



# Medical Coverage Policy

Effective Date..... 7/15/2021  
Next Review Date..... 7/15/2022  
Coverage Policy Number ..... 0502

## Bronchial Thermoplasty

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### Overview

This Coverage Policy addresses bronchial thermoplasty (BT) for adults with severe, persistent asthma that is refractory to other therapies. Bronchial thermoplasty is a minimally invasive technique which has been proposed to decrease the number of severe asthma attacks on a long-term basis by reducing, debulking, or partially eliminating excess smooth muscle tissue in an individual's distal airways by the application of radiofrequency energy.

### Coverage Policy

**Bronchial thermoplasty is considered experimental, investigational or unproven for any indication.**

### General Background

Asthma is a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Clinical studies have shown that asthma can be effectively controlled by intervening to suppress and reverse inflammation as well as treating the bronchoconstriction and related symptoms (Global Initiative for Asthma [GINA], 2021). The goal of the treatment of asthma is to achieve

and maintain clinical control by eliminating symptoms during both the day and night, to normalize measures of lung function, and to reduce the risk of future GINA, 2021). Depending on level of control, standard treatment options may include stimulus avoidance and an as-needed reliever medication (e.g., short acting Beta-2 Agonists [SABA] or Muscarinic Antagonists [SAMA]), reliever treatment with regular controller treatment (e.g., inhaled glucocorticosteroid, leukotriene modifier, theophylline), oral glucocorticosteroids, or a combination of these and other medications.

### **Bronchial Thermoplasty**

While the patient continues to take standard asthma medications as scheduled, bronchial thermoplasty (BT) has been proposed for adults with severe, persistent asthma that is refractory to other therapies as a potential treatment option by the application of radiofrequency energy. The Alair® System is designed for treatment of the airways distal to the main stem bronchi, down to airways of  $\geq 3$  mm in diameter (Boston Scientific, 2021).

BT using this system comprises a series of procedures, with one bronchial area being treated per session. To treat all accessible airways in both lungs, three sessions are required at a minimum of three-week intervals. Treatment takes about 45 minutes for lower lobes and 60 minutes for upper lobes (Boston Scientific, 2021). With the patient undergoing moderate sedation or general anesthesia a flexible bronchoscope is placed into the bronchial tree via the oral or nasal route. The Alair catheter is introduced into the airways through the working channel of the bronchoscope. The bronchoscope is navigated to the first target site, typically the most distal airway in the targeted lobe. The electrode array at the tip of the catheter is expanded to gain contact with the airway wall and radiofrequency energy is delivered to the tissue. Energy delivery during activation is limited to a temperature of 65°C (149°F). During the first treatment, the physician ablates the rings of airway smooth muscle in the bronchioles of the lower lobe of the right lung. At least three weeks later, the left lung's lower lobe is treated. Finally, at least three weeks later, both upper lobes are treated (Boston Scientific, 2021).

### **U.S. Food and Drug Administration (FDA)**

In April 2010, the FDA granted Asthmatx, Inc. (Boston Scientific, Marlborough, MA) premarketing approval for the Alair Bronchial Thermoplasty System for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta<sub>2</sub> agonists. As a condition of approval, Asthmatx must conduct two five-year post approval studies to investigate the system's long-term safety and effectiveness. This requirement includes a continuation of the AIR-2 Trial with longitudinal data on the durability of effectiveness of BT out to five years and a new prospective open-label, single-arm, multi-center study in the U.S. to demonstrate durability of treatment effect and safety out to five years from treatment. The Alair System is currently the only bronchial thermoplasty (BT) device approved by the FDA.

### **Literature Review**

**Randomized Controlled Trials:** Bronchial thermoplasty (BT) is a novel treatment for adult patients with severe asthma who remain symptomatic despite adherence to the standards of medical care. Proper patient selection and optimal pre- and post-procedural management are essential for a successful outcome and additional studies are needed to determine the durability of clinical effects, assess long-term adverse events, and further understand the mechanism of BT on asthma pathobiology (Wahidi, 2012).

Several randomized clinical trials (RCT) have published two-year outcome data suggesting improved Asthma Quality of Life Questionnaire (AQLQ) scores and some improvement in the rate of severe exacerbations, emergency department (ED) visits and days lost from school/work in a small number of patients. Three follow-up studies have also reported five-year outcomes in subsets of the patients who underwent treatment with BT.

According to Wahidi (2012), whether the findings can be generalized to all patients with severe asthma is unclear, given the exclusion of patients with severe asthma who exacerbate frequently, require multiple bursts of oral corticosteroids, and demonstrate low lung function. Additional investigation is needed to identify disease and patient characteristics that would enable accurate phenotyping of positive responders to avoid unnecessary procedures and risks. Additionally, there is a need to understand the underlying mechanism of BT and how its delivered heat is translated into clinical benefit. Wahidi also notes that ongoing and future studies should attempt to obtain endobronchial biopsies from treated areas with close examination of alterations in anatomical structures and inflammatory markers.

