

## Medical Policy



### Title:        **Bronchial Thermoplasty**

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<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals with: <ul style="list-style-type: none"> <li>• With asthma refractory to standard treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Bronchial thermoplasty added to medical management</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Continued medical management</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Quality of life</li> <li>• Hospitalizations</li> <li>• Treatment-related morbidity</li> </ul>

#### **DESCRIPTION**

Thermoplasty is a potential treatment option for patients with severe persistent asthma. It consists of radiofrequency energy delivered to the distal airways with the aim of decreasing smooth muscle mass believed to be associated with airway inflammation.

**OBJECTIVE**

The objective of this evidence review is to determine whether bronchial thermoplasty improves the net health outcomes in patients with treatment-refractory asthma.

**BACKGROUND****Asthma**

Asthma, a chronic lung disease, affects approximately 7.7% of adults and 7.5% of children in the U.S. and, in 2018, accounted for approximately 1.6 million emergency department visits and 3564 deaths.<sup>1</sup> Asthma symptoms include episodic shortness of breath that is generally associated with other symptoms such as wheezing, coughing, and chest tightness. Objective clinical features include bronchial hyperresponsiveness, airway inflammation, and reversible airflow obstruction (at least 12% improvement in forced expiratory volume in 1-second post-bronchodilator, with a minimum of 200 mL improvement). However, there is substantial heterogeneity in the inflammatory features of patients diagnosed with asthma, and this biologic diversity is responsible, at least in part, for the variable response to treatment in the asthma population.

**Management**

Management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow-up for affected patients, as well as a stepped approach to medication treatment. Guidelines from the National Heart, Lung and Blood Institute have defined 6 pharmacologic steps: step 1 for intermittent asthma and steps 2 through 6 for persistent asthma.<sup>2</sup> The preferred daily medications: step 1: short-acting b-agonists as-needed; step 2: low-dose inhaled corticosteroids (ICS); step 3: ICS and long-acting b-agonists (LABA) or medium-dose ICS; step 4: medium-dose ICS and LABA; step 5: high-dose ICS and LABA; and step 6: high-dose ICS and LABA, and oral corticosteroids. A focused update in 2020 addressed the use of add-on long-acting antimuscarinic agents (LAMA), immunotherapy, and bronchial thermoplasty (see Practice Guidelines and Position Statements).<sup>3</sup>

Despite this multidimensional approach, many patients continue to experience considerable morbidity. In addition to ongoing efforts to implement optimally standard approaches to asthma treatment, new therapies are being developed. One recently developed therapy is bronchial thermoplasty, the controlled delivery of radiofrequency energy to heat tissues in the distal airways. Bronchial thermoplasty is based on the premise that patients with asthma have an increased amount of smooth muscle in the airway and that contraction of this smooth muscle is a major cause of airway constriction. The thermal energy delivered via bronchial thermoplasty aims to reduce the amount of smooth muscle and thereby decrease muscle-mediated bronchoconstriction with the ultimate goal of reducing asthma-related morbidity. A typical full course of treatment consists of 3, one hour sessions, given 3 weeks apart under moderate sedation. All accessible airways distal to the main stem bronchus that are 3 to 10 mm in diameter are treated once, except those in the right middle lobe; the lower lobes are treated first followed by the upper lung. Bronchial thermoplasty is intended for consideration as a supplemental treatment for patients with severe persistent asthma (i.e., steps 5 and 6 in the stepwise approach to care).

**REGULATORY STATUS**

In April 2010, the Alair® Bronchial Thermoplasty System (Asthmatx, now Boston Scientific) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process (P080032) for use in adults with severe and persistent asthma whose symptoms are not

adequately controlled with low-dose ICS and LABA. Use of the treatment is contraindicated in patients with implantable devices and those with sensitivities to lidocaine, atropine, or benzodiazepines. It should also not be used while patients are experiencing an asthma exacerbation, active respiratory infection, bleeding disorder, or within 2 weeks of making changes in their corticosteroid regimen. The same area of the lung should not be treated more than once with bronchial thermoplasty. FDA product code: OOO.

## **POLICY**

Bronchial thermoplasty for the treatment of asthma is considered **experimental / investigational**.

## **RATIONALE**

The evidence review has been updated with searches of the PubMed database. The most recent literature update was performed through May 7, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## **BRONCHIAL THERMOPLASTY FOR THE TREATMENT OF ASTHMA**

### **Clinical Context and Therapy Purpose**

The purpose of bronchial thermoplasty in patients who have asthma refractory to standard treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does bronchial thermoplasty improve health outcomes in patients with treatment-refractory asthma?

The following PICO was used to select literature to inform this review.

**Populations**

The relevant population of interest is individuals with persistent and severe asthma whose symptoms are not adequately controlled with low-dose inhaled corticosteroids and long-acting beta-agonists (LABAs). Asthma symptoms can vary between individuals but may include bronchial hyperresponsiveness, airway inflammation, and reversible airflow obstruction.

**Interventions**

The therapy being considered is bronchial thermoplasty as an add-on treatment in patients whose asthma is not adequately controlled with medical management.

