EXPERT REVIEWS

Cost–effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma

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Objectives: We examined the cost–effectiveness of treating poorly controlled, severe, persistent asthma patients with bronchial thermoplasty (BT), a novel technology that uses thermal energy to reduce airway smooth muscle mass, with 5-year outcome data demonstrating a durable reduction in asthma exacerbations. Study design: We conducted a model-based cost–effectiveness analysis assessing 5-year healthcare utilization, patient quality of life and adverse events. Methods: We utilized Markov modeling to estimate the costs and quality-of-life impact of BT compared with high-dose combination therapy among poorly controlled, severe, persistent asthma patients: those requiring high-dose combination therapy and having experienced an asthma exacerbation-related ER visit in the past year. Results: The cost–effectiveness of BT was US$5495 per quality-adjusted life year; and approximately 22% of sensitivity analysis iterations estimated BT to reduce costs and increase quality of life. Conclusions: BT is a cost–effective treatment option for patients with poorly controlled, severe, persistent asthma.

KEYWORDS: asthma • bronchial thermoplasty • bronchoscopy • cost–effectiveness • respiratory disease

Background

Asthma is one of the most common chronic diseases affecting the US population. More than 25 million people in the USA have the disease, and asthma exacerbations account for nearly 500,000 hospitalizations per year [1]. The standard care for treating severe, persistent asthma has long been pharmacological treatments, including a combination of long-term β2 agonists and long-term corticosteroid medications, while attempting to minimize the need for short-acting β2 agonists to treat acute exacerbations. Medication adherence issues, socioeconomics, social determinants and many other factors complicate optimal asthma treatment. Researchers have called for novel strategies and interventions to address severe persistent asthma patients who continue to experience exacerbations despite treatment with what is considered optimal pharmacological therapy [2–4].

Increased mass and contractility of the smooth muscle lining the airway can increase asthma morbidity by causing bronchoconstriction, obstruction of the airway and difficulty breathing [5–7]. Bronchial thermoplasty (BT) is a bronchoscopic procedure developed for the treatment of severe, persistent asthma patients 18 years or older whose asthma is not well-controlled with pharmacological treatments. BT is based on the hypothesis that reducing airway smooth muscle mass will reduce physiologic bronchoconstriction in the target airways and thus attenuate asthma symptoms [4,8]. BT is performed with the Alair™ System (Boston Scientific Corporation, Marlborough, MA, USA) as a series of 3 outpatient bronchoscopic procedures. Published, clinical data have demonstrated the safety and efficacy of BT out to at least 5 years in patients with severe, persistent asthma [9–14]. Among those treated with BT, researchers observed a 32% reduction in the severe

exacerbations and a 84% reduction in emergency room (ER) visits due to asthma, compared with those who received sham treatment [9]. This reduction in healthcare use was shown to persist out to at least 5 years in the follow-up study [11].

While there is evidence for the clinical benefits of BT, there are currently no published analyses assessing the cost–effectiveness of BT. The objective of this study was thus to develop a cost–effectiveness model to evaluate the costs and benefits of BT compared with standard care (SC) – defined as β2 agonists, steroids and in some cases additional controller medications such as leukotriene modifiers – in treating poorly controlled, severe, persistent asthma over a 5-year time period. Cost–effectiveness models commonly evaluate the benefit of treatments using quality-adjusted life years (QALYs), which incorporate both the quantity and quality of life. QALYs allow therapies for different therapeutic areas to be compared using the same metric. Cost–effectiveness information can thus assist decision-makers in evaluating the overall value of a new technology such as BT.

Methods
Overview
A cost–effectiveness model was developed to estimate, from the private, commercial payer perspective, the cost–effectiveness of treating asthma patients with BT in addition to SC (hereafter referred to as BT), compared with SC alone. SC is defined as inhaled corticosteroids (ICS) and long-acting β2 agonists (LABA), with additional controller medications as necessary (e.g., leukotriene modifiers). For each treatment option, we projected 5-year costs and QALYs to calculate incremental cost–effectiveness ratios (ICERs) (i.e., the ratio of incremental costs to incremental QALYs). Model inputs were based primarily on BT clinical trial data [9] and supplemented with data from published literature and publicly available databases when not available from the clinical trial data.