Goorsenberg et al. (2021) conducted a randomized controlled trial that assessed the effect of bronchial thermoplasty (BT) on airway smooth muscle (ASM) mass in the airways of severe asthma patients. Adults aged 18–65 years with severe asthma were included in the study if asthma was confirmed in the five years prior to inclusion by one of the following parameters: reversibility to  $\beta$ 2-agonists in FEV1 of  $\geq 12\%$  predicted and  $\geq 200$ ml, bronchial hyper-responsiveness to methacholine or histamine (PC 20 < 4 mg/ml), peakflow variability of > 20% over a two week period or a fall in FEV1 of > 12% predicted and > 200 ml after tapering down asthma treatment. Patients (n=40) were randomized to immediate BT treatment (n=20) or six month delayed (n=20) BT treatment. Prior to randomization, clinical, functional, blood and airway smooth muscle mass in bronchial biopsies were collected on all patients. In the delayed control group, re-assessment, including biopsies, was performed after six months of standard clinical care, followed by BT. In both groups, post-BT data including biopsies were obtained after six months. BT using the Alair System (Boston Scientific, USA) consisted of treatment sessions of the right lower lobe (RLL), left lower lobe (LLL) and both upper lobes with at least a three weeks between procedures. The right middle lobe (RML) was not treated. The primary outcome measured was the absolute difference in ASM change between the direct BT treatment group and the delayed control group. The outcome was measured six months after BT using asthma control questionnaires (ACQ-6), asthma quality of life questionnaires (AQLQ), exacerbation rates and lung function parameters. The secondary outcome measured ASM mass change after BT in the total group and in the untreated right middle lobe (RML) using the ACQ-6 and AQLQ scores after BT, exacerbation rates and lung function parameters. The delayed group had additional scheduled visits after six months of standard clinical care which included a research bronchoscopy with endobronchial biopsy sampling. There were no device related complications. Following 43 of the 119 BT procedures (36%) patients experienced an asthma exacerbation that was treated with conventional asthma medication such as oral corticosteroids and nebulized bronchodilators. Patients required hospitalization following nine of these exacerbations with a median length of hospital stay of four days. Other adverse events reported were chest pain or discomfort (12%), dyspnea (15%), (productive) cough (16%), hemoptysis (7%), common cold (1%), bronchitis or sinusitis (3%), fever (1%) and lower respiratory tract infection (3%). The results reported that median ASM mass decreased by > 50% in the immediate BT group (n=17) compared to no change in the delayed control group six (n=19) (p=0.0004). ACQ and AQLQ scores improved significantly in the immediate BT group compared to the delayed group (p=0.006, p=0.04; respectively). The results for the total group of patients that completed the three BT procedures and clinical follow-up (n=35) the ACQ and AQLQ scores improved significantly (p=0.0005, p=0.0023; respectively). Additionally, the ASM mass was reduced in the total group (n=34) from 8.6% before BT to 4.02% after BT (p<0.0001). It was reported that baseline blood eosinophils and total IgE counts were associated with improvements in ACQ and AQLQ scores after BT. This suggests that patients with high blood eosinophil counts and/or IgE levels are more likely to respond to BT treatment. Author noted limitations included potential bias due to taking the biopsies different predefined (sub)segmental airway carinas. Secondly, although not clinically significant, the immediate treatment group had a higher ACQ and lower AQLQ score at baseline compared to the delayed control group. The questionnaires were not associated with ASM mass and an influence on the primary outcome of this study is not likely. Lastly, the authors stated that this study was powered for the assessment of ASM mass reduction and a clinical response analysis could not reveal an association between ASM reduction and response. The results need to be confirmed in a larger cohort.

### **Asthma Intervention Research Trial (AIR)**

Cox et al. (2007) reported outcomes of an RCT (Asthma Intervention Research [AIR] trial) involving 109 adults with moderate to severe persistent asthma comparing outcomes between individuals who received BT plus standard of care asthma medical therapy (n=55) or asthma medical therapy alone. (n=54). The primary outcome was noted to be the frequency of mild exacerbations calculated during three scheduled two-week periods of abstinence from long-acting B<sub>2</sub> agonists (LABA) at three, six, and 12 months. Secondary endpoints included airflow, airway responsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the AQLQ and the Asthma Control Questionnaire (ACQ). The difference between the two groups in the change from baseline was significant at three and 12 months (p=0.03 for both comparisons) but not at six months. There was an increase in adverse respiratory events immediately after the procedure for subjects undergoing bronchial thermoplasty (BT), with a return to baseline values during the post-treatment period. Overall, there were 407 adverse respiratory events in the BT group, and 106 in the control group, with a majority of events occurring within one day after the procedure. The number of hospitalizations was also greater in the BT group compared to the control group. During the post-treatment period, the proportion of subjects with adverse respiratory events and the rate of hospitalization did not differ between groups. Regarding severe exacerbations at 12 months, the difference between the two groups in the change from baseline was not significant at any time

point. As compared with baseline, the average number of exacerbations during the two-week periods at three, six, and 12 months when subjects in the two groups were treated with inhaled corticosteroids alone was reduced in the BT group but was not significantly changed in the control group ( $p=0.005$ ). Overall, improvements in health outcomes were noted in both the BT and control groups. Further, there were increased adverse events and hospitalizations in the BT group compared with the control group. Although promising, the role of BT for the treatment of asthma is unknown at this time.

In an extension of the Asthma Intervention Research (AIR) trial, Thomson et al. (2011) reported outcomes up to five years (i.e., three years for control group [ $n=24$ ], five years for BT group [ $n=45$ ]) for 69 individuals with moderate to severe asthma who had completed 12 month follow-up as part of the AIR study. Endpoints were not stated. During years two and three, results between the BT and control groups were comparable for respiratory adverse event rates, and the number of emergency room (ER) visits during years 2 and 3 ( $p=0.41$  and  $p=1.00$ , respectively). During Year 1 and Year 2, more subjects in the BT group required hospitalizations for respiratory symptoms than the control group (no  $p$  value reported). Over the course of the five year post-BT follow-up, the number of hospitalizations, and the proportion of subjects in the BT group experiencing hospitalizations for respiratory symptoms did not get worse compared to Year 1 after BT ( $p=0.16$ ). The number of ED visits for respiratory symptoms were comparable in years 2, 3, 4, and 5 compared to Year 1 ( $p=0.55$ ) for the BT group. The authors note oral corticosteroid usage for asthma symptoms was comparable between the BT and control groups during Years 1, 2 and 3 (no  $p$  value reported). The reduction in inhaled corticosteroids (ICS) was not significantly different between the BT group and the control group at years 2 and 3 ( $p=0.93$  and  $p=0.92$ , respectively). This data suggest that BT did not reduce ED visits, hospitalizations, or oral corticosteroid use. Other study limitations include uncontrolled design, small patient population size, and follow-up only to three years for control group.