Bronchial thermoplasty procedures are performed on an outpatient basis, and each session lasts approximately 1 hour. During the procedure, a standard flexible bronchoscope is placed through the patient's mouth or nose into the most distal targeted airway, and a catheter is inserted into the working channel of the bronchoscope. After placement, the electrode array in the top of the catheter is expanded, and radiofrequency energy is delivered from a proprietary controller and used to heat tissue to 65°C over a 5-mm area. The positioning of the catheter and application of thermal energy is repeated several times in contiguous areas along the accessible length of the airway. At the end of the treatment session, the catheter and bronchoscope are removed. A course of treatment consists of 3 separate procedures in different regions of the lung scheduled about 3 weeks apart.

**Comparators**

Currently, clinical response to continued medical management is being used to make decisions about the use of bronchial thermoplasty for treatment-refractory asthma. Continued medical management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow-up for affected patients, as well as a stepped approach to medication treatment.

**Outcomes**

Beneficial outcomes are symptom relief, improvement in QOL, reductions in medication adverse events and hospitalizations, reduced use of rescue medications, and treatment-related morbidity. Instruments such as the Asthma Quality of Life Questionnaire (AQLQ) score and the Asthma Control Questionnaire (ACQ) may be used to assess improvements in asthma symptoms. A minimal clinically important difference (MCID) in the AQLQ and ACQ is considered to be  $\geq 0.5$  points from baseline.<sup>3</sup>The MCID for daytime or nighttime rescue medication use is a decrease of 0.81 puffs/day.

Potential harms include periprocedural risk and risk for exacerbation of asthma during the treatment phase.

Short-term results are evaluated from weeks posttreatment to 12 months. Long-term follow-up studies have evaluated patients receiving bronchial thermoplasty up to 10 years posttreatment.

**Study Selection Criteria**

We selected methodologically credible studies, following these principles:

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for randomized controlled trials.

- To assess longer term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow up and/or larger populations.
- Within each category of study design, we preferred larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

For conditions such as asthma, where there are subjective outcomes such as self-reported symptoms and frequency of as-needed medication, placebo- or sham-controlled randomized trials are needed to demonstrate that the intervention has a benefit beyond the placebo effect.

## **REVIEW OF EVIDENCE**

### **Randomized Controlled Trials**

There are 3 industry-sponsored RCTs that have evaluated the efficacy and safety of bronchial thermoplasty. The study characteristics and results are summarized in Tables 1 and 2.

### **Research in Severe Asthma Trial**

Pavord et al (2007) published the initial results of the Research in Severe Asthma (RISA) trial.<sup>5</sup> Participants met multiple criteria for severe uncontrolled asthma. After a 2 week run-in period, participants were randomized to a control group that received continued medical management alone or to medical management plus treatment with the Alair Bronchial Thermoplasty System.

The primary objective of RISA was to determine the safety of bronchial thermoplasty. The rates of the procedure and post procedure respiratory adverse events as well as more serious adverse events (defined as any event that was fatal, required prolonged hospitalization, caused substantial immediate risk of death, resulted in permanent impairment, or required intervention to prevent permanent impairment). No overall statistical analysis was done that compared serious adverse events in the 2 groups.

Secondary objectives included an evaluation of the effect of bronchial thermoplasty on asthma symptoms and daily medication requirements as an indication of efficacy. At 52 weeks, bronchial thermoplasty patients had a significantly greater improvement in b-agonist use than control patients (decrease of 26 puffs per week vs 6 puffs per week, respectively,  $p < 0.05$ ). There were no significant differences between groups in other efficacy variables including morning and evening peak expiratory flow, symptom scores, number of symptom-free days, percent predicted improvement in forced expiratory volume in 1-second (FEV<sub>1</sub>) and QOL measures. The small sample size limited the power to detect differences in the efficacy outcomes.

Pavord et al (2013) published 5-year safety data on 14 (82%) of the 17 patients randomized to bronchial thermoplasty in the RISA trial.<sup>6</sup> All 14 patients completed the 3-year evaluation, and 12 patients completed evaluations at 4 and 5 years. As previously described, safety outcomes were the primary outcomes of RISA. In year 1, each asthma symptom was considered an adverse event and, in subsequent years, multiple asthma symptoms were considered to be a single adverse event. Among those with follow-up data available, the number of patients with asthma adverse events in years 2, 3, 4, and 5 were 5 (36%), 7 (50%), 2 (17%), and 5 (42%), respectively. Also, during years 2 to 5, there were 11 respiratory-related hospitalizations in 5 patients. The number of patients with data available was too small to draw reliable conclusions

about long-term safety, and there were no long-term data available on patients in the control group.

### **Asthma Intervention Research Trial**

Cox et al (2007) published findings of the Asthma Intervention Research (AIR) trial, which was designed to evaluate symptom control and adverse events following bronchial thermoplasty in patients with moderate-to-severe persistent asthma.<sup>7</sup> Participants were randomized to medical management with inhaled corticosteroids and LABA or to the same medical management strategy plus bronchial thermoplasty. At the end of the follow-up visits at 3, 6, and 12 months, there was a 2-week period of abstinence from LABA, during which data on exacerbations were collected. Between data collection periods, patients could use all maintenance therapies.

The primary outcome was the difference between groups in the rate of mild exacerbations from the baseline 2 week abstinence period. An exacerbation was defined as the occurrence on 2 consecutive days of a reduction in the morning peak expiratory flow of at least 20% below the average value (recorded during the week before the abstinence period), the need for more than 3 additional puffs of rescue medication compared with the week before the abstinence period, or nocturnal awakening caused by asthma symptoms. The trial was powered to detect a difference between groups of 8 mild exacerbations per person per year. Data were available at 3 months for 100 (89%) of 112 patients and at 12 months for 101 (90%) patients; all patients were included in the safety analysis.

