Washington State Health Care Authority
Health Technology Assessment

Bronchial Thermoplasty

Clinical Expert

Amy Markezich, MD

Physician, Pulmonary and Critical Care Medicine
Overlake Medical Clinics, Bellevue, WA

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I do the bronchial thermoplasty procedure as part of my clinical practice

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 5/4/16 Amy Markezich

Signature *Date* *Print Name*

So we may contact you regarding this information, please provide the following:

Email Address: amy.markezich@overlakehospital.org

Phone Number: [redacted]

Amy Markezich, M.D.

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Positions

2012-present	Physician, Pulmonary and Critical Care Medicine, Overlake Medical Clinics, Bellevue, WA
2012-2015	Associate Medical Director, Pulmonary Clinic, Overlake Medical Clinics, Bellevue, WA
2009-2012	Physician, Pulmonary and Critical Care Medicine, Overlake Internal Medicine Associates, Bellevue, WA

Education

7/2005 – 7/2009	Harvard Fellowship Program in Pulmonary and Critical Care Medicine – Fellowship	
7/2004 - 6/2005	Brigham and Women's Hospital Internal Medicine Residency Program – Residency	
6/2002 - 6/2004	Stanford Medical Center Internal Medicine Residency Program – Internship and Residency	
9/1997 – 6/2002	Stanford University School of Medicine	M.D. – 2002
9/1993 - 4/1997	Stanford University – Psychology with Distinction, and Biological Sciences	B.A., B.S. – 1997

Academic Honors

1998, 1999	Recipient of Stanford Medical Scholars Research Fellowship
1996-1999	Excellence in Teaching Award, Department of Biological Sciences, Stanford University
1996-1997	Psi Chi National Psychology Honor Society
1994-1997	Academic All-American, National Collegiate Athletics Association
1994-1996	Scholar Athlete, Stanford University Athletics

Research Experience

2010-2012 Site Principle Investigator, AEGIS Study Group, AEGIS Clinical Trial

Research Subject: Prospective evaluation of a bronchial airway gene expression classifier for the detection of lung cancer.

2007-2009 Research Fellow, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School

Supervisor: Dr. Elliot Israel, MD, Associate Professor of Medicine

Research Subject: The effect of long-acting beta agonists versus long-acting anticholinergics on asthma exacerbations in patients with specific single nucleotide polymorphisms of the beta-2 adrenergic receptor.

1998-2000 Medical Scholars Fellow, Division of Vascular Surgery, Stanford University School of Medicine

Supervisor: Dr. Ronald Dalman, MD, Associate Professor of Surgery

Research Subject: The role of matrix metaloproteinases in flow-mediated arterial enlargement.

1996-1997 Research Assistant, Division of Transplant Surgery, Stanford University School of Medicine

Supervisor: Dr. Edward Alfrey, MD, Assistant Professor of Surgery

Research Subject: Determination of when to perform a single vs. dual cadaveric kidney transplant with expanded criteria donor kidneys.

Publications

1. Silvestri GA, Vachani A, Whitney D, Elashoff M, Porta Smith K, Ferguson JS, Parsons E, Mitra N, Brody J, Lenburg ME, Spira A; **AEGIS Study Team**. A bronchial genomic classifier for the diagnostic evaluation of lung cancer. *N Engl J Med.* 2015 Jul 16;373(3):243-51.

2. Israel E, Lasky-Su J, **Markezich** A, Damask A, Szefler SJ, Schuemann B, Klanderman B, Sylvia J, Kazani S, Wu R, Martinez F, Boushey HA, Chinchilli VM, Mauger D, Weiss ST, Tantisira KG; SHARP Investigators. Genome-wide association study of short-acting beta2-agonists. A novel genome-wide significant locus on chromosome 2 near ASB3. *Am J Respir Crit Care Med.* 2015 Mar 1;191(5):530-7.

3. Himes BE, Jiang X, Hu R, Wu AC, Lasky-Su JA, Klanderman BJ, Ziniti J, Senter-Sylvia J, Lima JJ, Irvin CG, Peters SP, Meyers DA, Bleecker ER, Kubo M, Tamari M, Nakamura Y, Szefler SJ, Lemanske RF Jr, Zeiger RS, Strunk RC, Martinez FD, Hanrahan JP, Koppelman GH, Postma DS, Nieuwenhuis MA, Vonk JM, Panettieri RA Jr, **Markezich** A, Israel E, Carey VJ, Tantisira KG, Litonjua AA, Lu Q, Weiss ST. Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene. *PLos Genet.* 2012 Jul;8(7):e1002824

4. Tantisira KG, Damask A, Szefler SJ, Schuemann B, **Markezich** A, Su J, Klanderman B, Sylvia J, Wu R, Martinez F, Boushey HA, Chinchilli VM, Mauger D, Weiss ST, Israel E; SHARP Investigators. Genome-wide association identifies the T gene as a novel asthma pharmacogenetic locus. *Am J Respir Crit Care Med.* 2012 Jun 15;185(12):1286-91

5. Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, Ameredes BT, Castro M, Craig TJ, Denlinger L, Fahy JV, Jarjour N, Kazani S, Kim S, Kraft M, Lazarus SC, Lemanske RF Jr, **Markezich** A, Martin RJ, Permaul P, Peters SP, Ramsdell J, Sorkness CA, Sutherland ER, Szefler SJ, Walter MJ, Wasserman SI, Israel E; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomized, placebo-controlled, crossover trial. *Lancet.* 2009 Nov 21;374(9703):1754-64

6. **Markezich**, A. European Respiratory Society/American Thoracic Society Asthma Task Force Report. *The Respiratory Report*. 2007; 3(2):12-18

7. **Markezich**, A. Emerging concepts in asthma. *The Respiratory Report*. 2006; 2(1):21-28

8. Karwowski, JK; **Markezich**, A; Whitson, J; Abbruzzese, TA; Zarins, CK; Dalman, RL. Dose-dependent limitation of arterial enlargement by the matrix metalloproteinase inhibitor RS-113,456. *Journal of Surgical Research*. 1999 Nov, 87(1):122-9.

