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Bronchial Thermoplasty/Targeted Lung Denervation

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Bronchial Thermoplasty
Initial Bronchial Thermoplasty
Bronchial thermoplasty **may be considered medically necessary** when **ALL** the following criteria are met:

1) The patient is 18 years of age or older; AND
2) The patient is a non-smoker; AND
3) The patient has chronic, severe persistent asthma (see **NOTE 1**) that has been managed by an asthma specialist (pulmonologist, allergist, immunologist) for at least 6 months prior to considering bronchial thermoplasty; AND
4) Forced expiratory volume in one second (FEV1) cannot be <50% predicted; AND
5) There is documentation that the patient is compliant on maximum preferred asthma medications, but therapy has not been effective or is not tolerated, as evidenced by 2 or more exacerbations requiring oral corticosteroids, (e.g., acute attacks, emergency room [ER] visits, hospitalizations) in the preceding 12 months; AND

6) Documented current use of an inhaled corticosteroid for at least three consecutive months; AND
7) Documented current use of a long-acting beta agonist or leukotriene inhibitor for at least three consecutive months; AND
8) The patient is taking, or is being considered for, chronic oral corticosteroids to maintain asthma control; AND
9) The patient is not a candidate for, or has failed, treatment with a U.S. Food and Drug Administration (FDA) approved anti-asthma biologic therapy (e.g., omalizumab, reslizumab, etc.).

Bronchial thermoplasty **is considered not medically necessary** when the following clinical scenarios are present:

- Presence of a pacemaker, internal defibrillator, or other implantable electronic device; OR
- Known sensitivity to medications required to perform bronchoscopy (e.g., lidocaine, atropine, and benzodiazepines); OR
- Active respiratory infection; OR
- Asthma exacerbation; OR
- Change in dose of systemic corticosteroids for asthma (up or down) in the past 14 days; OR
- Known coagulopathy.

Bronchial thermoplasty **is considered experimental, investigational and/or unproven** when the above criteria are not met, and for all other indications.

Repeat Bronchial Thermoplasty

One complete thermoplasty procedure is performed in three treatment sessions with a recovery period of 3 weeks or longer between sessions. All repeat procedures of bronchial thermoplasty, beyond the initial 3 treatments **are considered experimental, investigational and/or unproven** because the safety and efficacy of repeat procedures have not been studied.

NOTE 1: *Definition of Chronic Severe Persistent Asthma

Asthma is considered severe persistent if, without treatment:

- Symptoms occur throughout each day;
- Nighttime symptoms occur often, sometimes every night;
- Daily physical activities are extremely limited;
- Forced expiratory volume in one second (FEV1) is <60% predicted.

NOTE 2: Bronchial thermoplasty should be performed by clinicians who are experienced in bronchoscopy and have completed the bronchial thermoplasty training curriculum.

Targeted Lung Denervation

Targeted lung denervation **is considered experimental, investigational and/or unproven** for all indications, including but not limited to, treatment of chronic obstructive pulmonary disease (COPD).

Policy Guidelines

None.

Description

Bronchial 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.

Asthma

Asthma, a chronic lung disease, affects approximately 8.0% of adults and 6.5% of children in the United States (U.S.) (1) As of 2018, 14.3% of Black children under 18 in the U.S. had asthma, followed by 8% of Hispanic children, 5.6% of White children, and 3.6% of Asian children. (2) In the U.S., the burden of asthma falls disproportionately on Black, Hispanic, and American Indian/Alaska Native individuals; these groups have the highest rates, deaths, and hospitalizations. (3) Compared to White Americans, Black Americans are 1.5 times more likely to have asthma, and Puerto Rican Americans are almost 2 times more likely to have asthma. In 2020 and 2021, asthma exacerbations accounted for approximately 1.2 million emergency department visits and 3517 deaths overall, respectively. (1) Black Americans are 5 times more likely than White Americans to visit the emergency department for asthma and 3 times more likely to die from asthma. (3) 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.

<u>Management</u>

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 (NHLBI) has defined 6 pharmacologic steps. Step 1 is for intermittent asthma and steps 2 through 6 is for persistent asthma. (4) The preferred daily medications:

- Step 1: short-acting beta-agonists as needed;
- Step 2: low-dose inhaled corticosteroids (ICS);
- Step 3: ICS and long-acting beta-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.

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. Bronchial thermoplasty is intended as a supplemental treatment for patients with severe persistent asthma (i.e., refer to the steps 5 and 6 for the stepwise approach to care).

Chronic Obstructive Pulmonary Disease (COPD)
Chronic obstructive pulmonary disease or COPD includes emphysema and chronic (long-term) bronchitis. A progressive disease, it will get worse over time as less air flows in and out of the airways, making it difficult to breathe. In the United States (U.S.), COPD affects more than 15 million adults and more may not know they have it. More than half of those diagnosed are women. It is a major cause of disability and fourth leading cause of death in the U.S. according to the Centers for Disease Control and Prevention (CDC). (5)

COPD can cause coughing that produces large amounts of mucus, shortness of breath, chest tightness and other symptoms. The airways and air sacs lose their elasticity; and the walls between the air sacs are destroyed. Treatment may include bronchodilators, a combination of bronchodilators and steroids, pulmonary rehabilitation, or oxygen therapy. Some individuals may benefit from surgery, which is usually a last resort for those with severe symptoms that have not improved from other treatment options. (5)

<u>Targeted Lung Denervation</u>
Individuals with COPD have overactive nerves in their airways, leading to symptoms and flare-ups which can further damage the lungs. Targeted lung denervation (TLD) is being investigated as a non-surgical procedure that involves passing a specialized catheter through a flexible bronchoscope to complete a full circumferential ablation in the main bronchi of each lung. It permanently disrupts pulmonary nerve input to the lung, reducing airway nerve activity, potentially reducing the risk of COPD flare-ups. (6)

Regulatory Status
In April 2010, the Alair® Bronchial Thermoplasty System (Asthmatx, Sunnyvale, CA, now part of 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 inhaled corticosteroids and

LABAs. 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: OOY.