The rate of adverse events was higher in the bronchial thermoplasty group during the active treatment period, but the proportion of adverse events was similar in the 2 groups in the posttreatment period. Posttreatment, 3 patients in the bronchial thermoplasty group required hospitalization and 2 patients in the control group required a total of 3 hospitalizations. A trial limitation is the lack of a sham intervention and, consequently, an inability to blind patients to the treatment group.

Thomson et al (2011) published 5-year data from the AIR trial.<sup>8</sup> All trial participants who completed the 1-year follow-up visit were invited to participate in the extension study; 45 (87%) of 52 in the bronchial thermoplasty group and 24 (49%) of 49 in the control group opted to participate. Follow-up was done on an annual basis. Patients in the control group were followed for 2 additional years, and patients in the bronchial thermoplasty group were followed for 5 years. Twenty-one (88%) of 24 patients in the control group and 42 (93%) of 45 in the bronchial thermoplasty group completed the final follow-up. No instances of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death were reported during the extension study. In the first year (year 2 of the study), the rate of hospitalizations was 3 (7%) of 45 in the bronchial thermoplasty group and 0 in the control group ( $p=0.55$ ). In year 3, the rate of hospitalizations in the bronchial thermoplasty group was again 3 (7%) of 45, and 1 (5%) of 21 patients in the control group ( $p=1.00$ ). Rates of emergency department visits in year 2 were 3 (7%) and 3 (12.5%) in the bronchial thermoplasty and control groups, respectively ( $p=0.41$ ); in year 3, rates were 3 (5%) and 3 (5%), respectively ( $p=1.00$ ). There was 1 hospitalization each of years 4 and 5 in the bronchial thermoplasty group.

In the extension study of the AIR trial, unlike the initial follow-up period, respiratory adverse events with multiple symptoms were recorded as a single adverse event. This could give a misleading impression of the total number of adverse events or relative number in the 2 groups.

The incidence of respiratory adverse events during year 2 was 24 (53%) of 45 in the bronchial thermoplasty group and 13 (54%) of 24 in the control group. During year 3, the incidence was 24 (56%) of 43 in the bronchial thermoplasty group and 12 (57%) of 21 in the control group; differences between groups were not statistically significant in year 2 or 3. The incidence of respiratory adverse events in the bronchial thermoplasty group was similar in subsequent years; rates were 23 (53%) of 43 in year 4 and 22 (52%) of 42 in year 5.

The Thomson et al (2011) study also reported on 2 measures of lung function: post-bronchodilator FEV<sub>1</sub> and forced vital capacity. Exact numbers were not reported, but post-bronchodilator FEV<sub>1</sub> did not go below 80% of predicted in either group during years 2 to 5. The group comparisons of safety and efficacy in this follow-up trial were limited by the differential rate of follow-up between the 2 groups, with a lower percentage of patients in the control group agreeing to participate in the follow-up study.

### **Asthma Intervention Research 2 Trial**

The Asthma Intervention Research 2 (AIR2) Trial was an RCT evaluating the efficacy of bronchial thermoplasty at 30 sites in 6 countries (including the U.S.); findings were published by Castro et al (2010). Unlike the other 2 RCTs, the control condition was a sham intervention, and the trial was double-blind. Eligibility criteria were similar to those in the AIR trial; key differences were that a higher initial dose of inhaled corticosteroids was required (equivalent to at least 1000 µg beclomethasone), and patients were required to have experienced at least 2 days of asthma symptoms during the 4-week baseline period and have a baseline score on the AQLQ of no more than 6.25. (The possible range of the AQLQ score is 1 to 7, with a higher number representing a better QOL.) Also different from the AIR trial, patients were not required to experience symptom worsening during a period of abstinence from LABAs. Patients were stable on their asthma medication and continued their regimens during the study. The primary outcome was the difference between groups in the change from baseline in the AQLQ score, with scores from the 6-, 9-, and 12-month follow-ups averaged (integrated AQLQ score). A related outcome was the proportion of patients who achieved a change in their AQLQ score of 0.5 or greater, generally considered the minimally important difference for this scale. Bayesian analysis was used. The target posterior probability of superiority (PPS) of bronchial thermoplasty over sham was 95%, except for the primary AQLQ endpoint; there the target was 96.4% to adjust for 2 interim looks at the data. The prior for the analysis was not reported in the article.

Participants and outcome assessments were blinded but the intervention team was unblinded. The sham intervention was identical to the active treatment, except that no radiofrequency energy was delivered. Nine participants withdrew consent before beginning treatment, and 288 underwent bronchoscopy and were included in the intention-to-treat population. One hundred eighty-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same number of patients had the third bronchoscopy (it is not clear whether they were the same patients).

The superiority of bronchial thermoplasty was not achieved in the intention-to-treat population for the primary effectiveness outcome, mean change in the integrated AQLQ score. Mean standard deviation (SD) change was 1.35 (1.10) in the bronchial thermoplasty group and 1.16 (1.23) in the sham control group. Using Bayesian analysis, the PPS was 96%. This did not surpass the target PPS of 96.4%. However, the superiority of bronchial thermoplasty on a related outcome was achieved. In the intention-to-treat population, the percentage of patients achieving

an AQLQ score change of 0.5 or greater (i.e., at least the minimally important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The PPS at 99.6% surpassed the target probability for secondary outcomes of 95%. Additional analysis of data from the active treatment group suggested that responders (defined as a change in AQLQ score of at least 0.5) were more likely to have a lower baseline score than nonresponders (mean, 4.1 vs 5.1, respectively).

