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Cost-Effectiveness of Deep Brain Stimulation for Advanced Parkinson's Disease in the United States

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Objectives: Deep brain stimulation (DBS), which uses an implantable device to modulate brain activity, is clinically superior to medical therapy for treating advanced Parkinson's disease (PD). We studied the cost-effectiveness of DBS in conjunction with medical therapy compared to best medical therapy (BMT) alone, using the latest clinical and cost data for the U.S. healthcare system.

Materials and Methods: We used a decision-analytic state-transition (Markov) model to project PD progression and associated costs for the two treatment strategies. We estimated the discounted incremental cost-effectiveness ratio (ICER) in U.S. dollars per quality-adjusted life-year (QALY) from the Medicare payer perspective, considering a ten-year horizon, and evaluated the robustness of our projections through extensive deterministic sensitivity analyses.

Results: Over ten years, DBS treatment led to discounted total costs of $130,510 compared to $91,026 for BMT and added 1.69 QALYs more than BMT, resulting in an ICER of $23,404 per QALY. This ICER was relatively insensitive to variations in input parameters, with neurostimulator replacement, costs for DBS implantation, and costs for treatment of disease-related falls having the greatest effects. Across all investigated scenarios, including a five-year horizon, ICERs remained under $50,000 per QALY. Longer follow-up periods and younger treatment age were associated with greater cost-effectiveness.

Conclusions: DBS is a cost-effective treatment strategy for advanced PD in the U.S. healthcare system across a wide range of assumptions. DBS yields substantial improvements in health-related quality of life at a value profile that compares favorably to other well-accepted therapies.

Keywords: Cost-effectiveness, deep brain stimulation, Parkinson's disease

Conflict of Interest: Wing Tech Inc. (Jan B. Pietzsch, PhD; Abigail Garner, MS) receives compensation for provision of consulting services to Medtronic, Inc., the manufacturer of the DBS device. Jan B. Pietzsch, PhD is President, and CEO of Wing Tech Inc., a health-economics consultancy providing health economics research and consulting services for a variety of medical technology companies and research institutions, including Medtronic, Inc., the manufacturer of the DBS device. He receives salary payments from Wing Tech Inc. and also has stock ownership in the company. Abigail Garner, MS provides services as Senior Research Expert to Wing Tech Inc. In this role, she receives compensation from Wing Tech Inc. William J. Marks, Jr., MD, MS-HCM received compensation for provision of clinical education and consulting services to Medtronic, the manufacturer of the DBS device. Development of the health-economic model used in this analysis was supported by Medtronic, Inc. William J. Marks, Jr., MD, MS-HCM received compensation for provision of clinical education and consulting services to Medtronic, the manufacturer of the DBS device.

INTRODUCTION

Deep brain stimulation (DBS)—a device-based treatment that delivers adjustable neuromodulation to specific brain targets—has emerged as the treatment of choice for patients with advanced Parkinson's disease (PD) having motor fluctuations (1–3). Such patients suffer from disabling bradykinesia, rigidity, tremor, gait, and balance dysfunction, and/or dyskinesia—despite treatment with optimized pharmacotherapy. A large body of evidence demonstrates that DBS improves cardinal motor symptoms significantly, increases the quantity and quality of "on" time (periods of high-quality motor function), reduces "off" time (time with poor motor function due to Parkinsonian symptoms), reduces dyskinesia, and improves quality of life (1–5). In addition, PD medication requirements of DBS patients are typically reduced (2,6–8).

Because DBS therapy is associated with substantial upfront costs for device implantation, and eventually for neurostimulator replacement when the device battery reaches end of service, it is important that healthcare decision makers understand the health-economic

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profile of this technology based on a comparison of incremental costs and benefits, typically provided as the result of cost-effectiveness analysis (9).

A number of studies have previously investigated the cost-effectiveness of DBS in the settings of several healthcare systems (10–13), but no analysis has yet been conducted for the United States healthcare system based on the latest clinical evidence and current healthcare costs. Our objective was therefore to evaluate the long-term cost effectiveness of DBS therapy among advanced PD patients, as compared to best medical therapy (BMT), taking the U.S. Medicare payer perspective. Notably, our analysis did not consider other comparators, such as apomorphine and duodopa, as these therapies were not yet available or used in the U.S. healthcare system at the time of the current study.

METHODS

Overview

We developed a state-transition (Markov) model to assess the effects of DBS treatment using the Medtronic DBS Therapy device (Medtronic, Inc., Minneapolis, MN) compared to BMT. The model was based in significant part on a previously published cost-effectiveness model for the United Kingdom's National Health Service (10). Similar to the source model, our adaptation for the United States encompassed 21 health states, including Hoehn & Yahr (H&Y) disease stages 1 to 5, each further characterized by the percentage of "off" time (0–25%, 26–50%, 51–75%, 76–100%), and death.

Transition probabilities were based on patient-level data from the six-month randomized controlled trial by Deuschl et al. (3), the baseline characteristics of which are consistent with studies performed in the United States (4,5), and on Parkinson's disease progression data from prior published studies described in greater detail below. Data about adverse events such as infections and device complications, as well as changes in drug utilization, were obtained from recent DBS studies performed in the United States. Therapy- and procedure-related costs were obtained from average Medicare reimbursement rates for FY 2014, targeted database queries, and systematic searches of the published literature. The base-case cohort analysis was constructed in accord with current device type uses and corresponding percentage of staged (implanting the neurostimulator[s] subsequent to the hospitalization for DBS brain lead implantation) versus non-staged procedures (implanting all system components on the same day).