### **Asthma Intervention Trial 2 (AIR2)**

Castro et al. (2010) reported data from a multicenter blinded RCT ( $n=297$ ), the Asthma Intervention Trial 2 (AIR2) with BT ( $n=196$ ) compared with a sham control group ( $n=101$ ); each participant undergoing at least one bronchoscopy in the BT group and three bronchoscopies in the sham group. The bronchoscopy was not blinded to participants; however, BT use was blinded. In the BT group, a greater proportion of patients correctly guessed their treatment assignment after the first bronchoscopy (BT,  $p=0.011$ ; sham,  $p=0.342$ ). Although the data using the intent-to-treat population for analysis suggested the patients receiving BT experienced some improvement in quality of life and reduction in the rate of severe exacerbations, ED visits, and days lost from school or work in the post-treatment period (i.e., 6–52 weeks after BT) compared to baseline, individuals treated with sham also achieved improvement from baseline.

The primary endpoint of improvement on the Asthma Quality of Life Questionnaire (AQLQ) score and secondary endpoints (e.g., Asthma Control Questionnaire [ACQ] scores, percent of symptom-free days, rescue medication use, percentage and number of severe exacerbations, respiratory-related unscheduled physician office visits, emergency department visits, hospitalizations and days missed from work/school) were analyzed using the Bayesian method. The pre-specified posterior probability of superiority (PPS) that was considered significant for the primary outcome was 96.4% and 95% for secondary outcomes. Outcomes were reported from first day of bronchoscopy through 12-month follow-up, the treatment period: (bronchoscopy to six-weeks), and post-treatment (six weeks-52 weeks).

In the intent-to treat (ITT) population, BT was superior to sham for mean change in AQLQ integrated score (PPS 96%). Net benefit of AQLQ was 76% for BT vs sham (57%), (PPS, 100.0). Changes in individual domains of AQLQ between the BT and sham groups were not significant except for the emotional function domain.

Over the entire study period (from the day of first bronchoscopy to the 12-month follow-up), sham was superior over BT for the number of severe exacerbations, number of ED visits for respiratory symptoms per subject, and the number of respiratory-related hospitalizations per subject. Using the intent-to treat-population, secondary endpoint measures of morning PEF, symptom-free days, symptom score, ACQ, and rescue medication use showed an improvement over baseline in the bronchial thermoplasty (BT) and in the sham groups, differences between the groups were not statistically significant (PPS, < 95.0%). In the treatment period there were more adverse events (AE) in the BT group than the sham group (85% versus 76%, PPS not reported); in the post-treatment period, there were fewer AEs in the BT group compared to sham (70% versus 80%; PPS 95.5%).

During the post-treatment period BT was superior over sham for risk reduction for reported worsening of symptoms (PPS, 99.7%) and ED visits (PPS, 99.9%). Also in the post-treatment period, BT was superior over sham for fewer days lost from work/school/other activities (PPS 99.3%). Symptom-free days, symptom score, Asthma Control Questionnaire (ACQ) and rescue medication use improved in both groups; between group differences were not significant (PPS  $\leq$  95%). Variables which limit the ability to assess whether there is a net improvement in health outcomes include the fact that the study did not meet its primary endpoint and the superiority of sham over BT for several secondary endpoints.

In a five-year follow-up to the Asthma Intervention Trial 2 (AIR2), Wechsler et al. (2013) assessed the effectiveness and safety of BT in 162 of the 190 asthmatic patients who had received BT. Outcomes at five-year follow-up were compared with results in the 12 months prior to BT. Results for year one were calculated beginning from six weeks post the last BT procedure. Outcomes assessed after BT included severe exacerbations, adverse events, health care use, spirometric data, and high-resolution computed tomographic scans.

The proportion of subjects having severe exacerbations in years two-five compared with the first year after BT were not significantly different. The reduction in the proportion of subjects experiencing severe exacerbations in the year after BT compared with the 12 months before BT (51.6%) was maintained for the entire five-year follow-up period, with an average decrease of 44%. The decrease in severe exacerbation rates that was achieved in the post-treatment period after BT in year one was maintained out to five years. The authors reported that on average, both patients with FEV1 values of 60% to 70% of predicted value and those with FEV1 values >70% of predicted value had sustained improvements in exacerbations over the five-year period. There was an overall reduction of 18% in the average inhaled corticosteroid dose at five years. Of the 93 evaluable high resolution computerized tomography (HRCT) pairs at year five, 82% showed either no radiologic changes or improvement from baseline; 71% of the HRCT pairs showed no radiologic changes of clinical significance. Compared with 12 months before BT, the average reduction over five years in rates of ED visits was 88%. Five-year results are promising; however, an important limitation of the study includes the lack of comparison to outcomes of the sham control group participants of the original AIR2 trial.

### **Research in Severe Asthma Trial (RISA)**

In another randomized controlled trial (RCT), Pavord et al. (2007) (Research in Severe Asthma [RISA]) examined the safety and effectiveness of BT in patients with symptomatic, severe asthma. Adults who were symptomatic despite treatment were randomized to BT (n=15) or to a control group (n=17). Those treated with BT received three procedures, three weeks apart. All subjects maintained baseline asthma medications. After treatment, subjects entered a 16-week steroid stable phase (weeks 6 to 22), a 14-week steroid wean phase (weeks 22 to 36), and a 16-week reduced steroid phase (weeks 36 to 52). Investigators were not blinded to treatment. The primary study endpoint was to determine the safety of BT in subjects with symptomatic, severe asthma. Secondary endpoints were the evaluation of the effect of BT on asthma symptoms and daily medication requirements. Improvements in primary and secondary endpoints were noted in both treatment groups compared to baseline.