Several secondary outcomes favored bronchial thermoplasty over the sham control group. They included a reduction in the proportion of patients reporting asthma worsening during follow-up (27.3% vs 42.9%, respectively; PPS=99.7%) and a reduction in the number of emergency department visits (0.07 vs 0.43 visits per person per year, respectively; PPS=99.9%). Moreover, there was a reduction in severe exacerbations of 0.47 per person per year in the bronchial thermoplasty group compared with 0.70 per person per year in the control group (PPS=95.5%). There were no significant differences between groups in other secondary efficacy outcomes, including morning peak expiratory flow, the number of symptom-free days, symptom score, and rescue medication use.

For safety outcomes, during the treatment phase, there was a higher rate of respiratory adverse events in the active treatment group (85% of participants; mean, 1.0 events per bronchoscopy) compared with the sham group (76% of participants; mean, 0.7 events per bronchoscopy). A total of 16 (8.4%) patients in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared with 2 (2%) patients in the sham group, who required 1 hospitalization each. However, during the posttreatment period, 70% of patients in the bronchial thermoplasty group and 80% of patients in the sham group reported adverse respiratory events. During this phase of the trial, 5 (2.6%) patients in the bronchial thermoplasty group had a total of 6 hospitalizations for respiratory symptoms, and 4 (4.1%) patients in the sham group had 12 hospitalizations (1 patient had 9 hospitalizations).

In the AIR2 trial, the sham group had a relatively high response rate (e.g., 64% experienced a clinically significant increase in the AQLQ score). Blinding appeared to be initially successful and remained so for the sham group. Participants in both groups were unable to correctly guess their treatment group after the first bronchoscopy. During subsequent assessments, this continued among patients in the sham group, whereas in the bronchial thermoplasty group, a larger proportion guessed correctly.

Two- and 5-year follow-up data on patients in the treatment group of the AIR2 trial have been published. Castro et al (2011) reported on 2-year data on 166 (87%) of 190 patients randomized to the bronchial thermoplasty group.<sup>9</sup> In the second year after treatment, the proportion of participants who experienced severe exacerbations was 23.0% (95% confidence interval [CI], 16.6% to 29.5%). This compares with a 30.9% (95% CI, 24.2% to 37.7%) rate of exacerbations during year 1. The proportion who experienced asthma adverse events was 28.7% (95% CI, 22.1% to 35.3%) in year 1 and 26.5% (95% CI, 19.8% to 33.2%) in year 2. Wechsler et al (2013) reported on 5-year data for 162 patients in the AIR2 trial (85% of those randomized to the treatment group).<sup>10</sup> In a matched-pair analysis including the 162 study completers and the same group in previous years, the rate of severe exacerbations in years 1, 2, 3, 4, and 5 were 30.9%, 23.5%, 34.0%, 36.4%, and 21.6%, respectively. The proportion of patients experiencing severe exacerbations in years 2, 3, 4, and 5 did not differ significantly from the number of exacerbations in year 1. The proportion of patients who experienced adverse asthma events (at



least <sup>3</sup>2 asthma symptoms occurring at the same time) were 28.7%, 27.9%, 29.6%, 31.4%, and 24.7%, respectively. The proportion of patients with at least 1 hospitalization for respiratory adverse events these same years was 3.3%, 4.2%, 6.2%, 5.7%, and 1.9%, respectively. In the 12 months before bronchial thermoplasty, the rate of hospitalization for respiratory symptoms in this group was 4.2%. These follow-up studies are limited in that follow-up data were not collected on patients randomized to the sham group, and therefore outcomes (e.g., the rate of exacerbations, the rate of hospitalizations) cannot be compared in patients who did and did not receive bronchial thermoplasty.

Chaudhuri et al (2021) reported 10-year safety and efficacy results for patients enrolled in the AIR, RISA, and AIR2 trials, including 136 (52%) patients who had received bronchial thermoplasty and 56 (33%) sham or control patients.<sup>11</sup> Eighteen patients in the sham/control group received bronchial thermoplasty after participation in the original trials. Median patient follow-up was 12.1 years post-treatment (range, 10.8 to 15.6 years). The primary study effectiveness endpoint was the durability of treatment effect, described as the proportion of participants with severe exacerbations during years 1 and 5 compared to the proportion of patients who experienced severe exacerbations in the 12 months preceding the 10+ year visit. No formal hypothesis testing was planned. Severe exacerbations were defined as a self-reported worsening of symptoms requiring the use of systemic corticosteroids or increased dose of systemic corticosteroids. The primary safety endpoint was the absence of clinically significant respiratory changes, including bronchiectasis or bronchial, as confirmed by CT imaging. In the year preceding the 10+ year visit, 34/136 (24%, 95% CI, 18.0 to 33.1) patients treated with bronchial thermoplasty experienced severe exacerbations, which were similar to the year 5 (22%, 95% CI, 14.8 to 29.6) and year 1 (24%, 95% CI, 17.5 to 32.6) proportions. The number of severe exacerbations per patient were significantly higher compared to year 5 ( $p = .044$ ), but not significantly different compared to year 1 ( $p = .43$ ). In the year preceding the 10+ year visit, severe exacerbations were experienced in 14/38 (37%, 95% CI, 21.8 to 54.0) sham or control patients compared to 12/38 (32%, 95% CI, 17.5 to 48.7) in year 1. There was no change in the rate of severe exacerbations over time in the 24 sham participants from the AIR2 trial who had baseline, 1 year, and 10 year data. Both treated and non-treated groups experienced a reduction in emergency department visits. Six (7%) AIR2 patients treated with bronchial thermoplasty developed new cases of asymptomatic bronchiectasis compared to 0 cases in the sham group at the 10 year visit. Improvements in AQLQ and ACQ scores were sustained in patients treated with bronchial thermoplasty. However, these scores were not reported for sham/control patients. Interpretation of study results is limited by recall bias and low enrollment of sham-treated patients. While bronchial thermoplasty is only recommended for use in patients with severe asthma, 26% of participants did not fulfill these criteria. Additionally, the long-term effects of treatment on clinically significant respiratory changes requires further elucidation.