9. Lee, CM; **Markezich**, AJ; Scandling, JD; Dafoe, DC; Alfrey, EJ. Outcome in cadaveric renal transplant recipients treated with cyclosporine A and mycophenolate mofetil versus cyclosporine A and azathioprine. *Journal of Surgical Research*. 1998 May, 76(2):131-6.

10. Lee, CM; Scandling, JD; Pavlakis, M; **Markezich**, AJ; Dafoe, DC; Alfrey, EJ. A review of the kidneys that nobody wanted: determinants of optimal outcome. *Transplantation*. 1998 Jan 27, 65(2):213-9

11. Alfrey, EJ; Lee, CM; Scandling, JD; Witter, MM; Carter, JT; **Markezich**, AJ; Salvatierra, O; Dafoe, DC. Expanded criteria for donor kidneys: an update on outcome in single versus dual kidney transplants. *Transplantation Proceedings*. 1997 Dec, 29(8):3671-3.

12. Alfrey, EJ; Lee, CM; Scandling, JD; Pavlakis, M; **Markezich**, AJ; Dafoe, DC. When should expanded criteria donor kidneys be used for single versus dual kidney transplants? *Transplantation*. 1997 Oct 27, 64(8):1142-6.

Board Certification/Medical Licensure

2008	Critical Care Medicine – Board Certified
2007	Pulmonary Medicine – Board Certified
2005	Internal Medicine – Board Certified
2009-present	Washington State Medical License - current
2004-2009	Massachusetts Medical License
2003-2005	California Medical License

Other

2015-present	Committee Member, Professional Practice Committee, Overlake Medical Clinics
2015	Clinical Preceptor, ARNP student clinical practice rotation
2008-2009	Instructor, Harvard Medical School Pulmonary Physiology Course
1997-1998	Graduate Assistant Coach, Stanford University Varsity Synchronized Swim Team, 1998 NCAA National Champions
1996, 1997	Two-time NCAA All-American, Synchronized Swimming
1993-1997	Stanford University Varsity Synchronized Swim Team

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Agency Medical Director Comments

Bronchial Thermoplasty for Asthma

Charissa Fotinos, MD, MSc
Deputy Chief Medical Officer
Washington State Health Care Authority
March 20, 2016

Background

- In Washington, more than 600,000 people have asthma.
- Nearly 120,000 of these are children.
- WA prevalence in 2013: 9.9% (TN 7.1% and 12% RI)
- About 1 in 8 women and 1 in 14 men currently have asthma.
- Between 8% and 11% of children in middle and high school have asthma.
- More than 5,000 people with asthma are hospitalized each year.
- Nearly 100 people die each year of asthma in WA.

www.doh.wa.gov/DataandStatisticalReports/DiseasesandChronicConditions/AsthmaData

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Additional Background Considerations

- Baseline compliance with asthma controller medications is marginal
- Retrospective look at 69,000+ patients from 5 health plans
- Primary fill rate within 30 days of script
  - 14-20% of patients did not fill their initial script
- Mean proportions for days covered in 12 months were:
  - 19% for Inhaled Corticosteroids, ICS
  - 30% for Leukotriene antagonists, LTRA
  - 25% for ICS/LTRA combination

Ann Chen Wu, Melissa G. Butler, Lingling Li, et. al. "Primary Adherence to Controller Medications for Asthma Is Poor", Annals of the American Thoracic Society, Vol. 12, No. 2 (2015), pp. 161-166.

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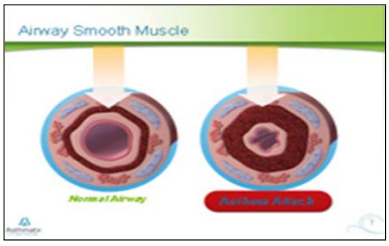

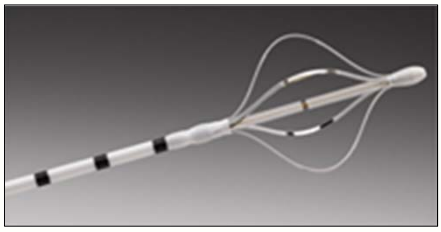

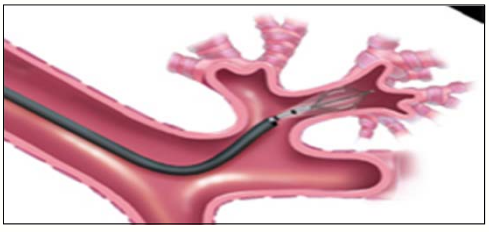

http://txpulmonary.com/bronchial-thermoplasty/

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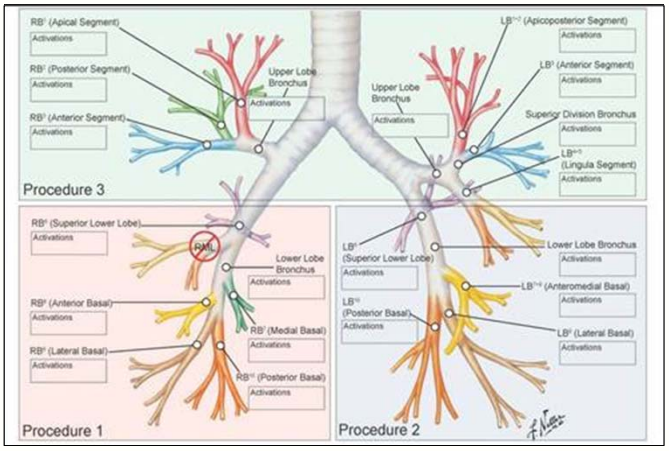
Lung Areas Treated