The safety of BT was assessed by monitoring adverse events and pulmonary function. Subjects completed diaries to report adverse events. Adverse events were designated as respiratory- or non-respiratory-related. In the treatment period there was an increase in respiratory adverse events and hospitalizations in the group undergoing BT compared with control. Two subjects in the BT group had segmental collapse involving the most recently treated lobe; one required mucus plug aspiration. In the post treatment period the rate of hospitalizations was similar in both groups (p=0.32).

At 22 weeks, patients who received BT had significant improvements versus those of control subjects in rescue medication use (p<0.05), and pre-bronchodilator forced expiratory volume in 1 second (FEV1) % predicted (p=0.04). Short-term improvements up to 52 weeks were seen during the steroid stable phase. The authors note that longer and larger studies of subjects with different asthma severity are required to determine whether or not there are delayed adverse effects. Although results are promising, small participant numbers and lack of blinding prohibit the ability to apply study results to use of BT in clinical practice.

In a five-year follow-up study of the RISA trial, Pavord et al. (2013) reported results of 14 of the 15 patients who received bronchial thermoplasty (BT) in the previous trial, comparing outcomes at three-five year follow-up with 52 week follow-up results. Fourteen patients completed follow-up evaluations at three years, 12 at four years, and 12 at five years. Patients were evaluated annually at the end of 12 months following BT and years two-five after their last treatment bronchoscopy. Subjects were evaluated for prebronchodilator and postbronchodilator spirometry, chest radiography, information on any adverse events (AEs), emergency department (ED) visits, and hospitalizations for respiratory symptoms, oral corticosteroid (OCS) pulses for worsening asthma symptoms, and any changes in maintenance asthma medications. Radiography was reviewed by unmasked radiologists and observations reported. Patients were questioned regarding satisfaction with the procedure and if they would recommend it to a friend or family member. There were 11 hospitalizations in years two-five versus 10 for the 12 months before study entry. The rate of respiratory AEs was unchanged in years two-five. The overall rate of respiratory hospitalizations during the five-year follow-up after BT of 0.23 per patient per year compared to a pre-procedure rate of 0.71 hospitalizations per patient per year reflected a 68% reduction. No significant changes were found in overall inhaled maintenance asthma medication use. There were no significant changes in radiographic findings over time. Mean prebronchodilator and postbronchodilator FEV1 values were also unchanged over time. Eleven patients, who completed the five-year follow-up, reported satisfaction with the procedure. Data suggest promising five-year outcomes for the twelve patients completing this study; however, small participant numbers limit the ability to translate results to a larger population.

**Prospective Studies:** Chaudhuri et al. (2021) conducted an international, multicenter, prospective follow-up study of participants who were previously enrolled in the AIR, RISA, and AIR2 trials with 10 or more years of follow-up since bronchial thermoplasty treatment. The primary effectiveness measured the durability of the thermoplasty treatment, determined by comparing the proportion of participants who had severe exacerbations during the first and fifth years after bronchial thermoplasty treatment with the proportion of participants who had severe exacerbations during the 12-month period before the BT10+ visit. The primary safety endpoint measured the absence of clinically significant post-treatment respiratory image changes after bronchial thermoplasty, defined as bronchiectasis or bronchial stenosis as confirmed by pulmonary volumetric high-resolution CT at the BT10+ visit for AIR2 participants. Additional endpoints measured included: severe exacerbation rates (exacerbations per participant per year), hospital emergency department visits and hospital admissions for asthma, and respiratory-related serious adverse events, defined as any respiratory-related adverse events that were life-threatening, led to hospital treatment or prolonged admission to hospital, disability, or death. Post-hoc comparisons were done between pre-treatment and post-treatment measurements to investigate the efficacy of bronchial thermoplasty in this current cohort.

The BT10+ study enrolled 192 (45%) of the 429 participants who were enrolled in the AIR, RISA, and AIR2 trials. The BT10+ participants comprised 136 who received bronchial thermoplasty (52% of the 260 participants who received bronchial thermoplasty in the original trials) and 56 sham or control participants (33% of 169 from the original trials). Eighteen of the sham or control participants (32%) received bronchial thermoplasty after the previous trials concluded. The participants included in BT10+ were followed for 10.8–15.6 years (median 12.1 years) post-treatment. Participants treated with bronchial thermoplasty had similar proportions of severe exacerbations at the BT10+ visit (34 of 136 participants) compared to one year (33 of 135 participants) and five years (28 of 130 participants) after treatment. Quality of life measurements and spirometry were similar between year one, year five and the BT10+ visit. At the BT10+ study visit, pulmonary high-resolution CT scans from AIR2 participants treated with bronchial thermoplasty showed that 13 (13%) of 97 participants had bronchiectasis. When compared with baseline high-resolution CT scans, six (7%) of 89 participants treated with bronchial thermoplasty who did not have bronchiectasis at baseline had developed bronchiectasis after treatment. Participants treated with bronchial thermoplasty after the original study and participants in the sham or control group also had reductions in severe exacerbations at the BT10+ visit compared to baseline. A number of study limitations have been identified by authors that include potential selection bias, the length of time between the three original trials and BT10+ caused a loss of patients to follow-up and the severe exacerbations results were reported using patient recollection supported by case note reviews. Additionally, bronchial thermoplasty is only recommended for use in patients with severe asthma and 26% of participants did not fulfill these criteria. Therefore, the improvements in asthma control seen in the BT10+ study population might not be applicable to patients with the most severe asthma who are seen in clinical practice. Lastly, this study was funded by the manufacturer of the bronchial thermoplasty system and could potentially lead to a perceived conflict of interest.

