cure rate, surgical complication rate	Endoscopic resection would be the most cost-effective strategy compared to microsurgical resection if cure rate was 90% & complication rate was 1%. No impact on surgery dominating medical management.
Johnston et al., 1999	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Size of aneurysm (> or <10 mm), symptomatic or not, previous SAH or not, untreated aneurysm rupture rate, utility for an untreated aneurysm, age, SAH rates	At the threshold of US\$100,000/QALY gained, every scenario besides the base case (asymptomatic <10-mm UIA) was cost-effective for coiling, w/ a cost-utility ratio of US\$5,000:US\$42,000/QALY gained. This did not change in the sensitivity analysis, w/ age & rupture rate having the greatest influence.
Jordan et al., 1996	1-way sensitivity analysis	Discount rates, morbidity/mortality ratio	No significant impact on conclusion.
Kallmes et al., 1998	1-way sensitivity analysis	Rate of aneurysm rupture, coil failure rate, procedure-related morbidity, recanalization of coiled aneurysms, rate of rupture of partially coiled aneurysms, life expectancy, QOL, discount rate	Most influential variable was annual rupture rate. Other variables impacting the cost-effectiveness ratio over the threshold of US\$50,000/QALY gained are life expectancy of patients, procedure-related morbidity rate, & recanalization rate.
Kameda et al., 2017	Not done	NA	NA
Kawamoto et al., 2016	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Health state; QOL score; costs of the main treatment strategies, follow-up treatment, & adverse events; discount rate	Most influential variables were cost of DBS, cost of medical treatment, probability of improvement w/ DBS, & QOL scores at advanced PD stage. Probability of DBS being below the threshold of US\$41,000 was 93%.

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TABLE 4. Summary of sensitivity analysis

Authors & Year	Sensitivity Analysis	Uncertainty Parameters	Impact on Conclusion
Khan et al., 2012	Probabilistic sensitivity analysis	Not stated	Net cost (95% CI) of CAS & CEA in the sensitivity analysis ranged from US\$18,264 to US\$20,156 & US\$13,076 to US\$15,084, respectively. At the threshold of US\$100,000/QALY gained, probability of cost-effectiveness of CAS was 1.3%.
King et al., 1995	1-way sensitivity analysis	Age, annual probability of SAH from a UIA, morbidity & mortality after elective surgery, postop recovery period duration, postop recovery period function, value of living w/ a neurological deficit, value of knowingly living w/ an asymptomatic UIA, discount rate	The most influential variables were the health utility value of knowingly living w/ untreated aneurysm, discount rate, & probability of SAH. Elective surgery crosses the WTP threshold of US\$50,000/QALY gained if surgery-related mortality is >2.2%, value of knowingly living w/ aneurysm is >0.98, discount rate is >10.8%, & life expectancy is <16.2 yrs.
King et al., 1997	1-way sensitivity analysis	Seizure free postop, improvement in QOL, long-term risk of death, cost of AEDs, protocol cost, income of patient, discount rate, age, surgery-related death rate	ATL crosses the threshold of US\$50,000/QALY gained if postop improvement in QOL is <0.08, discount rate >9%, or average protocol cost per patient is >\$63,600.
Koffijberg et al., 2011	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Age, sex, clinical condition, days of hospitalization, probability of outcome, size of aneurysm, location of aneurysm	Occlusion had no benefit in patients admitted in poor condition 10 days post-SAH. Other influencing variables were age, sex, days of hospitalization, treatment cost, & clinical condition of the patient.
Kunz et al., 2016	Probabilistic sensitivity analysis, 1-way sensitivity analysis	ASPECTS, mRS score, occlusion, time from symptom onset, NIHSS score	No impact on conclusion at the threshold of US\$50,000/QALY gained. Endovascular thrombectomy had a 100% probability of being below the threshold of US\$50,000/QALY gained.
Langfitt, 1997	1-way & multiway sensitivity analyses	Additional evaluation cost, age of patient, mortality, morbidity, seizure freedom, discount rate, follow-up cost, & QOL. Assumes seizure outcomes remain constant throughout the follow-up period.	No impact on conclusion at the threshold of US\$50,000/QALY gained.
Leppert et al., 2015	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Clinical efficacy of treatment, mortality rate, cost, utilities	No impact on conclusion at the threshold of US\$50,000/QALY gained. Endovascular thrombectomy had 98% probability of being below the WTP threshold of US\$50,000/QALY gained.
Lobotesis et al., 2016	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Cost, age, health state utility, death rate, recurrent stroke rate	No impact on conclusion at the threshold of £30,000/QALY gained. Endovascular thrombectomy had 99% probability of being below the WTP threshold of £30,000/QALY gained.
Martino et al., 2013	Not done	NA	NA
McIntosh et al., 2016	Probabilistic sensitivity analysis, 1-way & 2-way sensitivity analysis	Assumes 10-yr life span for the original pulse generator & electrodes, surgery QALY gains to increase by around 30%, annual follow-up costs in the medical therapy arm to increase by around ≥30%	Increasing utility gain in surgery arm by 50% of EQ-5D value at 1 yr reduces ICER to £184,517/QALY gained. Reducing total cost of surgery by 30% results in a reduction in ICER to around £179,014/QALY gained. Combining these 2 assumptions reduces ICER to £70,500/QALY gained. There was low probability of ICER being below the threshold of £20,000/QALY gained.
Mehta et al., 1997	1-way sensitivity analysis	Both cost & treatment effectiveness data were varied by 10%, 25%, 33%, & 50% (calculated one at a time while holding other variables constant to determine durability of results). Survival outcome of SRS & surgery were assumed to be equal.	SRS cost-effectiveness remains superior to that of surgery except for a single value; at 50% projected decline in health outcome after SRS, the incremental cost-effectiveness of surgery is better.