In July 2020, the Nuvaira lung denervation system (Nuvaira Inc.) was designated as a breakthrough device by the FDA. The Breakthrough Devices Program is intended to provide patients and health care providers with timely access to medical devices by speeding up development, assessment, and review for premarket approval, 510(k) clearance and De Novo marking authorization.

Rationale

The medical policy was originally created in September 2011 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 2, 2023.

Medical policies 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. Randomized controlled trials 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 individuals 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 following PICO was used to select literature to inform this policy.

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 ß-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.

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 with bronchodilators and corticosteroids.

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 ≥0.5 points from baseline. (7) 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.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought;

- Within each category of study design, larger sample size studies and longer duration studies were preferred;
- Studies with duplicative or overlapping populations were excluded.

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.

Randomized Controlled Trials

There are 3 industry-sponsored RCTs evaluating the efficacy and safety of bronchial thermoplasty; individual trials are described next.

Research in Severe Asthma Trial

This small Research in Severe Asthma (RISA) trial, published by Pavord et al. in 2007, was conducted at 8 centers in the United Kingdom (U.K.), Brazil, and Canada. (8) Eligibility criteria included age 18 or older; asthma diagnosis; uncontrolled symptoms, despite treatment with high-dose inhaled corticosteroids (ICSs; at least 750 µg fluticasone propionate per day or equivalent) and long-acting beta-agonists (LABAs; at least 100 µg salmeterol per day or equivalent), with or without other medications including oral prednisone or leukotriene modifiers; forced expiratory volume in 1 second (FEV1) at least 50% of predicted; demonstrated airway hyperresponsiveness by challenge with methacholine or reversible bronchoconstriction during the prior 12 months; abstinence from smoking for at least 1 year, and a smoking history of less than 10 pack-years. After a 2-week run-in period, 34 participants were randomized to a control group (n=17) that received continued medical management alone or to medical management plus treatment with the Alair Bronchial Thermoplasty System (n=17). The bronchial thermoplasty group received 3 procedures at least 3 weeks apart (weeks 0-6). During weeks 6 to 22, all participants remained on a stable dose of steroids, and then, during weeks 22 to 36, an attempt was made to reduce the dose of oral corticosteroids (or ICSs for patients not taking the oral medication). Between weeks 36 and 52, patients took the reduced dose of steroids. A total of 32 (94%) of the 34 participants completed the study.

The primary outcomes of the trial were the rate of adverse events and 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). In the initial treatment period, 4 patients in the bronchial thermoplasty group experienced 7 serious adverse events requiring hospitalization; none occurred in the control group. During the remainder of the trial, 3 patients in the bronchial thermoplasty group experienced 5 serious adverse events, and 1 patient in the control group experienced 4 serious adverse events; all events required hospitalization. There were an additional 5 severe adverse events in 2 bronchial thermoplasty group patients and 1 event in a control group patient that were medically treated without hospitalization (authors did not report whether these were the same patients who were hospitalized). No overall statistical analysis was done that compared serious adverse events in the 2 groups.

The trialists also reported a number of efficacy variables as secondary outcomes. At the end of the trial (52 weeks), bronchial thermoplasty patients had a significantly greater improvement in beta-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, improvement in FEV1 predicted, and several QOL measures. The small sample size resulted in limited power to detect differences in the efficacy outcomes.

In 2013, Pavord et al. published 5-year safety data on 14 (82%) of the 17 patients randomized to bronchial thermoplasty in the RISA trial. (9) 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. In addition, 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 (AIR) Trial

Cox et al. published findings of the AIR trial in 2007, which was designed to evaluate symptom control and adverse events following bronchial thermoplasty. (10) Patients were recruited from the same 3 countries as the RISA trial plus Denmark. The eligibility criteria included age 18 to 65 years with moderate-to-severe persistent asthma requiring daily therapy with ICSs (equivalent to at least 200 µg beclomethasone) and LABAs (at least 100 µg salmeterol or equivalent). Also required for study entry were an FEV1 of 60% to 85% of predicted, airway hyperresponsiveness, stable asthma in the 6 weeks before enrollment, no current respiratory infection, and not more than 2 lower respiratory infections requiring treatment in the past year. An additional criterion was worsening asthma control during a 2-week baseline test period during which time LABAs were withheld. A total of 112 patients met eligibility following the baseline test phase and were randomized to medical management with ICSs and LABAs (n=56) or to the same medical management strategy plus bronchial thermoplasty (3 sessions approximately 3 weeks apart) (n=56). After follow-up visits at 3, 6, and 12 months, there was a 2-week period of abstinence from LABAs, 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 change in 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 mean (SD) number of mild exacerbations per person per week in the bronchial thermoplasty group was 0.35 (0.32) during the baseline test period and 0.18 (0.31) per person per week at 12 months (a decrease of 0.17 per person per week). In the control group, the mean (SD) number of mild exacerbations per person per week was 0.28 (0.31) at baseline and 0.31 (0.46) at 12 months (an increase of 0.03 per person per week). Compared with the control group, the bronchial thermoplasty group had a significantly greater reduction in mild exacerbations at the 12-month follow-up (p=0.003).

Overall, the average number of exacerbations during the 2-week data collection periods at 3, 6, and 12 months decreased in the bronchial thermoplasty group by a mean (SD) of 0.16 (0.37) per person per week, but not in the control group, which had a mean increase of 0.04 (0.29) mild exacerbations. This resulted in a mean difference of 20 mild exacerbations per week or about 10 per year. In contrast, there was no significant difference between the number of severe exacerbations at any time point compared with baseline, but the trial may not have had sufficient statistical power for this outcome. At the 12-month follow-up, the mean (SD) number of severe exacerbations in the bronchial thermoplasty group was 0.01 (0.08) per person per week compared with 0.07 (0.18) at baseline. By contrast, the mean (SD) number of severe exacerbations in the control group was 0.06 (0.24) per person per week compared with 0.09 (0.31) at baseline.