Chupp et al. (2017) reported three-year results of the first 190 participants of the five-year Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) study. This prospective, observational post-marketing study was initiated in 2011 as a requirement of FDA approval for the Alair bronchial thermoplasty device. One hundred sixty-eight of 190 PAS2 subjects completed three years of follow-up and their outcomes were compared with those seen in the 165 AIR2 subjects at three-year follow-up visit. The primary endpoint is the proportion of PAS2 and AIR2 subjects experiencing severe exacerbations, emergency department visits for respiratory symptoms and hospitalizations for respiratory symptoms during the 12-month period preceding bronchial thermoplasty (BT) treatment compared with outcomes three years after treatment completion. Outcomes from time of BT and for six weeks following BT (i.e., periprocedure period) were calculated separately and were not included in overall outcome calculations. Differences in eligibility criteria and baseline characteristics between studies were noted. Unlike the AIR2 trial, the PAS2 study did not include a doubling of inhaled corticosteroids (ICS) dose as part of the definition of a severe exacerbation. Other end-points related to the safety of the Alair system include respiratory adverse events, serious adverse events, and measurements for pre- and post-bronchodilator FEV1.

At three-year follow-up, there was a reduction in mean ICS daily dose for PAS2 and AIR2 ( $p=0.003$ ;  $p=0.006$ ). The percent of PAS2 study subjects who were taking daily OCSs to improve asthma control was reduced in the third year after BT ( $p=0.0004$ ); this decrease was not significant in the AIR2 trial ( $p=0.52$ ). There was a reduction in PAS2 study subjects experiencing at least one severe asthma exacerbation ( $p<0.0001$ ) during year three following BT and a 36.8% relative decrease in severe exacerbations was reported for the AIR2 trial. There was a decrease in PAS2 subjects with emergency department visits for respiratory symptoms in year three following BT, compared with 12 months prior to BT ( $p=0.0005$ ), and a 72.3% reduction was reported for AIR2 participants. The decrease in the number of hospitalizations in the 12 months prior to BT and at three years following BT was not significant in the PAS2 study ( $p=0.055$ ) with relative decreases of up to 25% in the three years post-BT reported for AIR2. Pre-bronchodilator FEV1 remained unchanged from baseline through three-year follow-up in both PAS2 study and AIR2 trial; however, an increase between pre- and post-bronchodilator % predicted was noted for PAS2 participants (76.3% vs 82.3%). Periprocedural adverse events requiring hospitalization or prolongation of hospitalization during the treatment phase were 13.2% and 8.4% for the PAS2 and AIR2 trials, respectively. Differences in periprocedural severe exacerbations (55.8% versus 40.5%;  $p=0.004$ ) and emergency department visits (15.8% versus 5.3%;  $p=0.0012$ ) were noted between studies. Differences in eligibility criteria and baseline characteristics between the PAS2 and AIR2 studies are noted. Study limitations include uncontrolled study design and interim outcomes.

Cox et al. (2006) published results of an uncontrolled prospective trial involving 16 patients with stable mild to moderate asthma who underwent 49 bronchial thermoplasty (BT) procedures. Results following BT were compared with baseline and 12-week post BT procedures. Baseline and 12-week post-treatment measurements included spirometry, methacholine challenge, daily diary recordings of peak flow, symptoms and medication usage. Subjects completed follow-up evaluations at 12 weeks, and one- and two-year periods. After BT, pre-bronchodilator forced expiratory volume at one second (FEV1) % predicted was maintained with no significant change from baseline at two-year follow-up. Significant increases were observed at 12 weeks ( $p=0.043$ ) and one year ( $p=0.030$ ). Post-bronchodilator FEV1 % predicted was maintained throughout the study period, with no significant change from baseline. The prebronchodilator FEV1/forced vital capacity (FVC) ratio was higher at one year than at baseline, but not significant at 12 weeks or two years post-treatment. There was no significant increase in the mean post-bronchodilator FEV1/FVC ratios after treatment. Compared with baseline, the authors report statistically significant improvements in morning and evening peak flows at 12 weeks post-treatment, which is the latest time data were collected by diary (no p values were reported). Regarding symptom-free days there was a statistically significant increase in mean percentage of symptom-free days between baseline and 12 weeks after treatment ( $p=0.015$ ). Changes from baseline in rescue medication use were not significant ( $p>0.05$ ). Study design and small patient population limit the ability to extrapolate these findings to the target population.

**Retrospective Studies:** Eisemann et al. (2019) reported results of a retrospective review of 17 patients with an established diagnosis of severe, poorly controlled asthma in which BT was performed. All patients received maximum maintenance medication including high-dose inhaled corticosteroids (ICS), long-acting beta agonists (LABA), long-acting muscarin antagonist (LAMA), Anti-IgE-antibody treatment, and oral corticosteroids (OCS) as needed. Patients were included if they were in a stable stage of disease and were free of exacerbations at least 4 weeks prior to BT. In contrast to former randomized-control (RCT) studies, permanent decline of FEV1 was not

an exclusion criteria. The primary objective was to investigate the safety and efficacy of BT; including BT of the right middle lobe (RML), which was excluded from previously reported studies. Comparators were AQLQ scores and FEV1 prior to the BT.

Asthma Questionnaire of Life Quality (AQLQ), pulmonary function and the need for OCS use were assessed before the procedure and at 90 days after the complete BT cycle, which included three BT procedures. BT bronchoscopies were performed at 4–8 week intervals. Treatment of the RML was performed with right lower lobe treatment in the first session in each patient. The second treatment session was conducted in the left lower lobe, the final treatment in both upper lobes. Clean-up bronchoscopy was performed after each of the three BT treatment interventions in 10 patients. Significant fibrin plugs were observed in all treated airways on the segmental or sub-segmental level. Adverse events: wheezing in 66.6% of patients, requiring intense reliever medication for several days; longer duration of higher OCS dosage in 11% of patients and nosocomial pneumonia (two weeks after BT) in one patient. FEV1 and AQLQ were significantly improved 90 days after BT ( $p=0.002$  and  $p<0.5$ , respectively). Reduction of median OCS dosage was statistically significant ( $p=0.003$ ), OCS was terminated in seven patients. Data suggest that FEV1 and AQLQ were improved in this small cohort of patients which included treatment of the RML and clean-up bronchoscopy.