Analyses
In the base case analysis, we assessed the cost–effectiveness of BT compared with SC to treat poorly controlled, severe, persistent asthma patients – those requiring high-dose combination therapy (i.e., ICS + LABA), yet still experiencing exacerbations requiring at least one ER visit in the past 12 months. This criterion is broadly in line with that used in prior epidemiological studies [15–18]. While a broad range of patients may potentially benefit from BT, some commercial private payers have instituted policies that make access to BT conditional on prior healthcare utilization – as a base case, we consider the cost–effectiveness of BT to treat this population.

An additional exploratory scenario analysis was conducted to examine the cost–effectiveness of BT among severe, persistent asthma patients; this is a similar population to that analyzed in the base case, but without a specific requirement for ER use in the prior year. The population in this scenario is consistent with the inclusion criteria from the Asthma Intervention Research (AIR)2 trial, which examined the efficacy of BT compared with sham bronchoscopy among a population of symptomatic severe, persistent asthma patients. While some of the trial patients had prior healthcare utilization, such use was not required for trial inclusion [9].

For both the base case and the scenario analyses, the model predicted 5-year costs, quality-adjusted survival and ICERs for patients treated with BT versus SC alone.

Model structure
FIGURE 1 shows patients' flow through the model health states and events. The cost–effectiveness analysis was conducted using a Markov model that evaluated a hypothetical cohort of poorly controlled, severe, persistent asthma patients for 5 years (Microsoft® Excel™ 2010). Markov models evaluate the progression of disease over time and allow for patients to transition between health states, such as 'healthy' or various asthma exacerbations, at specified time intervals. Patient characteristics, such as average age and healthcare resource utilization, were informed by the characteristics of patients in the AIR2 trial, which examined the clinical impact of BT versus sham bronchoscopy [9]. In this model, the Markov cycle length was 2 weeks, during which patients could be 'healthy' with chronic asthma or experience asthma exacerbations requiring a physician visit, ER visit or hospitalization. At each 2-week cycle, costs, quality of life and clinical events were calculated. Patients were at risk of dying from the hospitalization or the chronic asthma state in the model. Both costs and benefits (i.e., QALYs) were discounted at 3% annually. The model structure and comparator is similar to a previously published model examining the cost–effectiveness of omalizumab [19].

Clinical inputs
Clinical inputs for both the BT and SC arms of the model such as incidence rate of exacerbations, efficacy of BT to reduce the rate of these exacerbations and patient quality of life were estimated from results of the AIR2 trial [9] and The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) population [15–17]. Briefly, the AIR2 trial was a randomized controlled trial (RCT) to assess the efficacy of BT compared with sham bronchoscopy; all subjects were required to be severe, persistent asthma patients with baseline Asthma Quality of Life Questionnaire (AQLQ) score of 6.25 or lower, prebronchodilator forced expiratory volume in 1 second ≥60%, at least 2 days of asthma symptoms during the 4-week baseline period in spite of treatment with maintenance asthma medications, and having been a non-smoker for at least 1 year, with less than 10 pack-years smoking history [9]. The TENOR study was an epidemiological study to investigate the natural history of asthma; all subjects were considered by physician evaluation to have severe or difficult-to-treat asthma, as evidenced by care from their physician for asthma for at least 1 year, had high use of the healthcare system (i.e., ≥2 unscheduled care visits for asthma or ≥2 ICS bursts) and/or high medication use (i.e., ≥3 medications

including high-dose ICS), each in the previous 12 months [15–17].

Exacerbation rates were modeled as constant for SC patients throughout the 5-year period. For patients treated with BT, exacerbation rates were calculated by applying relative risks from the AIR2 trial to the SC rates of those patients with 1+ ER exacerbations in the TENOR population. These rates varied over time within the model to capture differences in rate of resource utilization observed within the AIR2 study during the 12-week treatment period and over the long-term (TABLE 1). Data from the AIR2 trial was divided into treatment period and thereafter to inform these varying rates. In the model, the time periods were split between before and after week 14 (n.b. due to the 2-week cycle of the model, the next cycle after the treatment period is week 14; TABLE 1). Maintenance medication usage was assumed to be equivalent across both the BT and the SC arms of the model. Risk of mortality due to asthma exacerbations requiring hospitalization was modeled as occurring at 1.1% [20]. Background mortality due to all-other causes was derived from CDC age-specific mortality rates (TABLE 1) [21].