Model Structure and Modeling Framework

The Markov model was used to direct the progress of two simulated cohorts with advanced PD: patients treated with DBS (in conjunction with BMT) and patients treated with BMT alone. Both of the competing cohorts were analyzed using the same model structure, which employed a cycle length of six months. In each cycle of the model, patients could worsen by one H&Y stage, progress by one level of "off" time, or both. If none of these events occurred, patients remained in the same stage of the model throughout the following cycle.

Except where otherwise indicated, all analyses were conducted using a ten-year horizon. This time horizon was chosen to reflect the chronic nature of PD. A graphical representation of the model is shown in Figure 1.

The primary outcome measure was the incremental cost-effectiveness ratio (ICER), defined as the incremental direct costs of medical treatment and consequences divided by the incremental health benefits expressed as quality-adjusted life-years (QALYs). The ICER is a common metric used in health-economic analyses to assess the value of an intervention. A therapy is considered to be a good value investment for the healthcare system if its associated ICER is below the respective healthcare system's willingness-to-pay threshold (9). In the U.S., the commonly referred threshold is between $50,000 and $150,000 per QALY gained (14). In accordance with current health-economic guidelines, costs and effects were discounted at 3% per year in this analysis (15).

Input Parameters

All baseline patient characteristics were modeled identically to those observed in the Deuschl et al. randomized controlled trial (average age 60.5 years; 64% male; H&Y staging based on patient-level data) (3). For both study strategies, trial-reported data at six months were used to define the initial effectiveness of the therapy. All other input parameters, including disease progression beyond six months, were derived from systematic searches of the PubMed literature and from published statistics and databases (see Table 1).

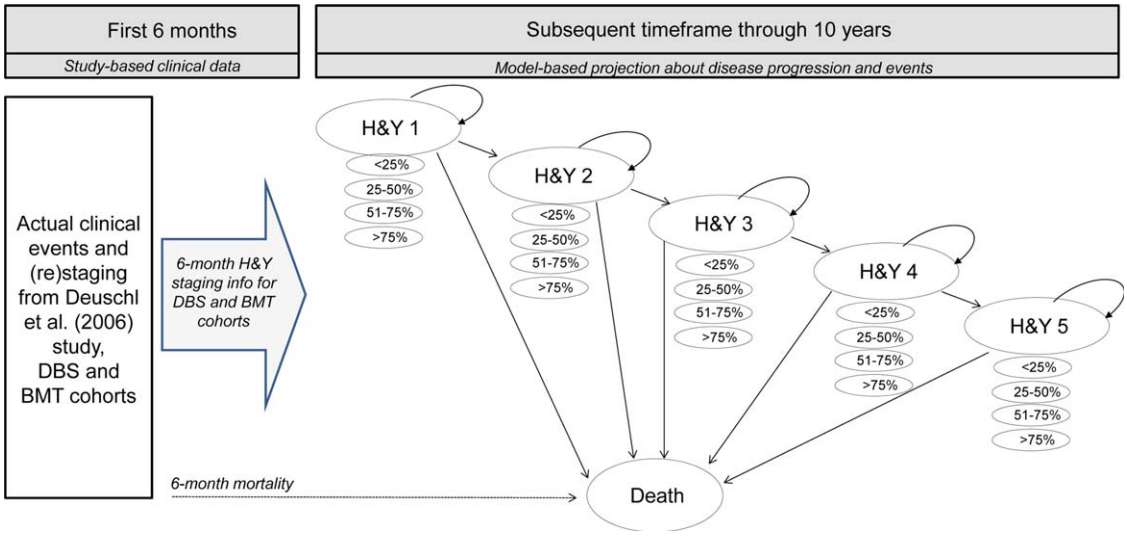

Figure 1. Schematic representation of study model.

Table 1. Model Input Parameters, Ranges Considered in Sensitivity Analyses, and Underlying Data Sources.