Bicknell et al. (2015) reported results of a retrospective cohort study comparing safety and efficacy outcomes at 12 months post procedure in 10 clinic patients in Glasgow and 15 patients previously recruited to clinical trials of BT (i.e., Cox, et al., 2007; Pavord, et al., 2007 and Castro, et al., 2010). The authors note that eligibility criteria for clinic patients were broadly similar, but not identical to, those employed in the clinical trials of BT. One difference in eligibility noted was that all patients on asthma medications and those with high frequency of exacerbations were not excluded compared to the clinical trials. At least seven of the 10 clinic patients would have failed prescreening for the AIR2 trial [Castro, et al., 2010], mainly due to the high levels of asthma therapy, frequency of exacerbations and high use of ICS. Clinical improvement was defined as achieving one or more of the following outcomes during the post-treatment period: reduction by at least one severe exacerbation (requirement for high-dose oral corticosteroids) or hospital admissions (for asthma), improvement in ACQ or AQLQ score by the minimum clinically important difference (MCID), without a worsening of the other ACQ or AQLQ score. Stepdown in treatment defined as half the maintenance oral prednisolone dose or stop Omalizumab without loss of asthma control (no increase in hospitalization/asthma exacerbations by one or worsening of ACQ/AQLQ scores by the MCID). One-half of clinic patients obtained clinical benefit either by a stepdown in treatment, an improvement in current asthma control, or a reduction in exacerbations at 12 months post procedure, compared to 73% in the clinical trials. Adverse events were similar to those reported in the clinical trials. Study limitations which preclude the ability to translate therapy to routine practice include heterogeneous eligibility criteria between the clinic and clinical trials groups, small sample size and uncontrolled study design.

Doeing et al. (2013) reported results of a retrospective analysis involving eight individuals with severe asthma who had previously undergone BT. All patients met criteria for a diagnosis of severe asthma as defined by the National Asthma Education and Prevention Program's Expert Panel Report 3 (NAEPP EPR-3) guidelines and had poorly controlled asthma, despite maintenance medical therapy including high dose ICS and LABA. BT was planned a same day stay procedure. Events post BT requiring overnight observation included wheezing, increased frequency of rescue bronchodilator use, lower lobe atelectasis in one patient and hemoptysis and lower respiratory tract infection in one patient six and 23 days following his third BT procedure. There was no change in percent predicted prebronchodilator FEV1 noted at least 15 weeks after BT compared with baseline ( $p=.4$ ). No increase in hospitalization rate was noted following the post-treatment period during the mean follow-up of 31 weeks compared to baseline. Small sample size and uncontrolled study design limit the ability to translate results of this study into routine clinical practice.

#### **Technology Assessments/Systematic Reviews/Meta-Analysis:**

Niven et al. (2018) published an indirect treatment comparison to evaluate the comparative effectiveness of bronchial thermoplasty (BT) and Omalizumab (OM). A systematic literature review was performed: one sham-controlled trial of BT and two placebo-controlled trials of OM were evaluated for the comparison. No significant differences in the rate ratios for severe exacerbations of BT versus OM ( $p=0.62$ ) or hospitalizations ( $p=0.53$ ) were noted comparing the BT post-treatment period to ongoing treatment with OM. Proportions of patients with clinically meaningful response on the asthma quality-of-life questionnaire were comparable ( $p=0.59$ ). The RR for

exacerbations reflected improvement with OM when the total study period in AIR2 was considered ( $p=0.009$ ). Emergency department visits were significantly reduced with BT ( $p=0.04$ ). The authors noted study results should be interpreted cautiously considering the differences between patient populations in the included trials and indirect nature of the methodology.

On behalf of ECRI Institute–Penn Medicine Evidence-based Practice Center, D’Anci et al. (2017) published a comparative assessment review of bronchial thermoplasty for the Agency for Healthcare Research and Quality Fifteen studies, including three randomized controlled trials (RCTs) with five-year single-arm Follow-up in BT-treated patients ( $n=432$  for the RCTs), examined the impact of BT on patients with severe asthma. The authors noted key findings of the review note, along with the strength of the evidence (SOE):

- Patients treated with BT and standard care (medical management) showed statistically greater improvements in asthma control (as measured by the Asthma Control Questionnaire [ACQ]) and quality of life (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) compared with patients undergoing standard of care medical management only. The clinical importance of the changes is unclear. (SOE: low).
- Evidence as to whether patients treated with BT and standard care versus standard care alone experienced different rates of severe exacerbations following treatment was inconclusive. (SOE: insufficient).
- While rates of mild exacerbations improved to a greater extent in the BT and standard care group than in the standard care only group, the clinical importance of the difference is unclear. (SOE: low).
- Patients treated with BT and standard care used statistically significantly less rescue medication than patients receiving standard care alone, but the clinical importance of the difference is unclear. (SOE: low).
- Patients given BT and standard care compared with patients given the sham bronchoscopy procedure and standard care had no difference in asthma control scores, as measured by ACQ; in hospitalizations for respiratory symptoms; in use of rescue medication; in number of days rescue medications were required; or in pulmonary physiology measures (forced expiratory volume in 1 second [FEV1] and morning peak expiratory flow [PEF]) (SOE for all outcomes: low).
- Patients treated with BT and standard care experienced statistically significantly fewer exacerbations compared with those receiving the sham bronchoscopy procedure and standard care after the treatment period was complete (3 procedures over 6 weeks, followed by an additional 6 weeks) through the 12-month follow-up (post-treatment period), but the clinical importance of this difference was unclear. (SOE: low).
- Patients treated with BT and standard care had fewer emergency department (ED) visits compared with those receiving the sham bronchoscopy procedure and standard care during the post-treatment period (SOE: moderate)
- Evidence as to whether patients receiving BT and standard care versus the sham bronchoscopy procedure and standard care had different quality of life (AQLQ) scores was inconclusive (SOE: insufficient).
- Analysis of results for the intention-to-treat population did not find improvement, but analysis of results for the per-protocol population found a difference that may not be clinically important, as it did not achieve the minimum important difference for this measure. A responder analysis (proportion of patients who achieved the minimum important difference) favored the BT and standard care group, but this outcome was not prespecified.
- Patients treated with BT developed the following common adverse events: bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Serious adverse events occurred more frequently in BT-treated patients than in patients receiving sham treatment and/or standard care during the 12-week treatment period. No deaths were attributed to BT.