Figure 1. Model schematic. Figure depicts the model structure, patient population and possible transitions within the model. The diamond represents the initial patient population, squares represent the model strategies and blue circles represent model health states.
ER: Emergency room.

Costs

Healthcare resource costs used in the model are shown in TABLE 1 (2013 USD). Costs associated with treating asthma exacerbations including physician office visits, ER visits and hospitalizations were derived from an analysis of private, commercial payers claims data from the Truven® MarketScan™ database for years 2006–2011 and inflated to 2013 [22]. The costs of BT were calculated based on private, commercial payer data and included both physician payments and procedure costs. At all points and for all model strategies (i.e., whether treated with BT or SC), patients received a combination of β2 agonists, steroids and in some cases additional controller medications such as leukotriene modifiers. These maintenance medication costs were estimated with whole-sale acquisition cost (WAC) pricing (Redbook 2009) [23] and inflated to 2013 USD using the Bureau of Labor Statistics' CPI-M data (TABLE 1) [24].

Utilities & quality of life

For the base case, the utility weights were derived from the AQLQ results from the AIR2 trial [9]. These data were collected during the trial for patients receiving SC plus a sham bronchoscopy, and for patients receiving SC plus BT. These data were transformed into health utilities using a previously described methodology to transform AQLQ scores to EQ-5D utility weights [25,26]. To reflect the population considered in the model, the SC utility weight was based on a previously published
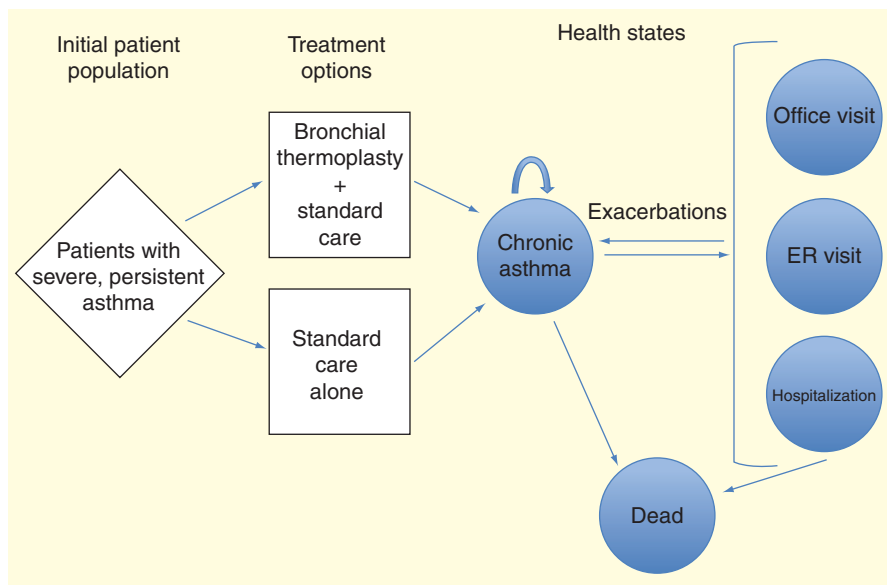
estimate [19]. The relative improvement in health utility for BT compared with SC plus sham bronchoscopy observed within the AIR2 trial was maintained in our analysis by applying that utility improvement to the baseline SC utility value. For the BT strategy, the utility weight was lower during the treatment period than in the post-treatment period, reflecting an initial, temporary destabilization immediately following the BT procedure. For a model cycle in which exacerbations requiring resource utilization occurred, literature-based [19] utility weights were used (TABLE 1).