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Bronchial Thermoplasty

Primary Ranking Criteria

- Safety: **High**
- Efficacy: **High**
- Cost: **Medium**

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Key Questions

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?
   Is there clinically meaningful improvement for patients with severe asthma?
2. What are the harms associated with bronchial thermoplasty?
3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?
4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

Outcomes of Interest

Effectiveness

- Quality of life
- Asthma control
- Exacerbations
- Lung function
- Reduced hospitalizations
- Reduced ED visits

Safety

- Procedure related events
- Mortality

Bronchial Thermoplasty

Current State Agency Policy

- **Medicaid** – Prior Authorization
- **PEBB** – Not covered
- **Labor & Industries –** Prior Authorization
- **Dept. of Corrections –** Prior Authorization

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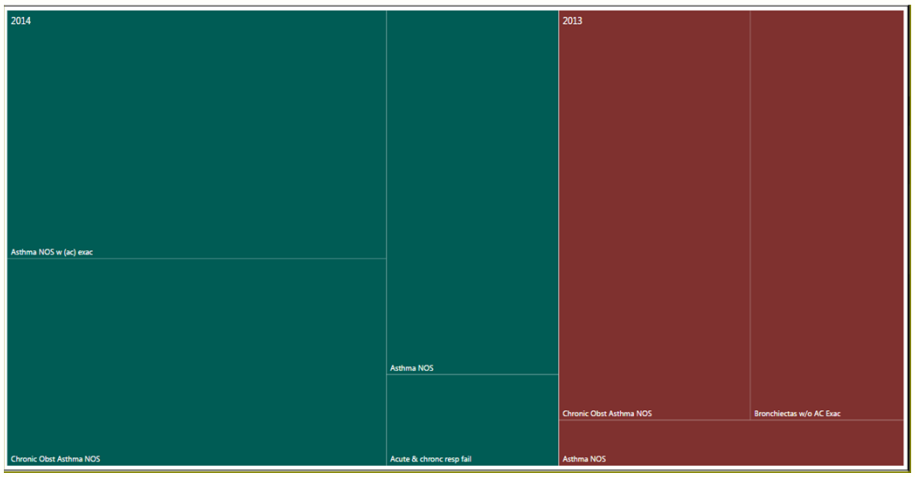
Bronchial Thermoplasty

UMP PEBB, Medicare, Medicaid Fee-for Service & Medicaid Managed Care

2012 – 2014 Primary Diagnoses for Patients Undergoing a

Bronchial Thermoplasty Procedure

2012 N = 0; 2013 N = 10; 2014 N=16



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Bronchial Thermoplasty

HCA Utilization

TABLE I
UMP PEBB, MEDICARE, MEDICAID FEE-FOR SERVICE & MEDICAID MANAGED CARE
2012 – 2014 Utilization: Bronchial Thermoplasty, CPT 31660, 31661
Includes all claims; paid and unpaid

Year	Unique Members by Year	Total Procedures*
2012	0	0
2013	6	11
2014	6	15
Grand Total	12	26

Recommended: up to three procedures/lobe

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Bronchial Thermoplasty

Diagnoses for Bronchial Thermoplasty

TABLE 2
UMP PEBB, MEDICARE, MEDICAID FEE-FOR SERVICE & MEDICAID MANAGED CARE
2012 – 2014 Primary Diagnoses for Patients undergoing a Bronchial Thermoplasty

Primary Diagnoses Short Desc -	2013	2014	Grand Total
Acute & chronic Resp Fail		1	1
Asthma NOS	1	4	5
Asthma NOS w (ac) Exac		6	6
Bronchiectasis w/o AC Exac	4		4
Chronic Obst Asthma NOS	5	5	10
Grand Total	10	16	26

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Overview of Findings

- 7 Studies (480 patients)
- 3 RCTs: (429 patients)
  - Castro 2010: 288 pts **AIR2**
  - Cox 2007: 109 pts **AIR**
  - Pavord 2007: 32 pts **RISA**
    - Primary objective was to assess safety & feasibility, secondary outcomes assessed efficacy
- 3 Case series
  - Cox 2006: 16 pts
  - Doeing 2013: 8 pts
  - Chakir 2015: 17 pts
- 1 Retrospective cohort
  - Bicknell 2015: 10 pts

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Stepwise Approach for Asthma Therapy In Youth ≥ 12 years and Adults

Intermittant Asthma	Persistent Asthma: Daily Medication Concult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
Step 1 *Preferred:* SABA PRN	**Step 2** *Preferred:* Low-dose ICS *Alternative:* Cromolyn, LTRA, Nedocromil or Theophylline	**Step 3** *Preferred:* Low-dose ICS + LABA OR Medium-dose ICS *Alternative:* Low-dose ICS + either LTRA or Theophylline	**Step 4** *Preferred:* Medium-dose ICS + LABA *Alternative:* Medium-dose ICS + either LTRA or Theophylline	**Step 5** *Preferred:* High-dose ICS + LABA	**Step 6** *Preferred:* High-dose ICS + LABA + oral corticosteroid

Castro

Pavord

Cox

Each step: Patient education, environmental control, and management of comorbidities.
Consider a step-up in therapy if the patient is experiencing any of the following: Symptoms >2 days/week, nighttime awakenings 1-3 times/week, limitation of normal activities, use of SABA >2 times/week, FEV_1 or peak flow <80% predicted/ personal best, or exacerbations requiring oral corticosteroids >2per year.
In the non-pregnant or lactating patient:
Steps 2-4: Consider subcutaneous allergen immunotherapy for those with allergies.
Steps 3-4: Consider Zileuton.
Steps 5-6: Consider Omalizumab for those with perennial allergies.