Zhou et al. (2016) published a systematic review of three RCTs and three extension studies with the primary objective to evaluate the long-term efficacy and safety of bronchial thermoplasty (BT). Analysis included 249 BT-treated subjects who were followed for one year; 216 completed a five-year follow-up. Inclusion criteria to select trials for inclusion in this study were as follows: age 18-65 years, diagnosed with moderate-to-severe persistent asthma according to Global Initiative for Asthma guidelines, study subjects should require daily therapy with

inhaled corticosteroid (ICS) equivalent to a dose of  $\geq 200$   $\mu\text{g}$  of beclomethasone and long-acting b-adrenergic agonist (LABA), at a dose of  $\geq 100$   $\mu\text{g}$  of salmeterol or the equivalent. Subjects should have received BT at least once, using the Alair system.

Reduction of ICS and LABAs doses varied over the five-year follow-up period. According to the study authors, greater than 10% of study subjects were weaned off LABA treatment without further maintenance medication for symptom control. Using spirometry, no evidence of significant decline was found in pre-bronchodilator FEV1 (% predicted) ( $p = 0.57$ ) or post-bronchodilator FEV1 (% predicted) ( $p = 0.65$ ) between one- and five-year follow-up. No statistically significant difference was found in the number of emergency room visit for respiratory adverse events between one- and five-year follow-up ( $p=0.71$ ). No statistically significant increase was found in the incidence of hospitalization for respiratory adverse events in the post-treatment period ( $p=0.32$ ). The author notes bronchial thermoplasty shows reasonable long-term safety and efficacy for moderate-to-severe asthmatic patients and a large scale clinical study should be performed for confirming these findings.

In a Medical Technology Assessment Directory report of bronchial thermoplasty, Hayes (2016, updated 2019) reviewed eleven studies, and noted the quality of the trials to be one good-quality randomized controlled trial (RCT), two fair-quality RCTs, one very-poor-quality retrospective cohort study, and three very-poor-quality case series. The assessment noted that a small, low-quality body of evidence suggests that during the first year following treatment, bronchial thermoplasty may improve quality of life outcomes. Some evidence also suggests symptom relief, reductions in emergency department visits, and reduced medication use; however, the results were inconsistent across studies. Hayes noted that bronchial thermoplasty did not reduce the rate of hospitalizations following treatment, and increased hospitalization during the treatment period. The report notes current evidence is insufficient to establish the long-term safety and efficacy of this procedure.

In a Cochrane systematic review by Torrego et al. (2014) the authors noted that bronchial thermoplasty for patients with moderate to severe asthma provides a modest clinical benefit in quality of life and lower rates of asthma exacerbation, but no significant difference in asthma control scores. The systematic review and meta-analysis included three trials (429 participants) and found improved quality of life at 12 months that did not reach clinical significance, no difference in symptoms, and no difference in pulmonary function parameters. According to the assessment, the quality of life findings are at risk of bias, as the main benefits were seen in the two studies that did not include a sham treatment arm. The author noted this procedure increases the risk of adverse events during treatment but has a reasonable safety profile after completion of the bronchoscopies. The overall quality of evidence regarding this procedure was deemed moderate. The author also noted that for clinical practice, it would be advisable to collect data from patients systematically in independent clinical registries. Further research should provide better understanding of the mechanisms of action of bronchial thermoplasty, as well as its effect in different asthma phenotypes or in patients with worse lung function.

### **Professional Societies/Organizations**

**American College of Allergy, Asthma and Immunology (ACAAI):** In a 2015 coverage statement on bronchial thermoplasty the ACAAI noted that bronchial thermoplasty is a well-studied treatment for patients with very severe asthma who continue to be symptomatic despite maximal medical treatment including steroids, long-acting beta agonists (LABAs), long-acting muscarinic agents (LAMAs), leukotriene antagonists and biologics. The device to deliver this therapy is FDA approved. The scientific literature supports bronchial thermoplasty as a therapeutic consideration for some carefully chosen patients with severe asthma. Carefully selected patients with severe, persistent asthma who have persistent burden of disease, asthma exacerbations, emergency department visits or hospitalizations despite maximal medical treatment may benefit from this procedure. Therefore, ACAAI recommended that insurers provide coverage bronchial thermoplasty for those adult patients who meet the stringent requirements.

**American College of Chest Physicians (CHEST, 2014):** In a document titled 'Coverage and Payment for Bronchial Thermoplasty for Severe Persistent Asthma' 2014, CHEST noted 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.