**Table 1. Summary of Key RCT Characteristics**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Pavord et al (2007) <sup>5</sup> ;RISA	U.K., Brazil, Canada	8	2004-2006	<ul style="list-style-type: none"> <li>≥18 y with uncontrolled asthma refractory to high-dose ICS<sup>a</sup> and LABA<sup>b</sup></li> <li>FEV<sub>1</sub>≥50% predicted</li> </ul>	<ul style="list-style-type: none"> <li>17 medical management and BT</li> <li>Weeks 0-6: 3 treatments</li> </ul>	<ul style="list-style-type: none"> <li>17 medical management alone</li> <li>ICS dose tapered in 3</li> </ul>

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
				<ul style="list-style-type: none"> <li>Airway hyperresponsiveness<sup>c</sup></li> <li>Abstinence from smoking for 1 y</li> <li>Smoking history ≤0 pack-years</li> </ul>	<ul style="list-style-type: none"> <li>at least 3 wk apart</li> <li>Weeks 6-22: steroid stable</li> <li>Weeks 22-36: protocol defined steroid wean</li> <li>Weeks 36-52: investigator-led steroid reduction</li> </ul>	<ul style="list-style-type: none"> <li>stages by 20%-25% of baseline dose every 4 wk to minimal dose of fluticasone propionate 100-600 mg/d or equivalent</li> </ul>
Cox et al (2007) <sup>7</sup> ;AIR	U.K., Brazil, Canada, Denmark	11	2002-2005	<ul style="list-style-type: none"> <li>18-65 y with moderate-to-severe persistent asthma requiring daily ICS<sup>d</sup> and LABA<sup>b</sup></li> <li>FEV<sub>1</sub> 60%-80% of predicted</li> <li>Airway hyperresponsiveness</li> <li>Stable asthma 6 wk prior to enrollment</li> <li>No current or recent respiratory infection<sup>e</sup></li> </ul>	<ul style="list-style-type: none"> <li>56 medical management and BT (3 treatments at least 3 wk apart)</li> <li>Follow-up at 3, 6, and 12 mo,<sup>f</sup> then 2-wk LABA abstinence</li> </ul>	<ul style="list-style-type: none"> <li>56 medical management alone</li> <li>Follow-up at 3, 6, and 12 mo,<sup>f</sup> then 2-wk LABA abstinence</li> </ul>
Castro et al (2010) <sup>12</sup> ;AIR2	U.S., EU, Canada, Australia	30	2000-2015	<ul style="list-style-type: none"> <li>≥2 d asthma symptoms during 4-wk baseline required high initial dosage of ICS<sup>g</sup></li> <li>Baseline AQLQ score ≤6.25</li> </ul>	<ul style="list-style-type: none"> <li>196 received BT (3 treatments at least 3 wk apart)</li> </ul>	<ul style="list-style-type: none"> <li>101 received sham procedure</li> </ul>

AIR: Asthma Intervention Research Trial, AQLQ: Asthma Quality of Life Questionnaire; BT: bronchial thermoplasty, FEV<sub>1</sub>: forced expiratory volume at 1 minute, ICS: inhaled corticosteroids, LABA: long-acting b-agonist, RCT: randomized controlled trial, RISA: Research in Severe Asthma.

a Treatment of fluticasone propionate ≥750 µg/d or equivalent.

b Treatment of salmeterol ≥100 µg/d or equivalent.

c Demonstrated by challenge with methacholine or reversible bronchoconstriction during prior 12 mo.

e No more than 2 respiratory infections requiring treatment in past year and required to undergo a 2-wk baseline test period without LABAs; eligibility depended on worsening asthma control during that time.

<sup>f</sup> Between data collection periods, patients could use all maintenance therapies

<sup>g</sup> Treatment of beclomethasone ≥1000 µg or equivalent.