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 2 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Step up if needed (first, check adherence, environmental control, and comorbid conditions)

Assess control

Step down if possible (and asthma is well controlled at least 3 months)

SABA - short-acting beta-agonist; *ICS* - inhaled corticosteroids; *LTRA* - leukotriene receptor antagonist; *LABA* - long-acting beta-agonist; *EIB* - exercise-induced bronchospasm

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Bronchial Thermoplasty

Components of Control	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms	≤ 2d/week	> 2d/week	Throughout the day
Nighttime awakenings	≤ 2x/month	1-3x/week	> 4x/week
SABA Use	≤ 2d/week	> 2d/week	Several times per day
Activity limitation	None	Some	Extremely limited
FEV1	>80%	60-80%	<60%
ATAQ ACQ ACT	0 ≤ 0.75 ≥ 20	1-2 > 1.5 16-19	3-4 NA ≤ 15
Exacerbation requiring systemic steroid	0-1/year	> 2/year	> 2/year
Adverse medication effects	–	–	–

Castro

Cox

Pavord*

www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf

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Bronchial Thermoplasty

Analysis 1.1. Comparison 1 Bronchial thermoplasty versus control, Outcome 1 AQLQ final scores at 12 months of follow-up.

Review: Bronchial thermoplasty for moderate or severe persistent asthma in adults

Comparison: 1 Bronchial thermoplasty versus control

Outcome: 1 AQLQ final scores at 12 months of follow-up

Study or subgroup	Bronchial Thermo-plasty N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Bronchial thermoplasty versus medical management							
AIR	55	6.18 (0.88)	54	5.72 (1.11)		32.3 %	0.46 [0.08, 0.84]
RISA (1)	15	5.49 (1.34)	17	5.14 (1.06)		6.4 %	0.35 [-0.49, 1.19]
Subtotal (95% CI)	**70**		**71**			**38.7 %**	**0.44 [0.10, 0.79]**
Heterogeneity: Tau² = 0.0; Chi² = 0.05, df = 1 (P = 0.82); I² =0.0%							
Test for overall effect: Z = 2.52 (P = 0.012)							
2 Bronchial thermoplasty versus sham bronchoscopies							
AIR 2	190	5.66 (1.06)	98	5.48 (1.04)		61.3 %	0.18 [-0.09, 0.45]
Subtotal (95% CI)	**190**		**98**			**61.3 %**	**0.18 [-0.09, 0.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.29 (P = 0.20)							
Total (95% CI)	**260**		**169**			**100.0 %**	**0.28 [0.07, 0.50]**
Heterogeneity: Tau² = 0.0; Chi² = 1.42, df = 2 (P = 0.49); I² =0.0%							
Test for overall effect: Z = 2.58 (P = 0.0099)							
Test for subgroup differences: Chi² = 1.37, df = 1 (P = 0.24), I² =27%							

-2 -1 0 1 2

Favours Control Favours BT

(1) Final scores with imputed SD from baseline in each group

Torrego, S.A. Munoz, AM, et. al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database of Systematic Reviews 2014. Issue 3. Art. No.: CD 009910.

Bronchial Thermoplasty

Analysis 1.2. Comparison 1 Bronchial thermoplasty versus control, Outcome 2 ACQ final scores at 12 months of follow-up.

Review: Bronchial thermoplasty for moderate or severe persistent asthma in adults

Comparison: 1 Bronchial thermoplasty versus control

Outcome: 2 ACQ final scores at 12 months of follow-up

Study or subgroup	Bronchial Thermo-plasty N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Bronchial thermoplasty versus medical management							
AIR	55	1.32 (0.85)	54	1.69 (0.99)		33.2 %	-0.37 [-0.72, -0.02]
RISA (1)	15	1.84 (1.02)	17	2.01 (0.78)		13.0 %	-0.17 [-0.81, 0.47]
Subtotal (95% CI)	**70**		**71**			**46.1 %**	**-0.32 [-0.63, -0.02]**
Heterogeneity: Tau² = 0.0; Chi² = 0.29, df = 1 (P = 0.59); I² =0.0%							
Test for overall effect: Z = 2.09 (P = 0.037)							
2 Bronchial thermoplasty versus sham bronchoscopies							
AIR 2	190	1.31 (0.94)	98	1.32 (0.91)		53.9 %	-0.01 [-0.23, 0.21]
Subtotal (95% CI)	**190**		**98**			**53.9 %**	**-0.01 [-0.23, 0.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
Total (95% CI)	**260**		**169**			**100.0 %**	**-0.15 [-0.40, 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 2.95, df = 2 (P = 0.23); I² =32%							
Test for overall effect: Z = 1.20 (P = 0.23)							
Test for subgroup differences: Chi² = 2.65, df = 1 (P = 0.10), I² =62%							

-1 -0.5 0 0.5 1

Favours BT Favours Control

(1) Final scores with imputed SD from baseline in each group

Torrego, S.A. Munoz, AM, et. al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database of Systematic Reviews 2014. Issue 3. Art. No.: CD 009910.

Bronchial Thermoplasty

Analysis 1.3. Comparison 1 Bronchial thermoplasty versus control, Outcome 3 Participants admitted to hospital because of respiratory adverse events (treatment period).