**European Respiratory Society (ERS)/American Thoracic Society (ATS):** On behalf of the ERS/ATS, Chung et al. (2014) published guidelines on the definition, evaluation and treatment of severe asthma. Regarding

bronchial thermoplasty, the quality of evidence is rated as very low. The guidelines recommended that it should be performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry or clinical study. The ERS/ATS noted this is a strong recommendation because of the low confidence in the currently available estimates of the effects of bronchial thermoplasty in patients with severe asthma. The guideline also noted both potential benefits and harms may be large and the long-term consequences are unknown and noted that studies are needed to define its effects on relevant objective primary outcomes, to better understand the phenotypes of responding patients, its effects in severe obstructive asthma, or in whom systemic corticosteroids are used, and its long-term benefits and safety.

### **Use Outside of the US**

On behalf of the Assembly on Interventional Pulmonology of the South African Thoracic Society, Dheda et al. (2015) published recommendations for the use of bronchial thermoplasty in the management of severe asthma. The society recommended that BT be considered and offered to patients who remain uncontrolled despite optimal therapy that includes maximal doses of ICS.

British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) published a joint guideline titled 'British guideline on the management of asthma' (2014, revised 2019), the BTS/SIGN noted:

- Bronchial thermoplasty may be considered for the treatment of adult patients who have poorly controlled severe asthma despite optimal therapy.
- If bronchial thermoplasty is being considered, an assessment should be done to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms, and that they are compliant with current treatment.
- Prior to undergoing treatment in a specialist center, patients should have an assessment done by an asthma specialist with expertise in bronchial thermoplasty.
- The center should have the appropriate resources and training, including access to an intensive care unit
- Patients undergoing bronchial thermoplasty should have their details entered onto the UK Severe Asthma Registry.

Canadian Agency for Drugs and Technologies in Health (CADTH) published a Rapid Response Report in 2015 to review the current evidence regarding the clinical efficacy, safety, and cost-effectiveness of bronchial thermoplasty (BT) as well as review of guidelines on the use of BT for the treatment of severe asthma. For patients with poorly controlled, severe asthma, CADTH noted that limited evidence suggests a marginal improvement in quality of life for some patients who received bronchial thermoplasty. However, the Report noted that two of the three RCTs analyzed in the review demonstrated evidence of performance bias and quality of life analysis demonstrated a large placebo effect. Twenty-one percent of patients receiving BT did not achieve any meaningful quality of life improvements. CADTH noted that this suggests the potential for improved patient selection for this intervention. Additionally the outcomes did not reflect consistent improvements in the Asthma Control Questionnaire (ACQ), significant reductions in the number of severe exacerbations and significant improvements in pulmonary function parameters. The Rapid Response report noted that professional guidelines included in this review were unclear with regard to specific indications for BT treatment. All recommendations acknowledged that further research is required to better establish which patients would benefit most from BT.

Global Initiative for Asthma (GINA) published the updated Global Strategy for Asthma Management and Prevention in 2021. GINA recommended the following:

- adult patients with uncontrolled asthma despite optimization of asthma therapy may be referred to a severe asthma specialty center where bronchial thermoplasty is a potential treatment option in some countries
- caution is needed when selecting patients for BT:
  - there is a limited number of studies
  - the pivotal sham-controlled study excluded patients with chronic sinus disease, frequent chest infections or FEV1 <60% predicted and patients did not have their asthma treatment optimized before bronchial thermoplasty was performed

- bronchial thermoplasty should be performed in the context of an independent Institutional Review Board-approved systematic registry or a clinical study only for adults with severe asthma, so that further evidence about effectiveness and safety of the procedure can be accumulated

Global Initiative for Asthma (GINA) published in a document in 2019 titled Difficult-To-Treat & Severe Asthma in Adolescents and Adult Patients. GINA noted if there is no evidence of type 2 inflammation, bronchial thermoplasty plus registry enrollment may be considered; however, the evidence for efficacy and long-term safety is limited. The document also notes if there is no good response to type 2-targeted therapy bronchial thermoplasty plus registry enrollment may be considered.

The National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (NAEPCC) 2020 focused update to the Asthma Management Guidelines stated that based on low certainty of evidence of benefit, individuals aged 18 years or older with uncontrolled, moderate to severe, persistent asthma should not undergo BT to treat asthma because the benefits are minimal, the risks are moderate and long-term outcomes are uncertain. However, BT may be offered in a clinical trial setting or a registry study to enable the collection of long-term data on the use of BT for asthma in individuals who are willing to accept the risks of BT and are 18 years or older with moderate to severe persistent asthma. The panel does not recommend BT as part of routine asthma care in individuals aged 18 years or older, even if these individuals have uncontrolled asthma despite using multicomponent medical therapy, because of the small benefit-to-risk ratio.

National Institute for Health and Care Excellence (NICE) published a guideline in 2018, titled Bronchial Thermoplasty for Severe Asthma. NICE notes current evidence on the safety and efficacy of 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. The procedure should only be done by a multidisciplinary team in specialist centers with on-site access to intensive care. It should only be done by clinicians with training in the procedure and experience in managing severe asthma. Further research should report details of patient selection and long-term safety and efficacy outcomes. Committee commented:

- There is uncertainty about which patients may benefit from the procedure.
- The committee noted that the device used in this procedure does not have a CE mark for use in people younger than 18 years.
- The committee noted that there is some evidence to suggest this procedure may not be suitable for people with bronchiectasis.
- The procedure should only be used for severe asthma that is not controlled despite optimal drug treatment.
- The committee was informed that bronchial thermoplasty could complement the use of biological treatment in the future

Standard arrangements: This is our most positive recommendation. It means that there is enough evidence for doctors to consider this procedure as an option. Doctors don't have to offer this procedure to patients and should always discuss the available options with the patient before making a decision.

## Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

## Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.  
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible

for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

**Considered Experimental/Investigational/Unproven:**

<b>CPT®* Codes</b>	<b>Description</b>
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

**\*Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.**

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