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TABLE 4. Summary of sensitivity analysis

Authors & Year	Sensitivity Analysis	Uncertainty Parameters	Impact on Conclusion
Nussbaum et al., 1996	1-way sensitivity analysis	Costs of procedures & complications were estimated based on average reimbursement rates. Patients were assumed to be 65 yrs old at time of analysis & in a "well" state. Sensitivity analysis varied the costs by $\pm 20\%$ from baseline costs for stroke care, $\pm 20\%$ stroke rate, & $\pm 20\%$ for the weightings for minor & major stroke.	No significant impact on the conclusion except in the extreme range. An increase in CEA cost by 34% (US\$16,765) will result in the lifetime cost for CEA & observation becoming equivocal. If the perip stroke rate exceeds 12%, the relative benefit of CEA becomes small. At a stroke rate of 20% less than baseline, aspirin therapy costs US\$1759 less than the cost of CEA.
Ooms et al., 2017	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Types of DBS	With rechargeable DBS batteries, ICER was reduced to €65,394/QALY gained, or 57% probability of being cost-effective. At long-term outcome (4 yrs post-DBS), there was a 50% probability of being more cost-effective at the threshold of €80,000/QALY gained.
Pollock & Ecker, 2005	1-way sensitivity analysis	Cost & morbidity of the treatments	Reduction in cost of morbidity & additional surgeries did not make either MVD or SRS more cost-effective than glycerol rhizotomy. Both MVD & SRS would be more cost-effective than glycerol rhizotomy if the cost of additional surgeries thereafter increased 79% & 83%, respectively.
Porter et al., 1997	1-way sensitivity analysis	Surgery-related mortality, morbidity, cost, time, utility, discount rate	Most influential variables were surgery-related mortality & morbidity. Surgical management crossed the threshold of Can\$100,000/QALY gained when rate of morbidity exceeded 12% or surgery-related mortality rate exceeded 4%.
Ravikumar et al., 2017	Probabilistic sensitivity analysis, 2-way sensitivity analysis	Effectiveness & cost of treatment	Effectiveness & cost of FUS are the most influential factors in ICER compared to SRS.
Rudmik et al., 2015	1-way sensitivity analysis, multivariate probabilistic sensitivity analysis	Cost, probability of complications, utility, discount rate	There was a 79% chance that the endoscopic approach was cost-effective at the threshold of US\$50,000/QALY. Only if the cost of the microscopic approach were reduced to US\$6476 would it become more cost-effective compared to the endoscopic approach. No other variables significantly influenced the ICER.
Rutigliano et al., 1995	1-way sensitivity analysis	Performed threshold analysis on SRS average annual vol, SRS average procedure cost, resection average procedure cost, SRS average morbidity cost, resection average morbidity cost, SRS median survival, & resection median survival that would result in equalization of the incremental cost-effectiveness of the 2 treatments	To achieve equal incremental cost-effectiveness btwn surgery & SRS, the following variables need to be changed: SRS cost increased by 34.7%, SRS procedure vol decreased by 38.7%, increased SRS average morbidity by 240.5%, or reduced median survival after SRS by 12.7%. Also, a decrease in surgery cost by 18.8% or increase in median survival by 16.8% led to a similar ICER between the 2 arms.
Shireman et al., 2017	1-way sensitivity analysis	Sex, baseline age (<65, 65–75, >75 yrs), baseline NIHSS score, time from symptom onset to randomization, enrolling country, cost, utility, mortality	Lifetime cost-effectiveness findings were robust across a wide range of alternative assumptions. Stent retriever procedure remained under the threshold of US\$50,000/QALY gained in all circumstances.
Sivakanthan et al., 2014	Not done	NA	NA
Slof et al., 2015	1-way sensitivity analysis	Effectiveness of treatment, cost of new microscope	No impact on conclusion at the threshold of €30,000/QALY gained.
Stroupe et al., 2014	Probabilistic sensitivity analysis	Effectiveness of treatment, cost of procedure	At the threshold of US\$50,000/QALY gained, GPI was more cost-effective in 47% of cases regarding costs from the health care provider's perspective, & in 54% of cases from the societal perspective, compared to STN.