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 limitation of the trial is the lack of a sham intervention and, consequently, an inability to blind patients to treatment group.

In 2011, Thomson et al. published 5-year data from the AIR trial. (11) 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. As previously stated, data were collected on both treatment groups during the first 2 years of 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 (ED) 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, 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 study also reported 2 measures of lung function: postbronchodilator FEV1 and forced vital capacity. Exact numbers were not reported, but postbronchodilator FEV1 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 (AIR-2) Trial

The AIR2 was an RCT evaluating the efficacy of bronchial thermoplasty at 30 sites in 6 countries (including the U.S.); findings were published in 2010 by Castro et al. (12) 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 ICSs 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 end-point; 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.

A total of 297 patients were randomized, 196 to a bronchial thermoplasty group and 101 to a sham control group. The intervention for all participants consisted of 3 bronchoscopy procedures, performed 3 weeks apart. Participants and outcome assessment 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 (ITT) population. One hundred eighty-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same numbers of patients had the third bronchoscopy (it is not clear whether they were exactly the same patients). A total of 278 (94%) of the 297 enrolled patients completed the 12- month visit, 181 in the treatment group and 97 in the sham control group.

The superiority of bronchial thermoplasty was not achieved in the ITT population for the primary effectiveness outcome, mean change in the integrated AQLQ score. Mean (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, superiority of bronchial thermoplasty on a related outcome was achieved. In the ITT 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 include 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 ED 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, 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 rate of response (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. In 2011, Castro et al. reported 2-year data on 166 (87%) of 190 patients randomized to the bronchial thermoplasty group. (13) 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.

In 2013, Wechsler et al. reported 5-year data on 162 patients in the AIR2 trial (85% of those randomized to the treatment group). (14) 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 asthma adverse events (at least ≥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%. The authors concluded that data demonstrated the 5-year durability of the benefits of bronchial thermoplasty with regard to both asthma control (based on maintained reduction in severe exacerbations and ED visits for respiratory symptoms) and safety. The authors stated that bronchial thermoplasty has become an important addition to our treatment armamentarium and should be considered for patients with severe persistent asthma who remain symptomatic despite taking inhaled corticosteroids and long-acting β_2-agonists.

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. (15) 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 stenosis, as confirmed by computed tomography 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 was 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.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Pavord et al. (2007) (8); RISA	U.K., Brazil, Canada	8	2004-2006	• ≥18 y with uncontrolled asthma refractory to high-dose ICS[a] and LABA[b] • FEV_1≥50% predicted • Airway hyperresponsiveness[c] • Abstinence from smoking for 1 y • Smoking history ≤0 pack-years • 100% of patients were White	• 17 medical management and BT • Weeks 0 to 6: 3 treatments at least 3 wk apart • Weeks 6 to 22: steroid stable • Weeks 22 to 36: protocol-defined steroid wean • Weeks 36 to 52: investigator-led steroid reduction	• 17 medical management alone • ICS dose tapered in 3 stages by 20% to 25% of baseline dose every 4 wk to minimal dose of fluticasone propionate 100 to 600 mg/d or equivalent
Cox et al. (2007) (10); AIR	U.K., Brazil, Canada, Denmark	11	2002-2005	• 18 to 65 y with moderate-to-severe persistent asthma requiring daily ICS[d] and LABA[b] • FEV_1 60% to 80% of predicted	• 56 medical management and BT (3 treatments at least 3 wk apart)	• 56 medical management alone • Follow-up at 3, 6, and 12 mo,[f] then 2-

				• Airway hyperresponsiveness • Stable asthma 6 wk prior to enrollment • No current or recent respiratory infection[e] • 92.6% of participants were White, 4.6% of participants were Black, and 2.8% of participants were Asian	• Follow-up at 3, 6, and 12 mo,[f] then 2-wk LABA abstinence	wk LABA abstinence
Castro et al. (2010) (12); AIR2	U.S. EU, Canada, Australia	30	2000-2015	• ≥2 d asthma symptoms during 4-wk baseline required high initial dosage of ICS[g] • Baseline AQLQ score ≤6.25 • 77.4% of participants were White, 11.8% of participants were Black, and 10.8% of participants did not have their race or ethnicity described	• 196 received BT (3 treatments at least 3 wk apart)	• 101 received sham procedure

AIR: Asthma Intervention Research Trial, AQLQ: Asthma Quality of Life Questionnaire; BT: bronchial thermoplasty, FEV1: forced expiratory volume at 1 second, ICS: inhaled corticosteroids, LABA: long-acting ß-agonist, RCT: randomized controlled trial, RISA: Research in Severe Asthma; wk: week.

[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.

[d] Treatment of beclomethasone ≥200 µg or equivalent.

[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.

[f] Between data collection periods, patients could use all maintenance therapies

[g] Treatment of beclomethasone ≥1000 µg or equivalent.

Table 2. Summary of Key RCT Results

Study	Respiratory AE (No. of Events)	Serious AE (Hospitalization)[b]	Reduction in SABA (puffs per 7 days)[c]	% Reduction in OCS Dosed	5 Reduction in ICS Dosed
Pavord et al. (2007) (8); RISA					

BT (n=15)[a]	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); <.05	NR (NR); 12	NR (NR); .059
	Change in Rate of Exacerbations[e]				
Cox et al. (2007) (10); AIR					
BT (n=52)[f]					
Baseline	0.35 (0.32)				
12 months	0.18 (0.31)				
MM (n=49)[f]					
Baseline	0.28 (0.31)				
12 months	0.31 (0.41)				
Effect 95% CI); p	NR (NR); .3				
	Change in AQLQ[h]				
Castro et al. (2010) (12); AIR2					
BT (n=190)[g]					
Baseline	4.30 (1.17)				
12 months	5.66 (1.06)				
Mean change	1.35 (1.10)				
BT sham (n=98)[g]					
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; RCT: randomized controlled trial. RISA: Research in Severe Asthma; SABA: short-acting β-agonist.