**Table 2. Summary of Key RCT Results**

<b>Study</b>	<b>Respiratory AE(No. of Events)</b>	<b>Serious AE (Hospitalization)<sup>b</sup></b>	<b>Reduction in SABA (puffs per 7 days)<sup>c</sup></b>	<b>% Reduction in OCS Dosed</b>	<b>% Reduction in ICS Dosed</b>
Pavord et al (2007) <sup>5</sup> ; RISA					
BT (n=15) <sup>a</sup>	136	7	-26.6 (40.1)	63.6 (45.4)	28.6 (30.4)
MM (n=17)	57	0	-1.5 (11.7)	26.2 (40.7)	20 (32.9)
Effect (95% CI); p			NR (NR); <0.05 <sup>d</sup>	NR (NR); 0.12	NR (NR); 0.059
	<b>Change in Rate of Exacerbations<sup>e</sup></b>				
Cox et al (2007) <sup>7</sup> ; AIR					
BT (n=52) <sup>f</sup>					
Baseline	0.35 (0.32)				
12 months	0.18 (0.31)				
MM (n=49) <sup>f</sup>					
Baseline	0.28 (0.31)				
12 months	0.31 (0.41)				
Effect (95% CI); p	NR (NR); 0.03				
	<b>Change in AQLQ<sup>h</sup></b>				
Castro et al (2010) <sup>12</sup> ; AIR2					
BT (n=190) <sup>g</sup>					
Baseline	4.30 (1.17)				
12 months	5.66 (1.06)				
Mean change	1.35 (1.10)				

Study	Respiratory AE (No. of Events)	Serious AE (Hospitalization) <sup>b</sup>	Reduction in SABA (puffs per 7 days) <sup>c</sup>	% Reduction in OCS Dosed	% Reduction in ICS Dosed
BT sham (n=98) <sup>g</sup>					
Baseline	4.31 (1.21)				
12 months	5.48 (1.15)				
Mean change	1.16 (1.23)				

AE: adverse events; AIR: Asthma Intervention Research Trial, AQLQ: Asthma Quality of Life Questionnaire; BT: bronchial thermoplasty; CI: confidence interval; ICS: inhaled corticosteroid; MM: medical management; NR: not reported; OCS: oral corticosteroid; SABA: short-acting  $\beta$ -agonist; RCT: randomized controlled trial. RISA: Research in Severe Asthma.

<sup>a</sup> There were 2 withdrawals from BT group prior to first treatment.

<sup>b</sup> There were no deaths or serious AEs other than hospitalization related to respiratory events in either group.

<sup>c</sup> Results at 22 wks.

<sup>d</sup> Results at 52 wks.

<sup>e</sup> Change from baseline in mean number of mild exacerbations per subject per week at 12 mo.

<sup>f</sup> Analyses based on participants available for evaluation at 12 mo.

<sup>g</sup> Intention-to-treat analyses based on participants who underwent at least 1 bronchoscopy procedure in either arm.

<sup>h</sup> Change from baseline in integrated AQLQ score at 12 months with higher score (0-7) indicating better quality of life. A score change of  $\geq 0.5$  defines minimal important difference.

### Post-U.S. Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Chupp et al (2017) compared 3-year follow-up results from 190 patients in the AIR2 trial with a subgroup (n=190) from a prospective nonrandomized clinical study (Post-U.S. Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma [PAS2]).<sup>13</sup> PAS2 is an ongoing open-label trial of the Alair system required for post premarket approval. Of those enrolled, 168 patients from PAS2 reached 3 years of follow-up and were compared with 165 patients from AIR2 who also had 3 years of follow-up. The primary outcome was comparing the incidence of severe exacerbation in each trial. In the 12 months before treatment, 74.2% of patients from PAS2 experienced severe exacerbations, which decreased significantly during the third year of follow-up to 39.9% ( $p < 0.001$ ). A similar reduction was observed in AIR2 patients, with the incidence of severe exacerbations decreasing 36.8%. Similar decreases in emergency department visits occurred in both groups when year 3 was compared with the 12 months before treatment (PAS2, 55% reduction; AIR2, 72.3% reduction;  $p < 0.001$ ); the incidence of hospitalization also decreased for both groups. In the first and second years after treatment, the incidence of hospitalization in PAS2 decreased to 14.4% and 12.7%, respectively; the incidence of emergency department visits decreased to 18.3% in the first year and 13.5% in the second year after treatment. Overall, patients from PAS2 showed improved results comparable to those observed in AIR2; however, there were a number of differences between the trials that limited conclusions. At baseline, patients enrolled in AIR2 had better asthma control than those in PAS2; PAS2 was restricted to North America, and different definitions of severe exacerbations were used in each trial.

A TEC Assessment (2014) assessed bronchial thermoplasty as a treatment for inadequately controlled severe asthma.<sup>4</sup> The Assessment included the 3 published RCTs discussed and

concluded, "the evidence is insufficient to determine whether potential improvements in some outcomes, but not others defining the net health outcome, outweigh the potential harms" and that the technology did not meet TEC criteria.

### Registries

Reports from the U.K. Severe Asthma Registry (UKSAR) are described in Tables 3 and 4. All UK centers performing bronchial thermoplasty provide data to the registry.

Burn et al (2017) reported on safety outcomes of bronchial thermoplasty outcomes in the U.K.<sup>14</sup>. The analysis combined data from 2 sources, UKSAR and the Hospital Episode Statistics warehouse. For 59 patients, data in the 2 databases could be matched and were used to calculate event rates for 4 binary safety outcomes. Procedural complications were reported in 17 (11%) of 152 procedures in 13 (22%) patients; emergency department readmissions within 30 days of the initial hospitalization were reported for 15 (11.8%) patients; and accident and emergency visits (i.e., emergency department) for any reason were reported for 13 (8.6%) patients. For the fourth outcome (post procedure overnight stay), 70 (46.1%) of 152 procedures were followed by an overnight stay. In total, 20.4% of procedures in the matched cohort were associated with at least 1 of the 4 safety issues. The authors noted that the relatively high rate of safety events might have been related to older patients with more severe disease being treated in clinical practice compared with patients included in clinical trials.