Sensitivity analyses

Sensitivity analyses were conducted to estimate the impact of parameter uncertainty on the model's base case results. In one-way sensitivity analyses, all parameters were varied individually ±25% of base case values. In probabilistic sensitivity analyses, using Monte Carlo simulation, all parameters were varied simultaneously for 1000 iterations, with cost inputs following gamma distributions, utility parameters following beta distributions and clinical estimates following log-normal distributions.

Results

Model results are shown in TABLE 2. Over the 5-year period, BT increased quality-adjusted life expectancy by approximately 0.18 QALYs (3.14 vs 2.96), driven primarily by the decrease in exacerbations for patients treated with BT. BT increased costs by US$960 (TABLE 2) when incorporating both the procedural costs as well as the costs of treating exacerbations. These findings resulted in an ICER of US$5495 per QALY.

The tornado diagram shows the parameters with the largest impact on results in one-way sensitivity analyses (FIGURE 2). The model was most sensitive to the cost of the BT procedure, as

Table 1. Cost–effectiveness of bronchial thermoplasty compared with standard care: model inputs.

Study (year)	Parameter	Base case[†]	Scenario analysis[‡]	One-way SA range[†]	PSA distribution	Ref.
Clinical events						
	SC exacerbation rate					
	Physician visits	5.38	0.74	4.30–6.46		
Castro *et al.* (2010)	ER visits	1.64	1.19	1.31–1.97	Log-normal	[9]
Miller *et al.* (2006)	Hospitalizations	0.53	0.06	0.42–0.64		[15]
	BT exacerbation relative risk					
	Weeks 0–13					
Castro *et al.* (2010)	Physician visits	1.55	1.55	1.24–1.86		[9]
Miller *et al.* (2006)	ER visits	0.67	0.67	0.54–0.80	Log-normal	[15]
	Hospitalization	4.90	4.90	3.92–5.88		
	Weeks 14+[§]					
Castro *et al.* (2010)	Physician visits	0.77	0.77	0.62–0.92		[9]
Miller *et al.* (2006)	ER visits	0.17	0.17	0.14–0.20	Log-normal	[15]
	Hospitalizations	0.26	0.26	0.21–0.31		
Sullivan *et al.* (2009)	Mortality[‡,††]	0.011	0.011			[20]
Costs (per event); 2013 USD						
	Asthma exacerbation-related					
Truven® MarketScan™ Database[§]	Physician visit	US$192		US$154–US$230		[22]
	ER visit	US$673		US$538–US$808	Gamma	
	Hospitalization	US$9801		US$7841–US$11,761		
	BT related[¶]:					
	Procedure and physician	US$14,100		US$11,280–US$16,920	Gamma	
Red Book (2009)	Maintenance medication[#]	US$4990		US$3992–US$5988		[23]
	Discount rate (costs and QALYs)	3%				
Utilities						
Castro *et al.* (2010) Yang *et al.* (2010) Tsuchiya *et al.* (2002)	SC	0.67	0.86	0.54–0.80	Beta	[9,25,26]
	BT related					
Campbell *et al.* (2010)	Weeks 0–13	0.58	0.74	0.46–0.70	Beta	[19]
	Weeks 14+[§]	0.70	0.90	0.56–0.84		
	Asthma exacerbation-related					
Campbell *et al.* (2010)	Physician visit	0.57	0.74	0.46–0.68	Beta	[19]
	ER visit	0.45	0.58	0.36–0.54		
	Hospitalization	0.33	0.43	0.26–0.40		

[†]Base case population defined poorly controlled severe, persistent asthma; those with >1 ER visit in prior 12 months.
[‡]Scenario analysis population defined as all patients with severe, persistent asthma.
[§]Due to the 2-week cycle of the model, the first instance of the post-treatment period is week 14; the treatment period is 12 weeks as evidenced by the AIR2 trial [9].
[¶]Claims analysis of Truven® MarketScan™ Commercial Claims and Encounters Database [21] 2006–2011. Subjects in the analysis were required to have a primary or secondary diagnosis of asthma and were excluded if the patient had chronic obstructive pulmonary disease during the baseline year (2006). Total number of subjects analyzed was 2543.
[#]BT is performed as a series of three procedures. Costs shown represent the total combined cost of all three procedures.
[††]1.1% chance of mortality from hospitalized state, all other health states' mortality based on CDC age-specific mortality rates [21].
[‡‡]Maintenance medications include β2-agonist, steroids and leukotriene modifiers, costs reported on an annual basis.
BT: Bronchial thermoplasty; ER: Emergency room; PSA: Probabilistic sensitivity analysis; SA: Sensitivity analysis; SC: Standard care.

well as the rates of exacerbations resulting in hospitalization and the related costs. Additionally, utility weights for patients without exacerbations receiving each treatment were found to be key drivers of results. The costs of maintenance medications and utilities associated with exacerbations had minimal impact.