Parameter	Value	Range	References/Comments
Age of cohort at start of model (years)	60.5	50–70	(3)
DBS neurostimulator life (years)	4.0	2.5–5.5	DBS product master file, Table 7-1
Proportion of males in the cohort (%)	0.64	0–100%	(3)
Probability of progression from H&Y 1 to 2, H&Y 2 to 3, H&Y 3 to 4, H&Y 4 to 5 (per six months)	0.040–0.188	±50%	(15) See Supporting Information Appendix for detail
Probability of "off" time increasing from 0–25% to 26–50% category, 26–50% to 51–75%, 51–75% to 76–100% (per six months)	0.043–0.127		(16,17) See Supporting Information Appendix for detail
Utility associated with H&Y stage 1, depending on "off" time	0.51–0.78	Scenarios computed: 1) all utility inputs increased by 0.1; 2) all utility inputs increased by 0.2;	(17), based on H&Y stage 1.5; see Supporting Information Appendix for further detail
Utility associated with H&Y stage 2, depending on "off" time	0.49-0.72	3) total discounted QALY gain calculated at 50%, 75%, 125%, and 150% of base-case gain.	(17), based on H&Y stage 2.5; see Supporting Information Appendix for further detail
Utility associated with H&Y stage 3, depending on "off" time	0.38–0.64		(18); see Supporting Information Appendix for further detail
Utility associated with H&Y stage 4, depending on "off" time	0.12–0.39		(18); see Supporting Information Appendix for further detail
Utility associated with H&Y stage 5, depending on "off" time	−0.13 to 0.13		(18); see Supporting Information Appendix for further detail
Rate of DBS-related infection, first cycle; subsequent cycles (infections per patient)	0.0625; 0.005	±50%	(19), see Supporting Information Appendix
Probability of device complication in DBS arm	0.026	±50%	(4), see Supporting Information appendix
Number of falls per one-year period in H&Y 3	1.0	−50% to 200%	(20), see Supporting Information Appendix
Relative risk of fall in H&Y 4 (vs. H&Y 3)	1.72	1.0	(20)
Relative risk of fall in H&Y 5 (vs H&Y 3)	2.96	1.0; 1.72	(20)
Relative risk of falls in first cycle for DBS vs. BMT patients (added falls for DBS patients)	3.12	1.0–6.24	(5), RR for falls in DBS vs. BMT patients, first six months
Probability of required medical care following a fall	0.62		(21), proportion of falls in which patient was injured
Probability of withdrawal from DBS, first cycle	0.1	±50%	(3,22)
Probability of withdrawal from DBS, subsequent cycles	0.02		Assumption
Relative risk of mortality for patients in H&Y 2; H&Y 3; H&Y 4 or 5 (vs. H&Y 1) >65 years	2.03; 2.16; 4.99	1.0–4.99	(23), see Supporting Information Appendix for detail
Total cost of DBS implantation (generator, leads, physician fees)	$33,319	±30%	Based on 2014 national average Medicare MS-DRG and physician fee schedule payments; base-case based on current device and implantation type shares; see Supporting Information Appendix
Cost of managing DBS-related infection	$23,441	±30%	FY 2014 Medicare reimbursement, see Supporting Information Appendix
Cost of managing DBS device complication	$15,902		FY 2014 Medicare reimbursement, see Supporting Information Appendix
Cost of DBS explantation	$4,918		FY 2014 Medicare reimbursement, see Supporting Information Appendix
Cost of DBS neurostimulator replacement procedure	$26,653		Assumed generator replacement cost: Activa SC (APC 0039 plus CPT 61885); Activa RC and Activa PC (APC 0315 plus CPT 61886)
Cost of pre-operative assessment and work-up for DBS	$432		CT (CPT 70450); MR (CPT 70551) plus CPT 99205 (E&M)

Table 1. *Continued*

Parameter	Value	Range	References/Comments
Cost of required medical care due to a fall	$5,030	50–200%	Assumption based on (23): 89.1% nonhospitalized, 10.9% hospitalized
Cost per cycle of drugs in BMT arm	$2,631	2,832–4,370; also ±50% utilization	MarketScan Medicare subcohort, see Supporting Information Appendix
Reduction in medication cost in DBS arm	27.3%–59.6%, (time-dependent)	±20% change relative to base-case	Based on reduction in drug utilization reported in (6) (first three years, using info from (24)), and (2,8,25) (subsequent periods); see Supporting Information Appendix

Therapy Effectiveness

In the Markov model, the effectiveness of DBS therapy was based on clinical trial data from the Deuschl et al. study (3). Specifically, baseline and six-month data on H&Y staging and "off" time informed the initial difference between the DBS and BMT treatment arms. Subsequently, both treatment arms were subject to long-term PD progression, informed by transition probabilities derived from literature-reported time-to-event data about H&Y stage progression (16) and from information about progression of "off" time based on a prior study (17,26). Based on different disease staging between the two cohorts, the likelihood of falls differed, as did the patients' health-related quality of life.

Costs

Costs were considered from the U.S. Medicare payer perspective and included only direct healthcare costs, in line with current U.S. guidelines for health-economic analyses (15). For the base-case analysis, the costs of DBS system implantation and eventual neurostimulator replacement were based on current device use patterns and on information about the respective percentages of non-staged versus staged implantation. Treatment costs associated with such DBS complications as infections were estimated on the basis of detailed calculations that took into account current practice of care (see Supporting Information Appendix). Treatment costs for PD-related falls requiring medical care were estimated on the basis of published data about necessary outpatient versus inpatient treatment and associated treatment costs (25,27). Unless derived from FY 2014 Medicare reimbursement schedules, all cost estimates were converted to 2014 U.S. dollars using the general consumer price index for the United States (28).

The costs used for baseline PD medications were based on a database query of Medicare Supplement enrollees with a claim for DBS lead implantation who had been continuously enrolled for the 12 months prior to lead implantation. For the base-case analysis, we conservatively considered only net payments (the amount of Medicare payments minus the amount of patient copayments).

Medication costs for BMT patients were conservatively presumed to remain at the baseline cost (i.e., utilization) level. The respective costs for DBS patients were presumed to be lower, with reduced medication use estimated for the first 36 months based on findings of a recent U.S. study (18), and on several long-term studies for the remaining years (2,8,29).

For both study cohorts, the model did not take into account baseline healthcare costs or medical care unrelated to DBS treatment or to the treatment of PD-related clinical events, such as falls.