Review: Bronchial thermoplasty for moderate or severe persistent asthma in adults

Comparison: 1 Bronchial thermoplasty versus control

Outcome: 3 Participants admitted to hospital because of respiratory adverse events (treatment period)

Study or subgroup	Bronchial Thermo-plasty n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AIR	4/55	2/54		37.8 %	1.96 [0.38, 10.28]
AIR 2	16/190	2/98		49.3 %	4.13 [0.97, 17.58]
RISA	4/15	0/17		12.8 %	10.13 [0.59, 173.83]
Total (95% CI)	**260**	**169**		**100.0 %**	**3.50 [1.26, 9.68]**
Total events: 24 (Bronchial Thermoplasty), 4 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.08, df = 2 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 2.41 (P = 0.016)					
Test for subgroup differences: Not applicable					

0.005 0.1 1 10 200

Favours BT Favours Control

Torrego, S.A. Munoz, AM, et. al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database of Systematic Reviews 2014. Issue 3. Art. No.: CD 009910.

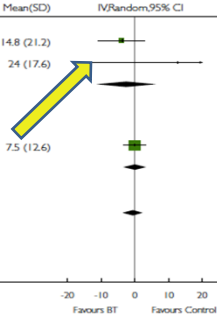
Analysis 1.5. Comparison 1 Bronchial thermoplasty versus control, Outcome 5 Use of rescue medication at 12 months of follow-up (short-acting bronchodilator puffs per week).

Review: Bronchial thermoplasty for moderate or severe persistent asthma in adults

Comparison: 1 Bronchial thermoplasty versus control

Outcome: 5 Use of rescue medication at 12 months of follow-up (short-acting bronchodilator puffs per week)

Study or subgroup	Bronchial Thermo-plasty N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Bronchial thermoplasty versus medical management							
AIR	55	10.9 (15)	54	14.8 (21.2)		18.3 %	-3.90 [-10.81, 3.01]
RISA (1)	15	36.7 (58.5)	17	24 (17.6)		0.9 %	12.70 [-18.06, 43.46]
Subtotal (95% CI)	**70**		**71**			**19.2 %**	**-2.65 [-11.24, 5.95]**
Heterogeneity: Tau² = 8.39; Chi² = 1.06, df = 1 (P = 0.30); I² =6%							
Test for overall effect: Z = 0.60 (P = 0.55)							
2 Bronchial thermoplasty versus sham bronchoscopies							
AIR 2	190	7.4 (15.01)	98	7.5 (12.6)		80.8 %	-0.10 [-3.38, 3.18]
Subtotal (95% CI)	**190**		**98**			**80.8 %**	**-0.10 [-3.38, 3.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.06 (P = 0.95)							
Total (95% CI)	**260**		**169**			**100.0 %**	**-0.68 [-3.63, 2.28]**
Heterogeneity: Tau² = 0.0; Chi² = 1.68, df = 2 (P = 0.43); I² =0.0%							
Test for overall effect: Z = 0.45 (P = 0.65)							
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² =0.0%							



(1) Final scores with imputed SD from baseline in each group

Torrego, S.A. Munoz, AM, et. al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database of Systematic Reviews 2014. Issue 3. Art. No.: CD 009910.

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Safety Concerns

- Short term increases in adverse effects noted in patients receiving thermoplasty.

  Of particular concern:

  - Increase in hospitalizations 8% vs. 2% ARI=6%
    - NNH=17
  - Increased incidence of bronchiectasis in Castro F/U of 2%, (usually reported per 100,000 person years)

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Guidelines Exist

- Recommendations by multiple agencies/society's are equivocal at best.
- There is not a National Coverage Decision and a number of commercial plans consider the treatment 'investigational'.
- Concerns cited include: approval based on a small body of evidence and long term safety questions remain.
- Many guidelines do recommend that if it occurs, treatment should occur in specialist centers or in the context of a clinical trial or systematic registry.

Agency Medical Director Summary

- The body of evidence supporting the wide spread adoption of bronchial thermoplasty is limited
- Concerns regarding the potential for industry bias, unequal comparators and issues of patient compliance suggest caution in interpreting the findings
- Concerns regarding the potential for harm are significant

Agency Recommendation

- Do not cover.
  - Agencies will cover in the context of appropriately designed clinical trials and/or systematic registries.

Questions?

More Information
www.hca.wa.gov/hta/Pages/rhino_screening.aspx

Washington State Health Care Authority
Health Technology Assessment

Order of Scheduled Presentations:

Bronchial Thermoplasty for Asthma

	Name
1	Michael Wechsler, MD

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	x	
2.	Equity interests such as stocks, stock options or other ownership interests.		
3.	Status or position as an officer, board member, trustee, owner.		x
4.	Loan or intellectual property rights.		x
5.	Research funding.		x
6.	Any other relationship, including travel arrangements.	x	x

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

In last year, Dr. Wechsler received consulting fees/ honoraria of $10000 TO $20000 from Teva and Sanofi. He also received honoraria in lesser amounts <$10,000 from Gliacure, Genentech, Novartis, Meda pharmaceuticals, Theravance, Boston Scientific, and Vectura.