In the probabilistic sensitivity analysis, BT both reduced costs and resulted in increased QALYs in 21.5% of iterations. In 45% of iterations, BT increased costs and resulted in increased QALYs, with an ICER below US$50,000 per QALY. Therefore, BT increased QALYs and was either cost reducing or had a favorable attractive cost–effectiveness ratio (i.e., below US$50,000 per QALY) in approximately 66% of iterations. In only 8% of iterations did BT reduced costs and lowered QALYs (Figures 3 & 4).

In the exploratory scenario analysis of severe, persistent asthma patients (i.e., regardless of prior healthcare use), treatment with BT increased quality-adjusted life expectancy by approximately 0.16 QALYs compared with SC alone (4.13 vs 3.98 QALYs) and increased costs by US$9959 (US$39,983 vs US$30,024). This resulted in an ICER of US$62,922 per QALY.

Discussion

These results supplement the existing BT clinical literature, which shows reduced exacerbations over a 5-year period [11]. This analysis estimates the economic efficiency of BT to produce health benefits and finds that BT has favorable cost–effectiveness – improving quality of life at low cost – compared with standard care alone among private, commercially insured patients with poorly controlled, severe, persistent asthma.

The cost–effectiveness ratio of BT observed in the base case of approximately US$5500 among those with poorly controlled, severe, persistent asthma is significantly less than the commonly cited cost–effectiveness threshold of US$50,000 [27] and is less than the reported cost–effectiveness of inhaled corticosteroids compared with no inhaled corticosteroids [28]. This favorable cost–effectiveness ratio is generated through two mechanisms: improving quality of life through a reduction in the frequency of asthma exacerbations, and reducing the commensurate costs of these exacerbations. The cost–effectiveness ratio of US$62,922 among severe, persistent asthma patients without a specific requirement for an ER visit in the prior year is higher than the US$50,000 threshold; however, clinicians have noted that strict application of the US$50,000 threshold may be inconsistent with societal preferences [27,29]. These results suggest targeting BT to those patients who continue to experience breakthrough symptoms requiring resource utilization who are poorly controlled in spite of standard care (i.e., ICS + LABA) is an extremely cost-effective treatment option. Sensitivity analyses suggest that the greater the history of healthcare utilization, the more favorable the anticipated cost–effectiveness ratio.

Strengths of the present analysis include the application of data from the most recent clinical trials to describe the quality of life and treatment effects of BT [9,11]. Approaching the model from the commercial payer perspective is particularly helpful for those currently grappling with evaluating the potential economic as well as clinical impacts of BT.

This research is subject to several limitations. While the economic model was populated with data from the most recent BT clinical trial, that study did not segment the population by those who did and did not have an ER visit or hospitalization in the previous 12 months. In the absence of these data, we used the relative benefits reported from the entire population. It is conceivable that BT may have a different treatment effect on this patient population – either more or less efficacious – which would influence cost–effectiveness. Nevertheless, there is no evidence that suggests a different treatment effect for this more healthcare-dependent patient population. For example, the Research in Severe Asthma (RISA) [10] trial was a small (n = 32) RCT that examined a more poorly controlled asthma population than that examined by the AIR2 trial (baseline AQLQ score among those receiving BT 3.96 vs 4.3, respectively for RISA and AIR2, with lower scores indicating more poorly controlled asthma). These two trials found similar changes in AQLQ score (increasing 1.21 ± 1.05 for RISA vs 1.35 ± 1.1 for AIR2), suggestive of similar changes in utility and quality of life for patients receiving BT treatment.