Mortality and Health-Related Quality of Life

Age- and gender-specific baseline mortality rates were based on the latest U.S. life tables (30). These baseline mortality rates were multiplied by H&Y stage-dependent mortality risks to capture PD-related elevated mortality (see Table 1). For the first six months of modeled progress, mortality data for both comparators were directly based on information from the underlying trial (3).

As no preference-based scores for quality of life had been collected in the underlying trial that covered the modeled combinations of health states, state-specific utility values were based on two studies that reported utility information stratified by H&Y states and percent "off" time (18,31). We confirmed the consistency and overall validity of these utility assumptions by comparing them to the range of preference weights reported for H&Y states 1 to 5 in a prior study that collected EuroQoL 5D (EQ-5D) summary scores from 124 subjects (32).

To account for disutility associated with DBS implantation and neurostimulator replacement, we assumed temporary utility reductions for a period of three months, in line with prior studies (11,19).

Analysis of Uncertainty

Comprehensive deterministic sensitivity analyses were performed to evaluate the effects of parameter uncertainty. The parameter ranges were derived from the literature, trial data, and author estimates, and in the absence of appropriate data were defined to cover broad parameter ranges of −50% to +100% of baseline for effectiveness parameters and, per health-economic guidelines, ±30% for procedure cost parameters (see Table 1). For each scenario, total and incremental discounted costs, QALYS, and the resulting ICER were computed. The overall analysis and reporting of results were conducted in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (20).

RESULTS

Base-Case Results

At base-case assumptions, DBS was found to be associated with substantive improvements in symptom severity compared to BMT. The reduction in mean H&Y score for the DBS cohort—compared to the BMT cohort—was highest at the trial-documented six-month follow-up (−1.07; a 29% reduction), and then declined gradually over time (see Fig. 2). The model-projected DBS treatment effect, measured against baseline, was reduced by half at 3.5 years of follow-up and further declined to zero at eight years of follow-up, while maintaining continued benefit over the BMT cohort.

The projected differences in symptom severity and "off" times between the two cohorts led to meaningful improvements in

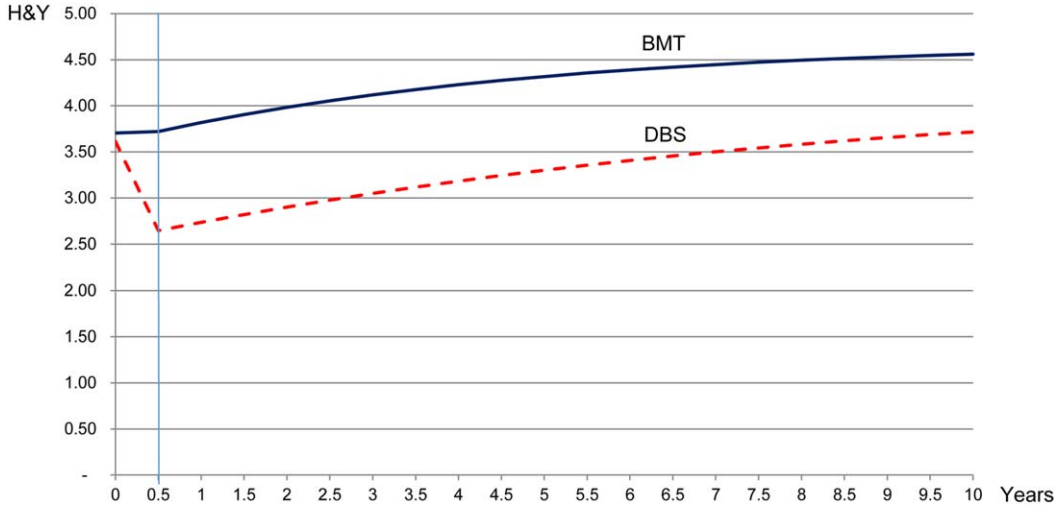

Figure 2. Model-based projection of mean H&Y staging scores for DBS and BMT cohorts through ten years. First six months based on Deuschl et al. (2006) trial data; subsequent periods based on natural PD progression.

health-related quality of life for the DBS cohort as compared to the BMT cohort. Over the ten-year study horizon, DBS therapy resulted in a discounted QALY gain of 1.69 more than BMT (3.19 vs. 1.50 QALYs). The corresponding ten-year costs for DBS and BMT were $130,510 and $91,026, respectively, leading to an ICER of $23,404. A breakdown of costs for both strategies, by cost type, is provided in the Supporting Information Appendix.

Sensitivity Analysis Results

Comprehensive deterministic sensitivity analyses found that variations across the assumed ranges shown in Table 1 did not materially change the cost-effectiveness results of the study (see Table 2 and Tornado Diagram in Supporting Information Appendix). Notably, the ICER remained below $50,000 per QALY gained across all considered scenarios.

Among the variables with the most significant impact on the ICER was the cost of DBS implantation and related procedures. Increasing this cost by 30% from baseline increased the ICER to $36,475 per QALY gained; reducing it by 30% led to an ICER of $10,704 per QALY. A shorter time to neurostimulator replacement of 2.5 years increased the ICER to $34,880 per QALY, while a replacement time of 5.5 years reduced the ICER to $15,555 per QALY.