[a] There were 2 withdrawals from BT group prior to first treatment.

[b] There were no deaths or serious AEs other than hospitalization related to respiratory events in either group.

[c] Results at 22 wks.

[d] Results at 52 wks.

[e] Change from baseline in mean number of mild exacerbations per subject per week at 12 mo.

[f] Analyses based on participants available for evaluation at 12 mo.

[g] Intention-to-treat analyses based on participants who underwent at least 1 bronchoscopy procedure in either arm.
[h] Change from baseline in integrated AQLQ score at 12 months with higher score (0-7) indicating better quality of life. A score change of ≥0.5 defines minimal important difference.

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

Post-U.S. Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) is an ongoing, open-label, nonrandomized trial of the Alair system, required for post premarket approval. Chupp et al. (2017) compared 3-year follow-up results from 190 patients in the AIR2 trial with a subgroup (n=190) from PAS2. (16) 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<.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<.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.

The 5-year follow-up results for the full PAS2 cohort are described in a study by Chupp et al. (2022). (17) Of the 284 individuals enrolled in PAS2, 227 (81%) completed 5 years of follow up; 84% of individuals included were White, 9% Black or African heritage, 3% Hispanic or Latino, 1.4% Asian, 1% American Indian or Alaska native, and 1.6% from other racial or ethnic groups that were not described by investigators. Of note, a larger proportion of the 52 individuals who were not followed for 5 years experienced severe exacerbations (92.3% vs. 74.4%), emergency department visits (51.9% vs. 24.2%), and hospitalizations (30.8% vs. 12.8%) during the 12 months before bronchial thermoplasty compared with the 227 individuals followed for 5 years, indicating that those who dropped out of PAS2 may have had more serious disease and were not included in the analysis. By year 5 posttreatment, the proportion of individuals with severe exacerbations was significantly lower at 42.7%, compared with 77.8% in the 12 months prior to treatment (p<.001). There was also a significant reduction in severe exacerbations from baseline (1.61 exacerbations/individual) to 5 years posttreatment (0.72 exacerbations/ individual; p<.001). Emergency department visits and hospitalizations were also significantly decreased by 5 years compared to 12 months prior to treatment, from a rate of 29.4% to 7.9% (p<.001) and 16.1% to 4.8% (p=.0003), respectively. At year 5 after bronchial thermoplasty,

annual hospitalization rates fell from 0.22 hospitalizations per individual at baseline to 0.06 hospitalizations per individual (p=.0012). Bronchial thermoplasty did not alter spirometric parameters as reported in previous studies but did reduce asthma maintenance medication use. The mean daily dose of inhaled corticosteroids (beclomethasone or equivalent) was reduced from 2272 microg/d at baseline to 1928 microg/d by year 5. The number of individuals on maintenance oral corticosteroids decreased from 19.4% at baseline to 9.7% at 5 years. Clinical improvement was statistically significant across all subgroup analyses, regardless of baseline eosinophil and neutrophil counts.

Registries

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

Burn et al. (2017) reported on safety outcomes of bronchial thermoplasty outcomes in the U.K. (18) 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 (postprocedure 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). (19) 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 months 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 FEV_1 at 12 or 24 months.

The BTGR is a prospective, open-label, multicenter study across 18 centers in Spain, Italy, Germany, the U.K., the Netherlands, the Czech Republic, South Africa, and Australia that enrolls adults indicated for and treated with bronchial thermoplasty. Torrego et al. (2021) reported on the 2-year outcomes from the BTGR. (20) One hundred fifty-seven adults were included in the registry at 2 years. Racial and ethnic demographics of participants were not described. A

comparison of the proportion of individuals experiencing asthma events during the 12 months prior to bronchial thermoplasty to the 2-year follow-up showed a reduction in severe exacerbations requiring corticosteroids (90.3% vs. 56.1%; p<.0001), emergency department visits (53.8% vs. 25.5%; p<.0001), and hospitalizations (42.9% vs. 23.5%; p=.0019). Asthma Control Questionnaire and AQLQ scores improved from 11.18 and 3.26 at baseline to 15.54 and 4.39 at 2 years, respectively (p<.0001 for both). The registry results were limited by a lack of a comparator arm, a high attrition rate, with approximately one-third of individuals dropping out, and variation in investigator experience with bronchial thermoplasty between clinical sites.

Table 3. Summary of Registry Study Characteristics

Study	Study Type	Registry	Dates	Participants	Treatment	Follow-Up
Burn et al. (2017) (18)	Registry	UKSAR and Hospital Episode Statistics warehouse	2001-2015	59 patients who received bronchial thermoplasty and had data in both UKSAR and the Hospital Episode Statistics database. Race and ethnicity of participants were not described.	3 bronchial thermoplasty sessions	30 days
Burn et al. (2019) (19)	Registry	UKSAR	2011-2016	133 patients who received bronchial thermoplasty and consented to be in the UKSAR Registry. Race and ethnicity of participants were not described.	At least 1 bronchial thermoplasty session	6 mo to 5 yr
Torrego et al. (2021) (20)	Registry	BTGR	2014-2019	157 adult patients who received bronchial thermoplasty and consented to be in the BTGR. Race and ethnicity of participants were not described.	3 bronchial thermoplasty sessions	Up to 24 mo

BTGR: Bronchial Thermoplasty Global Registry; UKSAR: U.K. Severe Asthma Registry; mo: months; yr: years.