Efficacy and Safety data from the UKSAR registry were subsequently reported by Burn et al (2019).<sup>15</sup> Efficacy data were available for 86 patients with at least 1 follow-up visit. Safety data were available for 131 patients, including the 59 in the previous report. Follow-up data up to 60 mo were recorded with counts of adverse events annualized to compare rates before and after bronchial thermoplasty. Comparison of the first year post-treatment with pre-procedure baseline showed a statistically and clinically significant improvement in the AQLQ of 0.75 ( $P < .001$ ) and EuroQoL-5D, but there was no significant improvement in other outcome measures when adjusted for multiple comparisons. There were trends for a decrease in unscheduled healthcare visits ( $-0.93$ ,  $P = .050$ ) and in hospital admissions in the year after bronchial thermoplasty ( $-2.0$ ,  $P = .056$ ). There was no significant change in mean forced expiratory volume ( $FEV_1$ ) at 12 or 24 mos. Because of the strong placebo effects noted in the controlled trials, interpretation of subjective quality of life measures is limited.

**Table 3. Summary of Registry Study Characteristics**

Study	Study Type	Registry	Dates	Participants	Treatment	Treatment 2	Follow-Up
Burn et al (2017) <sup>14</sup> ,	Registry	UKSAR and Hospital Episode Statistics warehouse	2011-2015	59 patients who received bronchial thermoplasty and had data in both UKSAR and the Hospital Episode Statistics database	3 bronchial thermoplasty sessions		30 days
Burn et al (2019) <sup>15</sup> ,	Registry	UKSAR	2011-2016	133 patients who received bronchial thermoplasty and	At least 1 bronchial thermoplasty session		6 mo to 5 yr

Study	Study Type	Registry	Dates	Participants	Treatment	Treatment 2	Follow-Up
				consented to be in the UKSAR Registry			

UKSAR: U.K. Severe Asthma Registry

**Table 4. Summary of Registry Study Results**

Study	AQLQ	ACQ	EQ-5D	Rescue Steroid (P)	Procedural Complications	Overnight Stay	Unscheduled or Emergency Department Visits	Hospital admissions
Burn et al (2017) <sup>14</sup> ,					17 (11%) of procedures	70 (46.1%) of procedures	13 (8.6%) of patients	15 (11%) of patients
Burn et al (2019) <sup>15</sup> ,								
Change from baseline (P)	0.75 (<.001)	-0.43 (p=.083)	.008 (.909)	-0.26 (.307)			-0.93 (.050)	-2.0 (.056)

AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire; EQ-5D: EuroQol-5D

### Summary of Evidence

For individuals who have asthma refractory to standard treatment who receive bronchial thermoplasty added to medical management, the evidence includes 3 RCTs and observational studies. Relevant outcomes are symptoms, QOL, hospitalizations, and treatment-related morbidity. Early studies (RISA, AIR) investigated safety outcomes, finding similar rates of adverse events and exacerbations between the bronchial thermoplasty and control groups. These trials were limited by their lack of sham control. The AIR2 trial is the largest of the 3 published RCTs, and the only 1 double-blinded and sham-controlled, with sites in the U. S. Over 1 year, bronchial thermoplasty was not found to be superior to sham treatment on the investigator-designated primary efficacy outcome of mean change in the QOL score but was found to be superior on a related outcome, improvement in the QOL of at least 0.5 points on the AQLQ. There was a high response rate in the sham group of the AIR2 trial, suggesting a large placebo effect, particularly for subjective outcomes such as QOL. There are limited long-term sham-controlled efficacy data. Findings on adverse events from the 3 trials have suggested that bronchial thermoplasty is associated with a relatively high rate of adverse events, including hospitalizations during the treatment period, but not in the posttreatment period. Safety data up to 10 years have been reported for patients in the AIR2 trial, with a higher rate of new cases of bronchiectasis observed in bronchial thermoplasty-treated patients.. Data from a U.K. registry showed that 20% of bronchial thermoplasty procedures were associated with a safety event (i.e., procedural complications, emergency respiratory readmissions, emergency department visits, and/or post procedure overnight stays), with uncertain benefit. Conclusions cannot be drawn about the effect of bronchial thermoplasty on the net health outcome due to the limited amount of sham-controlled data (1 RCT) on short-term efficacy, the uncertain degree of treatment benefit in that single sham-controlled trial, the lack of sufficient long-term sham-controlled data in the face of a high initial placebo response, and the presence of substantial adverse events. Also, there is a lack

of data on patient selection factors for this procedure and, as a result, it is not possible to determine whether there are patient subgroups that might benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **SUPPLEMENTAL INFORMATION**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

#### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

#### **2014 Input**

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2014. Input was mixed on whether bronchial thermoplasty is considered investigational for the treatment of asthma; 3 reviewers agreed with this statement and 2 reviewers disagreed. Reviewers who disagreed tended to use bronchial thermoplasty in patients who had not responded to other treatments and who did not think there were treatment alternatives.