When utilization of drugs–for both groups–was assumed to be 50% higher than the established baseline, the ICER decreased to $12,519 per QALY; when drug utilization was assumed to be 50% lower than baseline, it increased to $34,289 per QALY. Use of average wholesale prices for the PD drugs in the analysis—as opposed to Medicare net payments—decreased the ICER to $11,897 per QALY.

Reducing the horizon of the study analysis to five years increased the ICER to $38,567 per QALY; extending it to 15 years only minimally decreased the ICER to $21,633 per QALY. Assuming reduced or increased probabilities for PD progression did not have a material effect on the ICER, nor did uniform increases in utility inputs by 0.1 and 0.2 points. If the overall QALY gain was assumed to be only 50% of the base-case–a hypothetical assumption to evaluate the effect of extreme variation in this effectiveness parameter–the ICER increased to $46,808 per QALY.

Assuming no increased mortality for PD patients, compared to the general population, and no mortality differences between patients of different PD severity, led to a reduced ICER of $19,571 per QALY.

Consideration of individual device types, lead configurations, and staging revealed gradual differences in the resulting ICERs, as evidenced by an obtained range of $16,877 to $39,269 per QALY gained.

DISCUSSION

A variety of studies document the ability of DBS to significantly improve Parkinsonian motor symptoms, reduce motor fluctuation, and improve quality of life compared to treatment with pharmacotherapy alone (3–5,18). Our study, which was based on outcomes from a large-scale controlled clinical trial in Europe—which were consistent with outcomes reported in the United States (5)—found DBS to be associated with substantial gains in health-related quality of life over the ten-year time horizon of the analysis, primarily as a result of improvements in PD symptom severity over BMT. At the same time, DBS was associated with cost increases of approximately $40,000 over ten years. The resulting ratio of incremental costs to gained QALYs leads to a favorable cost-effectiveness profile, suggesting that DBS – which is reimbursed by Medicare and private payers – is a good investment for healthcare payers in the United States.

As in any health-economic model, accounting for the validity and appropriateness of study assumptions is critical. In our model, the assumptions about initial treatment effects were based directly on a randomized controlled trial of substantial size (3). Assumptions about subsequent disease progression beyond six months led to projections of treatment effect (Fig. 2) that are well supported by data from several recent studies reporting long-term outcomes of DBS. In a study of 37 bilateral subthalamic nucleus (STN) stimulation patients, Schupbach et al. report sustained improvement in motor fluctuations compared to baseline (2). Specifically, the authors observed reductions in motor disability (UPDRS III) scores for the "on" drug state through five years, and noted maintained substantial reductions of 50% in motor disability scores for the "off" drug state at five years. Fasano et al. found an improvement in the UPDRS motor scale of 55% over baseline at five years, and 39% at eight years (29). These findings were confirmed in a subsequent study by

Table 2. Base-case and Sensitivity Analysis Results for Scenarios Outlined in Table 1.

Scenario	Disc. Cost BMT	Disc. Cost DBS	Incr. Cost	Disc. QALY BMT	Disc. QALY DBS	Incr. QALY	ICER
Base-case (ten years)	$91,026	$130,510	$39,484	1.50	3.19	1.69	$23,404
Five year horizon	$53,550	$91,444	$37,894	1.20	2.19	0.98	$38,567
15 year horizon	$110,933	$154,293	$43,360	1.56	3.56	2.00	$21,633
Age 50 years	$104,061	$141,484	$37,423	1.57	3.36	1.79	$20,923
Age 70 years	$69,641	$111,436	$41,794	1.38	2.86	1.49	$28,106
Time to stimulator replacement 2.5 years	$91,026	$149,723	$58,697	1.50	3.19	1.68	$34,880
Time to stimulator replacement 5.5 years	$91,026	$117,313	$26,287	1.50	3.19	1.69	$15,555
100% female	$96,901	$135,484	$38,583	1.53	3.27	1.73	$22,248
0% female	$87,969	$127,891	$39,922	1.49	3.15	1.66	$24,028
Discount rate 0%	$103,329	$144,446	$41,118	1.64	3.56	1.92	$21,380
Discount rate 10%	$70,341	$107,322	$36,981	1.27	2.56	1.29	$28,729
PD Disease progression probabilities −50% of base-case	$87,182	$126,452	$39,270	1.97	3.77	1.80	$21,764
PD Disease progression probabilities +50% of base-case	$93,608	$133,983	$40,375	1.19	2.72	1.53	$26,402
UTILITIES							
Discounted incremental QALY gain 50% of base-case	$91,026	$130,510	$39,484			0.84	$46,808
Discounted incremental QALY gain 75% of base-case	$91,026	$130,510	$39,484			1.27	$31,206
Discounted incremental QALY gain 125% of base-case	$91,026	$130,510	$39,484			2.11	$18,723
Discounted incremental QALY gain 150% of base-case	$91,026	$130,510	$39,484			2.53	$15,603
All utilities 0.1 higher than in base-case assumption	$91,026	$130,510	$39,484	2.20	3.92	1.72	$22,958
All utilities 0.2 higher than in base-case assumption	$91,026	$130,510	$39,484	2.90	4.65	1.75	$22,529
No procedure-related disutility	$91,026	$130,510	$39,484	1.50	3.22	1.71	$23,068
Procedure-related disutilty twice as high as in base-case	$91,026	$130,510	$39,484	1.50	3.17	1.66	$23,750
ADVERSE EVENTS							
Rate of DBS-related infection low (50% of base-case)	$91,026	$128,479	$37,453	1.50	3.19	1.69	$22,200
Rate of DBS-related infection high (150% of base-case)	$91,026	$132,541	$41,515	1.50	3.19	1.69	$24,608
Probability of device complication low (50% of base-case)	$91,026	$128,067	$37,041	1.50	3.19	1.69	$21,956
Probability of device complication high (150% of base-case)	$91,026	$132,953	$41,927	1.50	3.19	1.69	$24,852
PROBABILITIES OF FALLS							
Number of falls in H&Y3 (also used for RR-based calculations of H&Y4, H&Y5) low (−50%)	$68,602	$114,762	$46,160	1.50	3.19	1.69	$27,362
Number of falls in H&Y3 (also used for RR-based calculations of H&Y4, H&Y5) high (+100%)	$135,875	$162,006	$26,132	1.50	3.19	1.69	$15,489
Relative risk of falls in H&Y5 same as in H&Y4 (1.72)	$77,434	$123,662	$46,227	1.50	3.19	1.69	$27,401
No increase of relative risk of falls in H&Y4, H&Y5, compared to H&Y3	$65,407	$115,379	$49,972	1.50	3.19	1.69	$29,621
No increased risk of falls first six months in DBS vs. BMT	$91,026	$125,651	$34,625	1.50	3.19	1.69	$20,524
Double of baseline relative risk of falls first six month in DBS vs. BMT	$91,026	$137,661	$46,635	1.50	3.19	1.69	$27,643