While the quality of life estimates we utilized in this analysis are based on clinical trial data, these baseline utility values are greater than other values used in the cost–effectiveness literature to describe asthma quality-of-life. Implementing lower utilities as baseline values for quality-of-life would result in lower cost–effectiveness estimates, suggesting the results may be a conservative estimate of the benefits of BT for decision makers considering a more poorly controlled patient population. Further research into how the severity of asthma exacerbations impacts costs and quality-of-life may influence these results.

Our results suggest that when BT is delivered to severe, persistent asthma patients without an ER visit, it will generate health benefits in a reasonably cost-effective manner. Restricting BT use to those poorly controlled, severe, persistent asthma patients with at least one exacerbation-related ER visit in the prior

Table 2. Cost–effectiveness of bronchial thermoplasty compared with standard care: model results.

Strategies	Costs		QALY		
	5-year	Δ	5-year	Δ	ICER (US$/QALY)
Base case†					
SC	US$49,510		2.964		
BT	US$50,470	US$960	3.138	0.175	US$5495
Scenario analysis‡					
SC	US$30,024		3.975		
BT	US$39,983	US$9959	4.133	0.158	US$62,922

†Base case population defined poorly controlled severe, persistent asthma; those with >1 ER visit in prior 12 months.
‡Scenario analysis population defined as all patients with severe, persistent asthma.