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **Global Initiative for Asthma**

Global Initiative for Asthma (GINA) is an international network of organizations and professionals with expertise in asthma. The group has been updating a report entitled *Global Strategy for Asthma Management and Prevention* annually since 2002; the most recent update was issued in 2021.<sup>3</sup> The organization has recommended stepped care for treatment of asthma. Step 5 options for patients with uncontrolled symptoms and/or exacerbations include referral for phenotypic investigation and potential add-on treatment. Add-on treatments may include long-acting muscarinic antagonists, biologics (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab), and systemic corticosteroids.

A guide for the diagnosis and management of difficult-to-treat and severe asthma was published in 2019.<sup>16</sup> For patients whose asthma remains uncontrolled despite GINA step 4 or 5 treatment with no evidence of type 2 inflammation (i.e., medium- or high-dose inhaled corticosteroids and long-acting beta-agonists), treatment options include a trial of tiotropium or macrolide if not already tried, low-dose oral corticosteroids, and consideration of bronchial thermoplasty with registry enrollment. Bronchial thermoplasty with registry enrollment may also be considered for patients who do not respond to type 2-targeted biologic therapy. The guidance notes that the evidence for the efficacy and long-term safety of bronchial thermoplasty is limited.

**American College of Chest Physicians**

In May 2014, the American College of Chest Physicians posted a position statement on coverage and payment for bronchial thermoplasty.<sup>17</sup> The document stated in part:

"...bronchial thermoplasty offers an important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment and, therefore should not be considered experimental. Randomized controlled clinical trials of bronchial thermoplasty for severe asthma have shown a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work. Additionally, data published in December 2013 demonstrates the persistence of the reduction in asthma symptoms achieved by bronchial thermoplasty for at least 5 years..."

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (2018) published guidance on bronchial thermoplasty for severe asthma.<sup>18</sup> The guidance stated: "Current evidence on the safety and efficacy on bronchial thermoplasty for severe asthma is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit." It was also noted that "further research should report details of patient selection and long-term safety and efficacy outcomes."

**National Asthma Education and Prevention Program**

In 2020, the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel Working Group published focused updates to the National Heart, Lung, and Blood Institute's guidelines for the diagnosis and management of asthma. This update was based on prior systematic reviews of the evidence published by the Agency for Healthcare Research and Quality.<sup>19,20</sup>

The following conditional recommendation based on low certainty evidence on the use of bronchial thermoplasty was issued:

- "In individuals ages 18 years and older with persistent asthma, the Expert Panel conditionally recommends against bronchial thermoplasty.
- Individuals ages 18 years and older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long term side effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty."

For patients who opt to choose this intervention via shared decision-making, the panel recommends that clinicians offer the procedure in the setting of a clinical trial or registry study to facilitate the collection of long-term outcomes.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.



**Table 3. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<b><i>Ongoing</i></b>			
NCT03765307 <sup>a</sup>	Safety and Efficacy of the SyMap Bronchial Ablation System for Treatment of Severe Asthma: A Prospective, Multicenter, Randomized Controlled Clinical Trial (Bronchial Ablation for Treatment of Asthma (BATA) Trial)	160	Dec 2022 (recruiting)
NCT02464995	Bronchial Thermoplasty in Severe Asthma With Frequent Exacerbations (THERMASCORT)	34	Nov 2022 (recruiting)
NCT03435237	Phenotyping Asthma for Bronchial Thermoplasty: Airway Smooth Muscle Structure and Function	50	Dec 2022 (recruiting)
NCT02975284	TASMA Extension Study: Long Term Efficacy and Safety of Bronchial Thermoplasty in Severe Asthma	30	Sep 2024 (ongoing)
NCT04077528	Research on Severe Asthma (RAMSES)	2000	Jun 2025 (recruiting)
<b><i>Unpublished</i></b>			
NCT01185275	A Prospective Observational Study of Biopredictors of Bronchial Thermoplasty Response in Patients With Severe Refractory Asthma (BTR Study)	133	Oct 2019
NCT02104856 <sup>a</sup>	Bronchial Thermoplasty Global Registry (BT Registry)	158	Jun 2019

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

### **CPT/HCPCS**

- 31660 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 1 lobe
- 31661 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 2 or more lobes

**DIAGNOSIS**

Experimental / Investigational for all codes related to this medical policy.

<b>REVISIONS</b>	
02-10-2011	Policy added to the bcbsks.com web site.
02-14-2012	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT codes: 0276T, 0277T (effective 01-01-2012)</li> <li>▪ Removed CPT code: 31899</li> </ul>
10-09-2012	Description section updated
	Rationale section updated
	References updated
12-11-2013	Description section updated
	Rationale section updated
	In coding section: Replaced CPT codes 0276T and 0277T with 31660 and 31661 respectively, which became effective 01-01-2013.
	References updated
10-13-2015	Description section updated
	Rationale section updated
	References updated
01-18-2017	Description section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Coding notations updated</li> </ul>
	Rationale section updated
	References updated
07-11-2017	Description section updated
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Coding notations updated</li> </ul>
	References updated
08-15-2018	Description section updated
	Rationale section updated
	References updated
08-28-2019	Description section updated
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Coding notations updated</li> </ul>
	References updated
08-21-2020	Description section updated
	Rationale section updated
	References updated
07-28-2021	Description section updated
	Rationale section updated
	References updated

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