Table 2. *Continued*

Scenario	Disc. Cost BMT	Disc. Cost DBS	Incr. Cost	Disc. QALY BMT	Disc. QALY DBS	Incr. QALY	ICER
PROBABILITY OF REQUIRED MEDICAL CARE FOLLOWING FALLS							
Probability of required medical care following a fall low (0.4)	$75,112	$119,334	$44,222	1.50	3.19	1.69	$26,213
Probability of required medical care following a fall high (0.9)	$111,280	$144,734	$33,454	1.50	3.19	1.69	$19,830
DBS THERAPY WITHDRAWAL							
Probability of DBS therapy withdrawal low (−50%)	$91,026	$133,462	$42,436	1.50	3.23	1.72	$24,664
Probability of DBS therapy withdrawal high (+50%)	$91,026	$127,944	$36,918	1.50	3.16	1.66	$22,267
MORTALITY							
Excess mortality low (RRs by H&Y stages 50% of base-case RRs)	$102,565	$140,174	$37,608	1.56	3.34	1.77	$21,195
Excess mortality high (RRs by H&Y stages 150% of base-case RRs)	$81,456	$122,268	$40,812	1.45	3.06	1.61	$25,396
No excess mortality associated with PD	$110,031	$144,810	$34,780	1.57	3.35	1.78	$19,571
DBS-RELATED PROCEDURE COSTS							
All DBS-related procedure costs low (−30%)	$91,026	$109,085	$18,059	1.50	3.19	1.69	$10,704
All DBS-related procedure costs high (+30%)	$91,026	$152,562	$61,536	1.50	3.19	1.69	$36,475
Cost of required medical care due to a fall low (50% of baseline)	$68,602	$114,762	$46,160	1.50	3.19	1.69	$27,362
Cost of required medical care due to a fall high (200% of baseline)	$135,875	$162,006	$26,132	1.50	3.19	1.69	$15,489
PHARMA COST							
Pharma cost for six-month cycle based on Average Wholesale Price (AWP)	$115,302	$135,373	$20,071	1.50	3.19	1.69	$11,897
Pharma cost for six-month cycle based on Total payment	$93,830	$131,072	$37,242	1.50	3.19	1.69	$22,075
Baseline pharma utilization low (50% of baseline)	$72,663	$130,510	$57,847	1.50	3.19	1.69	$34,289
Baseline pharma utilization high (150% of baseline)	$109,389	$130,510	$21,121	1.50	3.19	1.69	$12,519
Reduction in pharmaceutical dosage with DBS lower (20% relative difference from baseline assumptions)	$91,026	$133,016	$41,989	1.50	3.19	1.69	$24,889
Reduction in pharmaceutical dosage with DBS higher (20% relative difference from baseline assumptions)	$91,026	$128,005	$36,979	1.50	3.19	1.69	$21,919
DEVICE TYPE AND STAGING ASSUMPTION							
1 ACTIVA PC, staged implantation	$91,026	$134,516	$43,490	1.50	3.19	1.69	$25,778
1 ACTIVA PC, non-staged implantation	$91,026	$119,499	$28,473	1.50	3.19	1.69	$16,877
2 ACTIVA SC, staged implantation	$91,026	$157,274	$66,248	1.50	3.19	1.69	$39,269
2 ACTIVA SC, non-staged implantation	$91,026	$121,862	$30,836	1.50	3.19	1.69	$18,278

Zibetti et al., who found that STN-DBS was able to provide a considerable improvement in motor function as long as nine years after the initiation of therapy (7). A recent study of 26 STN-DBS patients with 11 years' follow-up showed gradually worsening UPDRS III scores in the on-medication state (20.7 pre-operative, 15.7 at one year, 18.8 at five years, and 29.8 at 11 years) (8). Off medication, patients still showed significant improvements in UPDRS III scores at 11 years of follow-up.