Boston Scientific made travel arrangements for my attendance at this meeting

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		x

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] MD — 5/6/2016 — Michael Wechsler

Signature — *Date* — *Print Name*

So we may contact you regarding your presentation, please provide the following:

Mail Address: 204 S Pontiac St, Denver, CO 80230

Phone Number: [redacted]

Bronchial Thermoplasty for Asthma

- **Michael Wechsler, MD**
  Director of Asthma Institute
  and Professor of Medicine
  National Jewish Health
  Denver, CO

  AIR2 Study Investigator and Lead Author
  for 5-Year Study

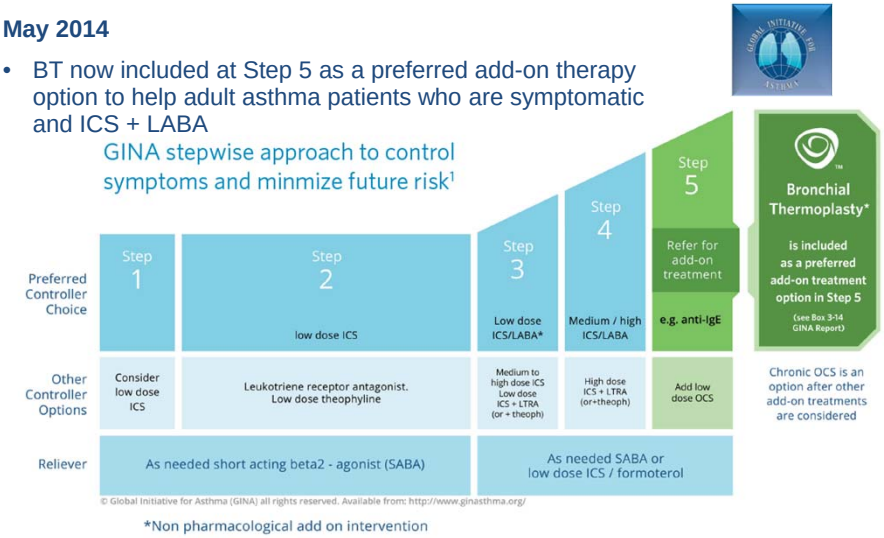
1

BT in Global Initiative for Asthma (GINA)

May 2014

- BT now included at Step 5 as a preferred add-on therapy option to help adult asthma patients who are symptomatic and ICS + LABA

GINA stepwise approach to control symptoms and minmize future risk[1]



*Non pharmacological add on intervention

Source: Adapted from Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, updated 2014. www.ginasthma.org/documents/4

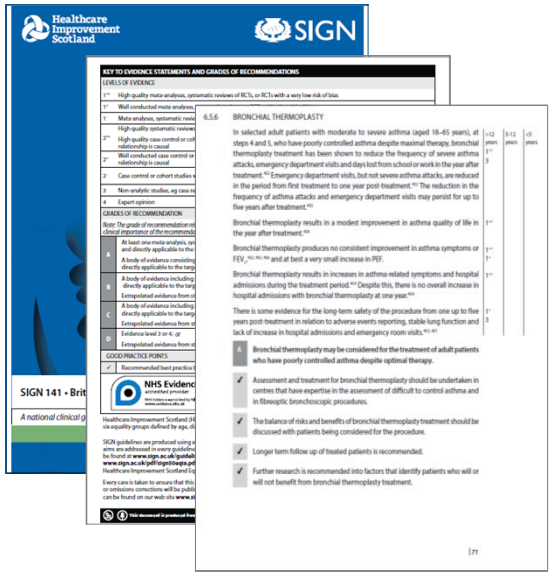
2

BT in British Thoracic Society Asthma Guidelines

October 2014

- "Bronchial Thermoplasty may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy."
- **Evidence level 1++ (highest) and Grade A recommendation (highest)**

British Thoracic Society



3

Society Support for BT Coverage

CHEST - May 2014

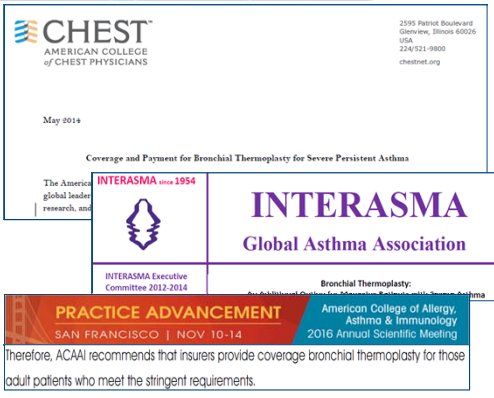
"CHEST believes that based on the strength of the clinical evidence, Bronchial Thermoplasty offers an important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment, and therefore should not be considered experimental."

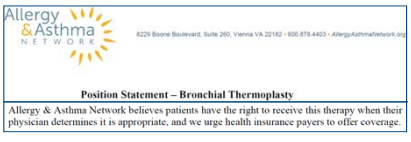
INTERASMA – Oct 2014

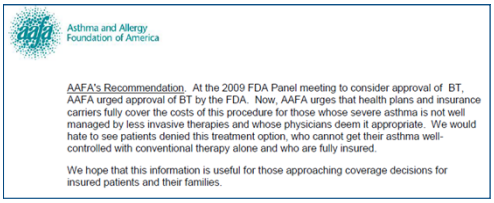
"…It should be considered an important option for patients suffering from this condition and should be covered and paid by the social security system and/or private insurances…"

ACAAI – Jan 2015

"…ACAAI recommends that insurers provide coverage for bronchial thermoplasty for those adult patients who meet the stringent requirements."







4

Mechanism of Action - Reduction of ASM Mass by BT in Patients with Severe Asthma

Reduction of Airway Smooth Muscle Mass by Bronchial Thermoplasty in Patients with Severe Asthma

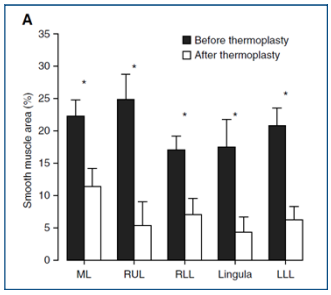
To the Editor:

Bronchial thermoplasty (BT) is a procedure that consists of the delivery of controlled radiofrequency-generated activations via a catheter inserted into the bronchial tree through a flexible

Supported by Legs Poix, Inserm.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Source: Marina Pretolani….. Pascal Chanez, Michel Aubier. Amer J Respir and Critical Care Medicine. 2014; 190:1452-1454