Table 4a. Summary of Registry Study Results

Study	AQLQ	ACQ	EQ-5D	Rescue Steroid
Burn et al. (2017) (18)				
Burn et al. (2019) (19)				
Change from baseline (p-value)	0.75 (<.001)	-0.43 (.083)	.008 (.909)	-0.26 (.307)
Torrego et al. (2021) (20)				
12 months prior to BT	3.26	11.18	NR	90.3%
2-years post BT	4.39	15.54	NR	56.1%
P-value	<.0001	<.0001		<.0001

AE: adverse events; AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire; BT: bronchial thermoplasty; EQ-5D: EuroQol-5D; NR: not reported.

Table 4b. Summary of Registry Study Results

Study	Procedural Complications	Overnight Stay	Unscheduled or Emergency Department Visits	Hospital admissions
Burn et al. (2017) (18)	17 (11%) of procedures	70 (46.1%) of procedures	13 (8.6%) of patients	15 (11%) of patients
Burn et al. (2019) (19)				
Change from baseline (p-value)			-0.93 (.050)	-2.0 (.056)
Torrego et al. (2021) (20)	**Respiratory AEs; Serious respiratory AE**s			
12 months prior to BT	During treatment period: 45.2%; 28%	NR	53.8%	42.9%
2-years post BT	0%; 0%	NR	25.5%	23.5%
P-value			<.0001	<.0019

AE: adverse events; AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire; BT: bronchial thermoplasty; EQ-5D: EuroQol-5D; NR: not reported.

Systematic Reviews

Several pooled analyses of the published RCTs were identified. In 2016, Zhou et al. published a systematic review of the published RCTs and extension studies, focusing on the durability and long-term responses for treated patients. (21) Reviewers pooled data on long-term effects in bronchial thermoplasty treated patients only (i.e., not in comparison groups). In an analysis of 216 patients with 5 years of follow-up, there was no significant decline in spirometry-detected prebronchodilator FEV1 (percent predicted) compared with 1-year findings (weighted mean difference [WMD], 0.75; 95% CI, -3.36 to 1.85; p=0.57; I2=0%). Similarly, there was no significant decline in postbronchodilator FEV1 (WMD=0.62; 95% CI, -3.32 to 2.08; p=0.65; I2=0%). In terms of adverse events over time, the rates of respiratory adverse events, ED visits for adverse events, and hospitalizations did not differ significantly after the 1- and 5-year follow-ups.

In 2014, a Cochrane review of RCTs was published by Torrego et al. (22) Reviewers included the 3 RCTs discussed herein. Potential trial limitations identified by reviewers were lack of blinding in 2 of the 3 trials and lack of a sham control in 2 trials. Pooled analyses were not conducted for asthma exacerbation outcomes. A meta-analysis of the 3 trials found significantly greater improvement in AQLQ scores at 12 months in the bronchial thermoplasty groups than in the control groups (mean difference [MD], 0.28; 95% CI, 0.07 to 0.40). However, at 12 months, the proportion of patients using rescue medication did not differ significantly between groups (MD = -0.68; 95% CI, -3.63 to 2.28). In terms of adverse events, a significantly higher number of patients were admitted to the hospital for respiratory events during the treatment period (relative risk [RR], 3.50; 95% CI, 1.26 to 9.68). There was no significant difference between groups in the proportion of patients admitted to the hospital for respiratory events in the posttreatment period (RR=1.12; 95% CI, 0.44 to 2.85).

Previously, in 2011, Wu et al. published a meta-analysis of the findings of the 3 published RCTs. (23) Pooled analyses of them found greater mean improvement in asthma QOL in the bronchial thermoplasty groups than in the control groups (WMD=0.63; 95% CI, 0.10 to 1.15) and greater improvement in the peak expiratory flow with bronchial thermoplasty treatment than with the control treatment (WMD=21.78; 95% CI, 8.06 to 35.50). During the treatment period (beginning on the day of the first treatment session and lasting 6 weeks after the last session), there were more respiratory adverse events in the bronchial thermoplasty groups (1113 events in 257 patients) than in the control groups (369 events in 164 patients) (p value not reported). Also, during the treatment period, there was a significantly higher risk of hospitalization with bronchial thermoplasty than with control (RR=3.78; 95% CI, 1.39 to 10.24). In the posttreatment period (end of treatment to the 12-month follow-up visit), there was no significant difference between groups in the risk of hospitalization (RR=1.15; 95% CI, 0.47 to 2.79).

Case Series

After publication of the 3 RCTs (described above), several case series have described outcomes in clinical practice. They generally had small sample sizes (e.g., N=7,14 N=10, 15 and N=2016).

In 2016 Arrigo et al. (24) evaluated available literature (RCTs) on the efficacy and safety of bronchial thermoplasty in severe asthmatics, in whom the exclusion criteria were not strictly controlled. A case series of seven asthmatics (Male/Female: 4/3; age: 54.6 ± 2.9 years) was reported. Subjects had a statistically significant improvement in AQLQ (from a mean of 3.96 ± 1.1 to 4.5 ± 1.2 and 5.5 ± 0.6 after 6 and 12 months of treatment; $p = 0.0007$) and in the ACQ score (from 2.77 ± 0.8 to 1.83 ± 1.2 and 1.5 ± 0.8 after 6 and 12 months; $p < 0.001$). In the year after BT, severe exacerbations, salbutamol use, and OCS use were significantly lower compared with the 1-yr pretreatment period ($p < 0.001$). No ED visits and hospitalization occurred in the year after bronchial thermoplasty. No changes in functional parameters were recorded. The investigation confirmed the safety and efficacy of bronchial thermoplasty (BT) in severe asthmatics in real life settings.