The gradual deterioration of the BMT cohort, as projected in our model, is in keeping with the literature, which shows not only the worsening of symptoms over time, but also the overall declining benefit of PD medications (7,21,22).

The Deuschl et al. randomized controlled trial underlying our study did not collect preference-based quality-of-life data, such as those gathered for an EQ-5D summary score. Consequently, our estimate of gains in quality-adjusted life years relies on utility scores from several previously published studies. These model inputs were generally consistent with the H&Y-stage-dependent EQ-5D scores reported in a study of 124 PD patients in the United Kingdom (32).

Collection of preference-based quality-of-life weights during DBS trials is very limited. Valldeoriola et al. conducted a clinical trial involving 29 patients (14 of whom were DBS patients), which is the only known study to report EQ-5D weights actually collected during a trial (12). That study found a DBS-related increase in utility of 0.276 between baseline and six-month follow-up (a 54% increase from 0.51 to 0.786). These data also formed the basis for QALY computations in a recent cost-effectiveness analysis of DBS conducted for the German healthcare system (11).

Using the utility assumptions of our model and patient-level data about disease staging, from the Deuschl et al. study (3), we find a utility gain of 0.22 at six months follow-up (a 57% increase from 0.39 at baseline to 0.613, reflecting a substantial increase in health-related quality of life. Although the baseline utility weights of the Valldeoriola et al. study are higher than those suggested by the PD quality-of-life data underlying our study (18,31,32), both studies capture the effects of DBS treatment in similar utility increases (12). Our sensitivity analyses showed that DBS would remain cost effective even at half the QALY gain projected in our base-case analysis.

Though international cost-effectiveness results—for a number of reasons—cannot serve as a direct reference for comparison, it is worthwhile to put our findings in perspective with findings of prior analyses. The Eggington et al. (10) UK analysis, which formed the basis of our model, found DBS to be cost effective at an ICER of £20,678 per QALY gained (five-year horizon). The Dams et al. (11) German analysis also found DBS to be cost effective at an ICER of €6,700 per QALY gained (over a lifetime horizon). This study differed from ours in assuming for the base-case a mixed cohort of early- and late-stage PD patients, and considering a neurostimulator replacement cost significantly lower than in our analysis. It also assumed that DBS yields benefits only up to four years after surgery. This highly conservative assumption led the researchers to report an incremental QALY gain slightly lower than the projection of our model at five-year follow-up (0.30 vs. 0.34), and an incremental QALY gain only about half of our projection at ten-year follow-up (0.87 vs. 1.69). A recent additional UK analysis by McIntosh et al. (23) based on PD SURG data did find DBS to be associated with improved outcomes, but at a less favorable ICER of £45,180 per QALY gained (at five-year horizon), and thus above the current UK willingness-to-pay threshold. This less favorable ICER, in part, stems from quality of life gains observed in PD SURG that were smaller than those observed in other recent RCTs (3,32). The Valldeoriola et al. (12) analysis conducted in the Spanish healthcare setting reported an ICER of €34,389 per QALY gained (using only a one-year horizon). That study's report of QALYs gained was more than double the single-year gain projected in our model (0.221 vs. 0.109). A modeling study conducted by Tomaszewski et al. (13) for the U.S. healthcare system reported an ICER of $49,164 per QALY gained (over a lifetime horizon). However, this study did not rely on actual PD states and disease progression (13).

Our study is subject to several limitations. First, it relies on the data of a randomized trial that reported only six-month outcomes and uses data from other published studies to model disease progression in subsequent periods. Though we have shown that our modeled progression and decreasing effect sizes are concordant with outcomes reported in long-term follow-up studies, additional long-term clinical data are desirable.

Second, in the absence of trial-collected utility data, we estimated health-related quality-of-life gains on the basis of utility data from other published studies. As our sensitivity analyses have shown that quality of life is a critical variable in our model, it would clearly have been preferable to use trial-collected data, which would have further increased the accuracy of our projections. Nevertheless, we have shown that even reducing the projected QALY gain by half still leads to a favorable incremental cost-effectiveness ratio.

Third, our cost assumptions are based on Medicare reimbursement amounts. Although this is a common assumption used in U.S. cost-effectiveness studies—and most advanced PD patients will be covered by Medicare—costs of non-Medicare patients might differ. However—directionally—similar findings can be expected in non-Medicare patients, as not only DBS costs might differ, but also costs of PD medications and treatment of PD-related events that are reduced by DBS.

Fourth, our sensitivity analyses were limited to deterministic one-way analyses, and did not include probabilistic multi-parameter sensitivity analysis (PSA). However, as variation in most of the parameters, such as disease progression and stage-specific mortality, affect both strategies, the added value of a PSA would be limited.

Fifth, our analysis conservatively assumes a neurostimulator life of four years. Rechargeable DBS devices, which might be more commonly used in the U.S. in future years, have a substantially longer lifetime of up to nine years. This increased lifetime would reduce neurostimulator replacement cost and thereby further improve the health-economic profile of DBS.