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TABLE 4. Summary of sensitivity analysis

Authors & Year	Sensitivity Analysis	Uncertainty Parameters	Impact on Conclusion
Tomaszewski & Holloway, 2001	1-way sensitivity analysis	Surgical complication rate, age, utility, effectiveness, cost	Most influential variables were QOL benefit of DBS, duration of effectiveness, cost of DBS, & frequency of battery change. If treatment benefit of DBS was <17.5%, DBS was above the threshold of US\$100,000/QALY gained.
Valdeorola et al., 2007	1-way sensitivity analysis	Removing patients w/ prolonged hospitalization or continuous infusion of apomorphine as treatment	Removal of a specific subset of patients in the best medical treatment group led to increase in ICER to €44,078–62,148/QALY gained.
Voigt & Barnett, 2016	Probabilistic sensitivity analysis, 1-way sensitivity analysis	Tumor progression, cost, probability of subtotal resection, use of Gliadel wafer	No impact on conclusion at the threshold of US\$50,000/QALY gained.
Vuong et al., 2013	Probabilistic sensitivity analysis	Cost, effectiveness of treatment	92% of cases showed that SRS was cheaper, & 59% of cases showed that SRS was dominant over resection.
Vuong et al., 2012	Probabilistic sensitivity analysis	Cost, effectiveness of treatment	34% of cases showed that SRS was dominant over resection.
Wernicke et al., 2016	Not done	NA	NA
Zhu et al., 2014	Not done	NA	NA
Zygourakis et al., 2014	1-way sensitivity analysis	Chance of death after observation, surgery, & RT; chance of developing vertigo after observation; costs of observation, RT, & surgery	RT remained dominant to observation in every scenario. ICER for surgery remained lower than the threshold of US\$150,000/QALY gained in patients 20–40 yrs old. ICER for surgery crossed the threshold when surgery-related death rate increased to 0.6% & RT-related death rate decreased to 0.3%.

EQ-5D = EuroQol-5D health survey; H & Y = Hoehn and Yahr, mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; PFS = progression-free survival; QOL = quality of life.

erogeneous for formal meta-analysis methodology. Specifically, the economic modeling, the source of cost and health outcome data, and the sensitivity analysis often differed widely. With the establishment of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), future methodology should be more standardized.²⁴ To address such variability, our review protocol was developed with stringent inclusion criteria that led to the exclusion of many studies that were partial economic evaluations, such as cost comparison studies. In addition, the determination of cost-effectiveness and WTP threshold is influenced by multiple factors and varies by country and health care payer system (i.e., public health care vs private insurance).⁴⁴ The WTP threshold used in this review may not be applicable to all readers, and should be interpreted in the context of their own health care systems. The WTP threshold remains highly variable between studies, with some US-based studies applying the WTP threshold up to US\$150,000/QALY based on the proposal from the WHO of 3 times the gross domestic product per capita.²⁰ For this review, the threshold of US\$50,000 per health outcome (QALYs, LYs) was used, given the heterogeneity of the study locations and their associated variability in gross domestic product. Finally, given the high cost of neurosurgical disorders and their treatment options, there may be a potential publication bias, especially for studies supported by industry funding; perhaps studies that show lack of cost-effectiveness may be not submitted for publication.

Conclusions

There is growing body of cost-effectiveness studies in cranial neurosurgery, especially within the last 5 years. Whereas there are numerous procedures, such as endovascular thrombectomy, that have been conclusively proven to be cost-effective for acute ischemic stroke, there remain promising interventions in our current practice that have yet to meet cost-effectiveness thresholds. This systematic review hopefully highlights the importance of high-quality cost-effectiveness research in neurosurgery, and would urge future clinical trials to incorporate cost-effectiveness into their study design as well as the usual establishment of clinical efficacy.

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