In addition, a rigorous U.K. registry study was published by Burn et al. (2017), which focused on safety outcomes. (18) The study combined data from 2 sources, the U.K. Difficult Asthma Registry and the Hospital Episode Statistics warehouse, and included patients treated with bronchial thermoplasty in the U.K. between June 2011 and January 2015. Eighty-three patients were identified in the Difficult Asthma Registry and 85 in the Hospital Episode Statistics database. For 59 patients, data in the 2 databases could be matched. Most patients had a course of 3 bronchial thermoplasty treatment sessions. Data from the matched cohort 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; ED readmissions within 30 days of the initial hospitalization were reported for 15 (11.8%) patients; and accident and emergency visits (i.e., emergency department) visits for any reason were reported for 13 (8.6%) patients. For the fourth binary 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 be related to older patients with more severe disease being treated in clinical practice compared with patients that were included in clinical trials.

Bicknell et al. (2015) published information on the effectiveness of bronchial thermoplasty for severe asthma. (25) Safety and efficacy outcomes 12 months post procedure in 10 clinic patients and 15 patients recruited to clinical trials of BT at the same center. Ten clinic patients underwent bronchial thermoplasty. Four of 10 patients were taking oral prednisolone daily and two of 10 were receiving omalizumab treatment (for over 3 years). Baseline forced expiratory volume in 1 s (FEV1) % predicted pre salbutamol ranged from 45% to 96%. Asthma control was poor (mean ACQ score 3.3). Exacerbations in the previous year ranged from zero to eight (mean three) and hospital admissions ranged from zero to five (mean one). The demography of clinic patients bore the closest resemblance to those in the RISA study where Step 5 asthmatics were included (Pavord et al. mentioned above), but the study extended this to include patients currently on omalizumab treatment. Clinical improvements occurred in 50% of the clinic patients compared with 73% of the research patients.

Langton et al. (2017) published the first 'real world' retrospective analysis from Australia. (26) Twenty patients were treated from June 2014 to December 2015 at three university teaching hospitals. Mean pre-bronchodilator forced expiratory volume in 1 s was 62.8 ± 16.6% predicted (range: 33–95%). All patients were being treated with high dose inhaled corticosteroids, long-acting beta2 agonists and long-acting muscarinic antagonists. Ten patients (50%) were taking maintenance oral prednisolone. Most subjects also required at least one of montelukast (65%), omalizumab (30%) and methotrexate (20%). ACQ-5 improved from 3.6 ± 1.1 at baseline to 1.6 ± 1.2 at 6 months, $P < 0.001$. Short-acting reliever use decreased from a median of 8.0–0.25 puffs/day, $P < 0.001$, and exacerbations requiring corticosteroids also significantly reduced. Five of 10 patients completely discontinued maintenance oral corticosteroids. Ten patients with a baseline forced expiratory volume in 1 s of <60% predicted significantly improved from 49.2 ± 9.6% to 61.8 ± 17.6%, $P < 0.05$. Only two procedures required hospitalization beyond the planned overnight admission.

Other Resources

In 2018, DynaMed (27) stated that bronchial thermoplasty should only be considered for select patients who have uncontrolled severe asthma despite optimal therapy as evidence is limited and long-term adverse effects are unknown. Bronchial thermoplasty is contraindicated in the following patients with:

- Electronic implantable devices such as pacemakers or internal defibrillators;
- Prior bronchial thermoplasty procedures;
- Contraindications to bronchoscopy including sensitivity to medications used during bronchoscopy;
- Active respiratory infection;
- Asthma exacerbation in previous 14 days;
- Change in systemic corticosteroids for asthma in previous 14 days;
- Known coagulopathy.

The authors reinforced that once an airway has been treated, it should not be retreated.

Targeted Lung Denervation

A 2018 prospective multicenter study by Valipour et al. evaluated 15 patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) who underwent bilateral targeted lung denervation (TLD) treatment following baseline assessment without bronchodilators. (28) The primary safety endpoint was freedom from documented and sustained worsening of COPD directly attributable to TLD up to 1 year. Secondary endpoints included technical feasibility, change in pulmonary function tests, exercise capacity, and health-related quality of life. Follow-up continued up to 3 years for subjects who reconsented for longer-term follow-up. A total of 15 patients (47% male, age 63.2±4.0 years) underwent TLD with a total procedure time of 89±16 min, and the total fluoroscopy time was 2.5±2.7 min. Primary safety end point of freedom from worsening of COPD was 100%. There were no procedural complications reported. Results of lung function analysis and exercise capacity demonstrated similar

beneficial effects of TLD without bronchodilators, when compared with long-acting anticholinergic therapy at 30 days, 180 days, 365 days, 2 years, and 3 years post-TLD. Five of the 12 serious adverse events that were reported through 3 years of follow-up were respiratory related with no events being related to TLD therapy. TLD delivered to both lungs in a single procedure is feasible and safe with few respiratory-related adverse events through 3 years.

A 2019 trial by Slebos et al. looked at safety and impact of targeted lung denervation (TLD) on respiratory adverse events. (29) This was a multicenter, randomized sham bronchoscopy - controlled double-blind trial in patients with symptomatic COPD. The primary endpoint was the rate of respiratory adverse events between 3 and 6.5 months after randomization (defined as COPD exacerbation, tachypnea, wheezing, worsening bronchitis, worsening dyspnea, influenza, pneumonia, other respiratory infections, respiratory failure, or airway effects requiring therapeutic intervention). Blinding was maintained through 12.5 months. Eighty-two patients (50% female; mean ± SD: age, 63.7 ± 6.8 yr; FEV1, 41.6 ± 7.3% predicted; modified Medical Research Council dyspnea scale score, 2.2 ± 0.7; COPD Assessment Test score, 18.4 ± 6.1) were randomized 1:1. During the predefined 3- to 6.5-month window, patients in the TLD group experienced significantly fewer respiratory adverse events than those in the sham group (32% vs. 71%, P = 0.008; odds ratio, 0.19; 95% confidence interval, 0.0750–0.4923, P = 0.0006). Between 0 and 12.5 months, these findings were not different (83% vs. 90%; P= 0.52). The risk of COPD exacerbation requiring hospitalization in the 0- to 12.5-month window was significantly lower in the TLD group than in the sham group (hazard ratio, 0.35; 95% confidence interval, 0.13–0.99; P= 0.039). There was no statistical difference in the time to first moderate or severe COPD exacerbation, patient-reported symptoms, or other physiologic measures over the 12.5 months of follow-up. Patients with symptomatic COPD treated with TLD combined with optimal pharmacotherapy had fewer study-defined respiratory adverse events, including hospitalizations for COPD exacerbation.