Finally, the cost-effectiveness of therapies for chronic conditions should usually be evaluated over a lifetime perspective. In light of the fact that the follow-up data from previous clinical studies are available only for periods of ten years to a maximum of 15 years, however, we opted to limit our base-case analysis to a ten-year horizon. Our sensitivity analyses and data from other studies suggest that a longer follow-up period would likely have made the cost-effectiveness profile of DBS even more favorable (11). The same holds for incorporation of indirect costs, which were not considered in our analysis.

In summary, our findings suggest that DBS is a cost-effective treatment for advanced Parkinson's disease in the U.S. healthcare system across a wide range of assumptions. DBS yields substantial improvements in health-related quality of life at a value profile that compares favorably to other well accepted and reimbursed therapies.

Authorship Statement

Jan B. Pietzsch, PhD, designed the study, performed statistical analyses and interpretation of findings, wrote portions of the first draft, and provided revisions to subsequent drafts. Abigail M. Garner, MS, performed literature and database searches and statistical analyses. William J. Marks, Jr., MD, MS-HCM, designed the study, provided interpretations of findings, wrote portions of the first draft, and provided revisions to subsequent drafts.

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REFERENCES

1. Deuschl G, Schupbach M, Knudsen K et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. *Parkinsonism Relat Disord* 2013;19:56–61.

2. Schupbach WM, Chastan N, Welter ML et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. *J Neurol Neurosurg Psychiatry* 2005;76: 1640–1644.
3. Deuschl G, Schade-Brittinger C, Krack P et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896–908.
4. Follett KA, Weaver FM, Stern M et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010;362:2077–2091.
5. Weaver FM, Follett K, Stern M et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301:63–73.
6. Weaver FM, Stroupe KT, Cao L et al. Parkinson's disease medication use and costs following deep brain stimulation. *Mov Disord* 2012;27:1398–1403.
7. Zibetti M, Merola A, Rizzi L et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord* 2011;26:2327–2334.
8. Rizzone MG, Fasano A, Daniele A et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord* 2014;20:376–381.
9. Cohen D, Reynolds MR. Interpreting the results of cost-effectiveness studies. *J Am Coll Cardiol* 2008;52:2119–2126.
10. Eggington S, Valldeoriola F, Chaudhuri KR, Ashkan K, Annoni E, Deuschl G. The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease. *J Neurol* 2014; 261:106–116.
11. Dams J, Siebert U, Bornschein B et al. Cost-effectiveness of deep brain stimulation in patients with Parkinson's disease. *Mov Disord* 2013;28:763–771.
12. Valldeoriola F, Morsi O, Tolosa E, Rumia J, Marti MJ, Martinez-Martin P. Prospective comparative study on cost-effectiveness of subthalamic stimulation and best medical treatment in advanced Parkinson's disease. *Mov Disord* 2007;22:2183–2191.
13. Tomaszewski KJ, Holloway RG. Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis. *Neurology* 2001;57:663–671.
14. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371:796–797.
15. Gold MR. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.
16. Zhao YJ, Wee HL, Chan YH et al. Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. *Mov Disord* 2010;25:710–716.
17. Palmer CS, Nuijten MJ, Schmier JK, Subedi P, Snyder EH. Cost effectiveness of treatment of Parkinson's disease with entacapone in the United States. *Pharmacoeconomics* 2002;20:617–628.
18. Weaver FM, Follett KA, Stern M et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 2012;79:55–65.
19. Spottke EA, Volkmann J, Lorenz D et al. Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. *J Neurol* 2002;249:759–766.
20. Husereau D, Drummond M, Petrou S et al. Consolidated health economic evaluation reporting standards (CHEERS)–explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231–250.
21. Chen JJ. Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. *Am J Managed Care*. 2010;16:S87–S93.
22. Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. *Pract Neurol* 2013;13:140–152.
23. McIntosh E, Gray A, Daniels J et al. Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: economic evaluation alongside the PD SURG trial. *Mov Disord* 2016; e-pub ahead of print. doi: 10.1002/mds.26423.
24. Schuepbach WM, Rau J, Knudsen K et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368:610–622.
25. Bohl AA, Phelan EA, Fishman PA, Harris JR. How are the costs of care for medical falls distributed? the costs of medical falls by component of cost, timing, and injury severity. *Gerontologist* 2012;52:664–675.
26. Palmer CS, Schmier JK, Snyder E, Scott B. Patient preferences and utilities for 'off-time' outcomes in the treatment of Parkinson's disease. *Qual Life Res* 2000;9:819–827.
27. Bohl AA, Fishman PA, Ciol MA, Williams B, Logerfo J, Phelan EA. A longitudinal analysis of total 3-year healthcare costs for older adults who experience a fall requiring medical care. *J Am Geriatr Soc* 2010;58:853–860.
28. Labor_USDo. http://www.bls.gov/data/inflation_calculator.htm. Accessed 12 18 2013.
29. Fasano A, Romito LM, Daniele A et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 2010;133:2664–2676.
30. Arias E. *United States Life Tables. 2008*. National Vital Statistics Reports; Vol. 61, No. 3. Hyattsville, MD: National Center for Health Statistics; 2012.
31. Lowin J, Bergman A, Chaudhuri KR et al. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. *J Med Econ* 2011;14:584–593.
32. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? a comparison with quality of life in the general population. *Mov Disord* 2000;15: 1112–1118.

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