Δ: Difference; BT: Bronchial thermoplasty; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.
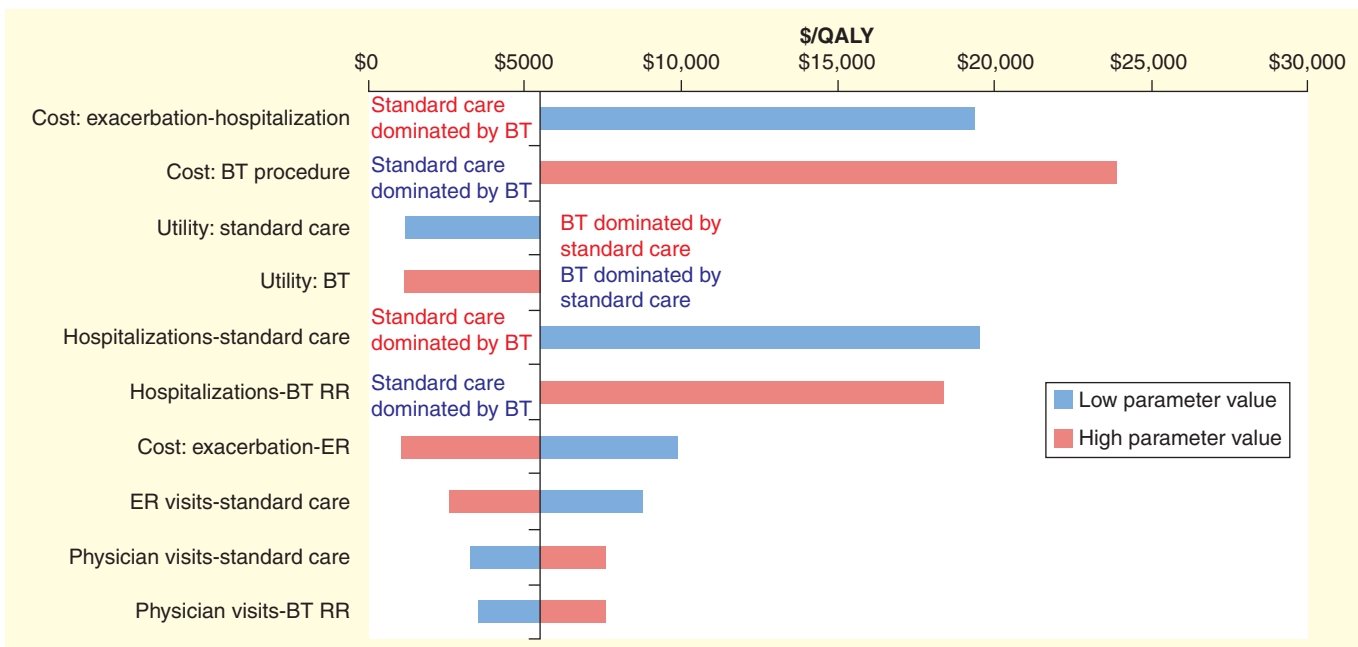
Figure 2. One-way sensitivity analysis: tornado diagram. Results represent difference between BT and SC. Figure includes 10 parameters with the greatest impact on model results.
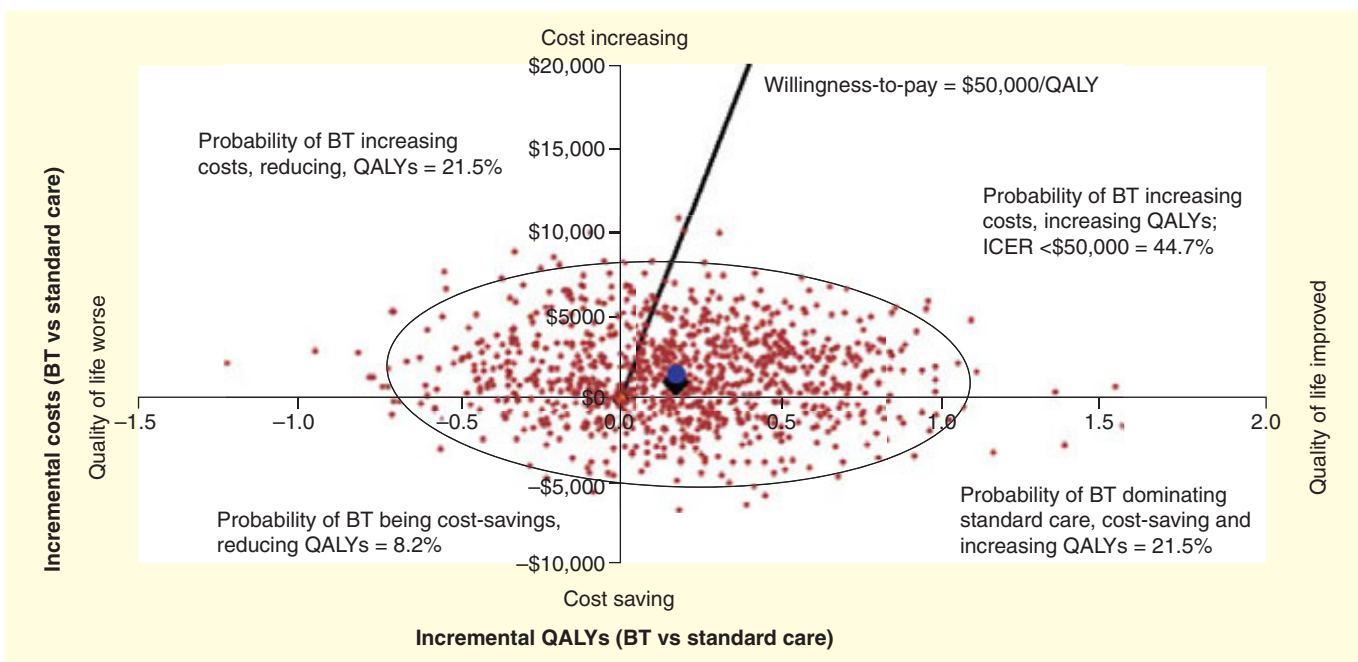BT: Bronchial thermoplasty; ER: Emergency room; QALY: Quality-adjusted life years; RR: Relative risk.

Figure 3. Probabilistic sensitivity analysis: cost–effectiveness scatter plot. Results shown for BT compared with standard care. Red points represent ICERs when all parameters are varied simultaneously for 1000 model iterations. Black diamond represents the base case, while blue circle (n.b. superimposed over diamond) represents the mean costs and QALYs from the 1000 iterations. Thin black line represents 95% confidence ellipse. Points to the right of the vertical axis denote increasing quality of life, while those to the left denote decreasing quality of life; points above the horizontal axis denote increasing costs, while those below the axis denote cost-savings. The solid black line represents a cost–effectiveness ratio of US$50,000; red dots to the right of that black line and above the horizontal axis have a cost–effectiveness ratio between US$0 and US$50,000 per QALY.
BT: Bronchial thermoplasty; QALY: Quality-adjusted life years.