In 2020 Valipour et al. published 2-year outcomes for a double-blind, randomized sham-controlled study of TLD in patients with moderate-to-severe COPD. (30) Eighty-two subjects (FEV1 41.6±7.4% predicted, 50.0% male, age 63.7±6.8 yrs, 24% with prior year respiratory hospitalization) were randomized. Time-to-first severe COPD exacerbation was significantly lengthened in the TLD arm (p=0.04, HR=0.38) at 2 years post-TLD therapy and trended towards similar attenuation for moderate and severe COPD exacerbations (p=0.18, HR=0.71). No significant changes in lung function or SGRQ-C were found 2 years post randomization between groups. TLD demonstrated a durable effect of significantly lower risk of severe adverse event COPD (AECOPD) over 2 years. Further, lung function and quality of life remained stable following TLD.

In 2021 Christophe et al. published 3-year outcomes for a prospective, randomized, multicenter study (NCT020584549) of TLD following targeted lung denervation therapy for COPD: AIRFLOW-1. (43) Three-year follow-up data were available for 73.9% of patients (n = 34). The annualized rate of moderate to severe COPD exacerbations remained stable over the duration of the study. Lung function (FEV1, FVC, RV, and TLC) and quality of life (SGRQ-C and CAT) remained stable over 3 years of follow-up. No new gastrointestinal adverse events and no unexpected serious

adverse events were observed. TLD in COPD patients demonstrated a positive safety profile out to 3 years, with no late-onset serious adverse events related to denervation therapy. Clinical stability in lung function, quality of life, and exacerbations were observed in TLD treated patients over 3 years of follow up.

Practice Guidelines and Position Statements

Global Initiative for Asthma (GINA)

The 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 2022. (7) 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. Bronchial thermoplasty may be considered as an add-on treatment in adults with severe asthma that remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center. GINA notes that bronchial thermoplasty should only be administered in the context of a systematic registry or a clinical study, as the evidence for efficacy and long-term safety is limited.

A guide for the diagnosis and management of difficult-to-treat and severe asthma was first published in 2019, with a goal to update annually. (31) The updated guidance has not yet been released to the public. (32) 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 ß-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.

European Respiratory Society and American Thoracic Society

In 2014, a joint task force of the European Respiratory Society and American Thoracic Society published guidelines on the definition, evaluation, and treatment of severe asthma. (33) The guidelines were based on a systematic review of the literature. It includes the statement: “We recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry of a clinical study.” The authors remarked: “This is a strong recommendation, because of the very low confidence in the available estimates of effects of bronchial thermoplasty in patients with severe asthma.”

American College of Chest Physicians (ACCP)

In May 2014, ACCP posted a position statement on coverage and payment for bronchial thermoplasty. (34) 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…."

British Thoracic Society and Scottish Intercollegiate Guidelines Network

In 2019, the British Thoracic Society and the Scottish Intercollegiate Guidelines Network published revised national guidelines on management of asthma. (35) The guidelines stated: "Bronchial thermoplasty may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy."

National Institute for Health and Care Excellence (NICE)

In 2018, the NICE updated the guidance on bronchial thermoplasty for severe asthma. (36) The guidance stated: "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 centres with on-site access to intensive care. It should only be done by clinicians with training in the procedure and experience managing severe asthma. Further research should report details of patient selection and long-term safety and efficacy outcomes."

American College of Allergy, Asthma, and Immunology (ACAAI)

A 2018 position statement by the ACAAI (37) states "bronchial thermoplasty (BT) is a drug free treatment option for people whose asthma symptoms are not improved by other medication. It helps people to better control their severe asthma and results in a decrease in the number and severity of asthma attacks. BT may improve a patient's quality of life by reducing the physical limitations, number of missed workdays, and visits to the emergency department all of which can lead to improved social, financial and emotional well-being. BT offers hope to people who want may feel that there are no medicines to make their asthma better."

INTERASMA (Global Asthma Association)

In October 2014, INTERASMA (38) provided guidance related to bronchial thermoplasty as an option for patients with uncontrolled, refractory, severe asthma. Bronchial thermoplasty can offer an excellent alternative as an add-on therapy in severe, carefully selected asthma patients. In this context, bronchial thermoplasty should not be considered "experimental". On the contrary, it should be considered an important option for patients suffering this condition for this special group of patients.

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. (39, 40)

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.

Summary of Evidence
For individuals who have asthma refractory to standard treatment who receive bronchial thermoplasty, the evidence includes observational studies, several randomized controlled trials (RCTs), and meta-analyses. Relevant outcomes are symptoms, quality of life (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. The AIR2 trial is the largest of the published RCTs, and the only trial that is double-blinded and sham-controlled, with sites in the United States. 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 QOL score but was found to be superior on a related outcome, improvement in quality of life of at least 0.5 points on the Asthma Quality of Life Questionnaire. Safety data up to 10 years have been reported in the RCTs for the patients treated with bronchial thermoplasty. Safety data from a United Kingdom (U.K.) registry study, published in 2016, found 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).