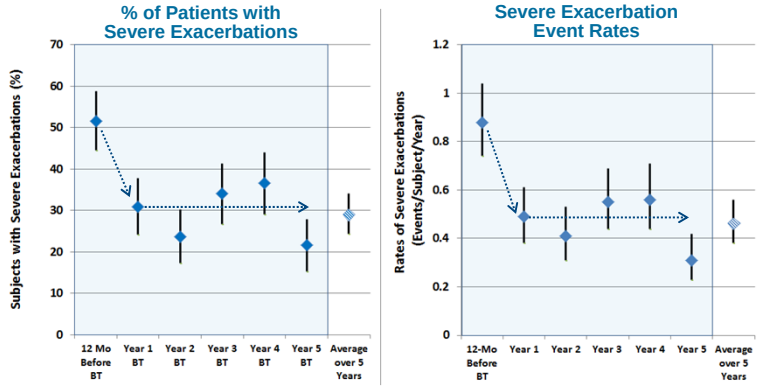
- Independent trial in France being conducted at 2 centers
- Study involves biopsy samples before and after BT plus assessments of other markers and clinical outcomes.
- FEV inclusion from >30% to <70%
- Interim data for the biopsy assessments from first 10 patients reported
  - Reduction in ASM ranged from 48.7% to 78.5%
- Additional patients being evaluated.

Patient	Sex	Asthma Duration (yr)	Number of Exacerbations in the Previous Year	FEV_1% Predicted	Oral Steroid (mg/d)	Omalizumab Treatment
1	F	13	9	63	20	Yes, failure
2	F	28	10	76	0	Yes, failure
3	M	24	6	48	20	No
4	M	12	12	56	40	Yes, failure
5	M	6	5	56	15	No
6	F	6	10	64	40	Yes, failure
7	M	5	12	42	10	Yes, failure
8	M	50	3	67	0	No
9	F	23	12	68	40	Yes, failure
10	M	50	3	43	0	Yes, failure

5

Durability of Efficacy - Reduction in Severe Exacerbations Maintained out to 5 years[1]

- The reduction in severe exacerbations requiring systemic corticosteroids at Year 1 was maintained out to at least 5 years.



Compared with 1 year prior to BT treatment (baseline):

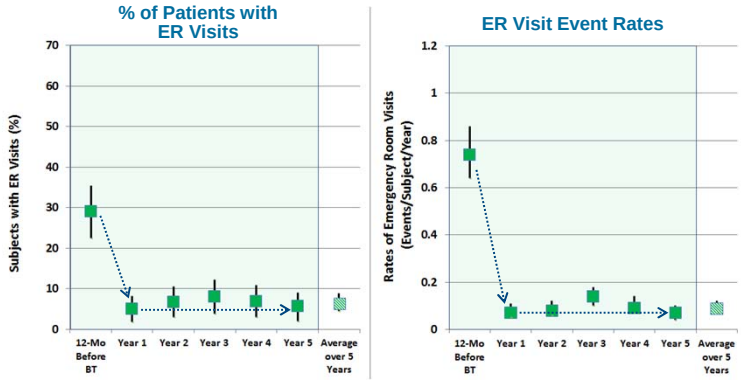
- **44%** average decrease in percentage of patients having severe exacerbations
- **48%** average decrease in severe exacerbation event rates

1. Wechsler ME, et al. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.

6

Durability of Efficacy - Reduction in ER Visits Maintained out to 5 years[1]

- The reduction in ER visits for respiratory symptoms at Year 1 was maintained out to at least 5 years.



Compared with 1 year prior to BT treatment (baseline):

- **78%** average decrease in percentage of patients having ER visits
- **88%** average decrease in ER visit event rates

1. Wechsler ME, et al. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.

7

7

Safe - Long-Term Safety Maintained out to 5 Years[1]

- No increase seen in hospitalizations, asthma symptoms, or respiratory adverse events over the course of 5 years
- No structural changes in airways that were clinically significant were due to BT at 5 years (based on HRCT review)

1. Wechsler ME, et al. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.

8

8

Most Appropriate Patient for Bronchial Thermoplasty

- 18 years and older
- Poor asthma control on combination therapies
- Using inhaled corticosteroids and long acting beta agonists
- Taking chronic oral systemic corticosteroids to control asthma
- Frequent exacerbations

1. Wechsler ME, et al. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.

9

9

Bronchial Thermoplasty for Asthma

Natalie R. Slezak, PhD
Hayes, Inc.
May 20, 2016

Shorthand and Abbreviations

- **ACQ** – Asthma Control Questionnaire
- **AEs** – adverse events
- **AQLQ** – Asthma Quality of Life Questionnaire
- **BD** – bronchodilator
- **BL** – baseline
- **BT** – bronchial thermoplasty
- **dx'd** – diagnosed
- **FQ** – fair quality
- **GQ** – good quality
- **grp(s)** – group(s)
- **ICER** – incremental cost-effectiveness ratio
- **ICS** – inhaled corticosteroid(s)
- **KQ** – Key Question
- **LABA** – long-acting β_2-agonist
- **MCID** – minimal clinically important difference
- **n** – number of patients
- **NR** – not reported
- **NS** – not statistically significant
- **PEF** – peak expiratory flow
- **PMA** – premarket approval
- **PPS** – posterior probability of superiority
- **pt(s)** – patient(s)
- **QALY**– quality-adjusted life-year
- **QOL** – quality of life
- **RCT** – randomized controlled trial
- **SABA** – short-acting β_2-agonist
- **sx** – symptom(s)
- **tx** – treatment/treat
- **tx'd** – treated
- **VPQ** – very-poor-quality