12 months, the health benefits of BT will be generated in an extremely cost-effective manner – approximately US$5500 per QALY. These results, when added to the existing evidence of a clinical benefit from treatment with BT, demonstrate that BT produces clinical benefits with minimal costs. Nevertheless, cost–effectiveness is one of many factors for consideration when evaluating new technologies; other important factors include efficacy, safety and patients' access. Decision-makers should consider existing clinical evidence alongside these current results when evaluating BT for poorly controlled severe, persistent asthma patients who are currently requiring significant healthcare resources.

While we did not examine the cost–effectiveness of BT among those with even more exacerbations (e.g., those with two or more exacerbations requiring ER care), the present analysis supports the inference that patients with a greater frequency of ER visits and hospitalizations – and thus greater costs of care – would likely be even more cost-effective.

This commercial payer perspective model excluded indirect costs such as losses to workplace productivity that may occur with asthma exacerbations. The results of this analysis could thus be considered a conservative estimate for self-funded employers, who may be able to capitalize on decreased indirect expenditures as well as improved health outcomes. Further, the results of this analysis do not include costs which may be borne by the patient instead of the payer, such as co-pays, out-of-pocket costs and time to obtain treatment for asthma exacerbations.

In conclusion, the existing clinical literature on BT demonstrates that BT is a clinically efficacious treatment with durable benefit. This analysis supplements that body of literature,
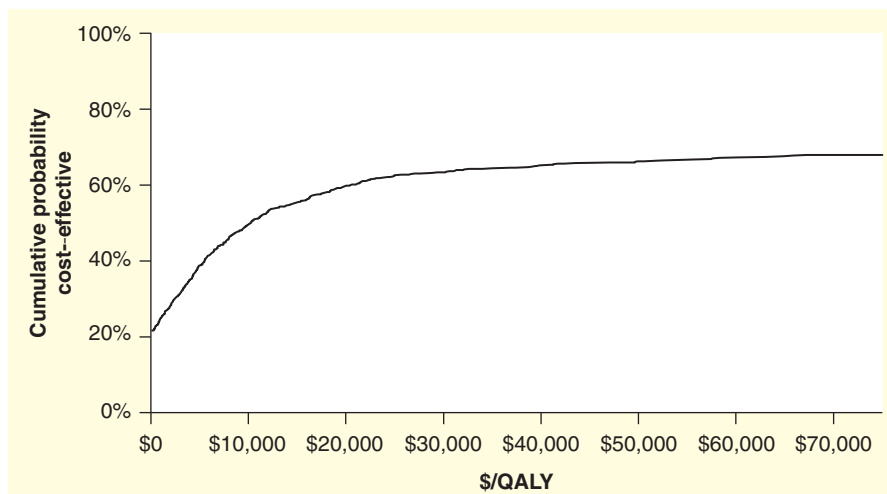

Figure 4. Probabilistic sensitivity analysis: cost–effectiveness acceptability curve.
Figure depicts the cumulative probability of meeting a given US$/QALY incremental cost–effectiveness ratio.

finding that BT is a cost-effective treatment option for patients with poorly controlled, severe, persistent asthma.

Financial & competing interests disclosure

Key issues

- Poorly controlled, severe, persistent asthma negatively impacts quality-of-life and healthcare costs. The FDA-approved pharmacological treatments for asthma do not address excessive airway smooth muscle mass (ASM), an anatomical feature associated with increased asthma severity and morbidity in some patients.
- Bronchial thermoplasty (BT) is a novel bronchoscopic procedure that uses thermal energy to reduce ASM, resulting in a durable reduction in ASM and asthma exacerbations.
- This analysis estimates the cost–effectiveness of adding BT to standard care. The incremental cost–effectiveness ratio is US$5495, well below commonly cited willingness-to-pay thresholds [26].
- BT is a cost-effective treatment option for patients with poorly controlled, severe, persistent asthma.

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