To date, several professional societies support the use of bronchial thermoplasty for a select subset of nonsmoking, adult patients with chronic, severe persistent asthma despite optimal therapy. Based on the Food and Drug Administration (FDA) device approval of the Alair® Bronchial Thermoplasty System, the available published literature and professional society support, bronchial thermoplasty may be considered medically necessary when all criterion are met. Based on the FDA product labeling, bronchial thermoplasty is contraindicated in patients with implantable devices and those with sensitivities to lidocaine, atropine, or benzodiazepines, in patients experiencing an asthma exacerbation, active respiratory infection, bleeding disorder, or within 2 weeks of making changes in their corticosteroid regimen therefore, bronchial

thermoplasty is considered not medically necessary in these situations. All repeat procedures, beyond the initial 3 treatments, are considered experimental, investigational and/or unproven because the safety and efficacy of repeat procedures have not been studied.

For individuals who undergo targeted lung denervation (TLD) the evidence includes a prospective multi-center study and several randomized controlled trials. Relevant outcomes are symptoms, quality of life (QOL), hospitalizations, and treatment-related morbidity. Study sizes have been small with relatively short follow-up. Early studies have shown some stability in lung function and quality of life but large scale sham-controlled RTC's comparing TLD with optimal care for patients with moderate-to-severe COPD against optimal medical care for COPD are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials – Bronchial Thermoplasty

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03765307[a]	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 2023 (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 2023 (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)
Unpublished			
NCT01185275	A Prospective Observational Study of Biopredictors of Bronchial Thermoplasty Response in Patients With Severe Refractory Asthma (BTR Study)	133	Oct 2019

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Ongoing and Unpublished Clinical Trials – Targeted Lung Denervation

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03639051[a]	Evaluation of the Safety and Efficacy of TLD in Patients with COPD	464	Sep 2028 (recruiting)
NCT05816616	Hyperpolarized Xenon Functional Lung Imaging in COPD Patients Undergoing Targeted Lung Denervation	10	Apr 2024 (not yet recruiting)
NCT05967091	Ryme Medical TLD Pilot Study	60	Dec 2025 (not yet recruiting)

NCT: national clinical trial; TLD: targeted lung denervation; COPD: chronic obstructive pulmonary disease.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	31660, 31661, 0781T, 0782T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/01/2023	Document updated with literature review. Coverage unchanged. Reference 41 added; others updated.
06/15/2023	Document updated with literature review. The following change was made to Coverage: Added “Targeted lung denervation is considered experimental, investigational and/or unproven for all indications, including but not limited

	to, treatment of chronic obstructive pulmonary disease (COPD).” Title changed from Bronchial Thermoplasty. References 36-40 added.
01/15/2023	Document updated with literature review. Coverage unchanged. References 2, 3, 5, 13-15, 17-18, 26, 27, 30, 34 and 35 added or updated; others removed.
11/01/2021	Reviewed. No changes.
02/15/2021	Document updated with literature review. The following change was made to Coverage: Revised to remove this phrase: “and is at Step 5 or Step 6 of NHLBI/NAEPP (National Heart Lung and Blood Institute/National Asthma Education and Prevention Program) Guidelines.” References updated; no references added.
11/15/2019	Reviewed. No changes.
10/15/2018	Document updated with literature review. The following changes were made in Coverage: 1) “The patient is not a candidate for, or has failed treatment with omalizumab” was changed to state, “The patient is not a candidate for, or has failed, treatment with a U.S. Food and Drug Administration (FDA) approved anti-asthma biologic therapy (e.g. omalizumab, reslizumab, etc.)” 2) Added not medically necessary statement for the following indications: Presence of a pacemaker, internal defibrillator, or other implantable electronic device; or known sensitivity to medications required to perform bronchoscopy (e.g. lidocaine, atropine, and benzodiazepines); or active respiratory infection; or asthma exacerbation; or change in dose of systemic corticosteroids for asthma (up or down) in the past 14 days; or known coagulopathy. The following references were added 11, 14, 15, 18, 22, 24-26.
11/01/2016	Reviewed. No changes.
09/15/2015	Document updated with literature review. The following was removed from the criteria for medical necessity in Coverage: “The patient has severe persistent allergic asthma with forced expiratory volume in one second (FEV1) < 60% predicted”. The following was added to the criteria for medical necessity in Coverage: “Forced expiratory volume in one second (FEV1) cannot be <50% predicted, and” The following change was made to the “Definition of Chronic Severe Persistent Asthma” in Coverage: “Lung function tests are abnormal (60% or less of expected value” was changed to “Forced expiratory volume in one second (FEV1) is <60% predicted.”
12/15/2014	Document updated with literature review. The following was changed in coverage: 1) Bronchial thermoplasty may be considered medically necessary for patients who are age 18 and over; are non-smokers; have had 2 or more exacerbations (e.g., emergency department visits or hospitalizations for asthma) in the previous 12 months; have chronic, severe persistent asthma that has been managed by an asthma specialist for at least 6 months prior to considering bronchial thermoplasty; have severe persistent allergic asthma with forced expiratory volume in one second (FEV1) < 60% predicted; have

	documentation of compliance with treatment outlined in Step 5 or Step 6 by the National Heart, Lung and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP) Guidelines for at least 3 consecutive months (as outlined in the Coverage section); are not a candidate for, or failed treatment with omalizumab; and have documentation that the outlined treatment has either not been effective or is not tolerated (as outlined in Coverage section). 2) One complete thermoplasty procedure is performed in three treatment sessions with a recovery period of 3 weeks or longer between sessions. Repeat procedures of bronchial thermoplasty, beyond the initial 3 treatments, are considered experimental, investigational and unproven because the safety and efficacy of repeat procedures have not been studied. 3) Bronchial thermoplasty remains experimental, investigational and unproven when the above criteria are not met, and for all other indications.
09/01/2013	Document updated with literature review. Coverage unchanged.
09/01/2011	New medical document. Bronchial thermoplasty is considered experimental, investigational and unproven for all conditions including but not limited to the treatment of asthma.