2

Presentation Overview

- Background
- Scope, Methods, and Search Results
- Findings
- Practice Guidelines and Payer Policies
- Overall Summary and Discussion

Background

Prevalence of Asthma

- Asthma is a chronic inflammatory disorder of the airways
  - Characterized by episodes of impaired breathing
  - Triggers: Exercise, allergen/irritant exposure, weather changes, viral respiratory infections
- Prevalence in Americans
  - 18.7 million adults in the US suffer from asthma
  - Women > men; boys > girls; children > adults
  - More common in poor socioeconomic groups
- Cost US $56 billion annually (CDC, 2011)

Current Tx for Asthma

- Goals of asthma tx are to achieve good control over asthma sx and maintain normal activity (GINA, 2015)
- Asthma severity is determined from the level of tx required to control sx (GINA, 2015)
  - Mild asthma (Step 1 or Step 2 tx)
    - Preferred tx: As-needed SABA plus low-dose ICS
    - Other options: Leukotriene modulators; sustained-release theophylline; cromones

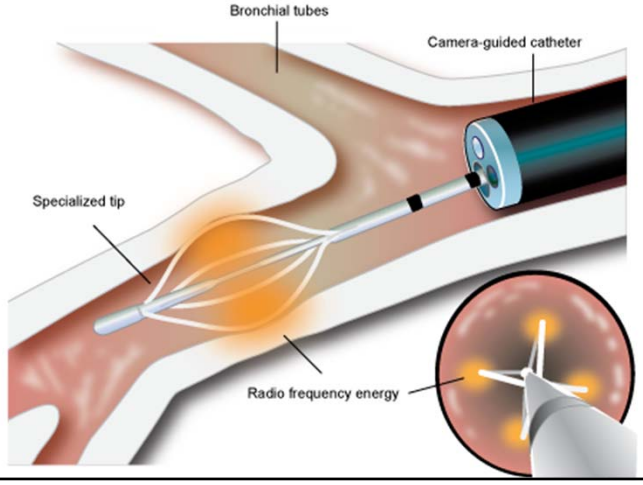
Current Tx for Asthma (cont'd)

- Asthma severity is determined from the level of tx required to control sx (GINA, 2015)
  - Moderate asthma (Step 3 tx)
    - Preferred tx: Low-dose ICS/LABA + as-needed SABA
    - Other options: Medium-dose ICS; low-dose ICS + leukotriene modifier; theophylline
  - Severe asthma (Step 4 or Step 5 tx)
    - Step 4: Medium-dose ICS/LABA + as-needed SABA
      - Other options: Medium-dose ICS + leukotriene modifier; theophylline
    - Step 5: Referral to specialist; add-on tx
      - Tiotropium; omalizumab; low-dose oral corticosteroids; bronchial thermoplasty

7

Bronchial Thermoplasty

- BT reduces smooth muscle that constricts the airway during asthma attacks



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Bronchial Thermoplasty (cont'd)

- BT is typically performed in 3 sessions
  - Allows for shorter procedure times and reduces risks associated with widespread irritation
- All accessible airways located beyond the mainstream bronchi are tx'd
  - Except right middle lobe
- Pt under moderate sedation or general anesthesia

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FDA Approval of BT

- Alair BT System regulated via PMA as Class III (high-risk) device
- Approved April 27, 2010
  - Severe asthma in adults (≥ 18 yrs)
  - Not well controlled with ICS and LABAs

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FDA: Contraindications to BT

- Pacemaker, internal defibrillator, or similar implanted electronic device
- Known sensitivity to the drugs employed during bronchoscopy (e.g., lidocaine, atropine, benzodiazepines)
- Prior BT procedure in same area
- Active respiratory infection
- Asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days
- Known bleeding disorder
- Need for aspirin, anticoagulants, antiplatelet agents, or NSAIDs that cannot be interrupted

FDA: Further Cautions

- The FDA warns caution in pts with the following conditions, as they were not studied in Castro (2010):
  - Post-BD FEV_1 < 65%
  - Respiratory diseases (emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis, uncontrolled obstructive sleep apnea)
  - SABA > 12 puffs per day (excl. exercise)
  - OCS > 10 mg per day
  - Increased risk of AEs associated with bronchoscopy of anesthesia (e.g., pregnancy, diabetes, coronary artery disease)
  - Intubation or ICU admission for asthma < 24 mos
  - In past yr: ≥ 4 lower RTIs, ≥ 3 hospitalizations, ≥ 4 OCS pulses

Scope, Methods, and Search Results

PICO

- **Population:** Adults dx'd with moderate or severe asthma
- **Interventions:** Bronchial thermoplasty
- **Comparisons:** Medical management; sham treatment; no comparator
- **Outcomes:** QOL; asthma control, including medication use; asthma exacerbations; lung function; safety; emergency department (ED) visits; hospitalizations; mortality; cost and cost-effectiveness

Key Questions

1. What is the **clinical effectiveness** of bronchial thermoplasty for treatment of asthma?
   1a. **Is there clinically meaningful improvement** for patients with severe asthma?

2. What are the **harms** associated with bronchial thermoplasty?

3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events **vary by clinical history or patient characteristics** (e.g., age, sex, prior treatments)?

4. What are the **cost implications and cost-effectiveness** of bronchial thermoplasty?

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Search Strategy

- Primary studies
  - PubMed and OVID: October 2, 2015
  - Inclusion criteria
    - Assessed efficacy/safety of BT in pts with moderate or severe asthma
      - BT is only FDA-approved for severe asthma—however, 1 RCT included pts with **moderate** or **severe** asthma
    - English-language journals
  - Exclusion criteria for all KQs
    - No quantitative data
    - Conference abstracts
    - Case reports/series of case reports
- Final update searches
  - March 18, 2016

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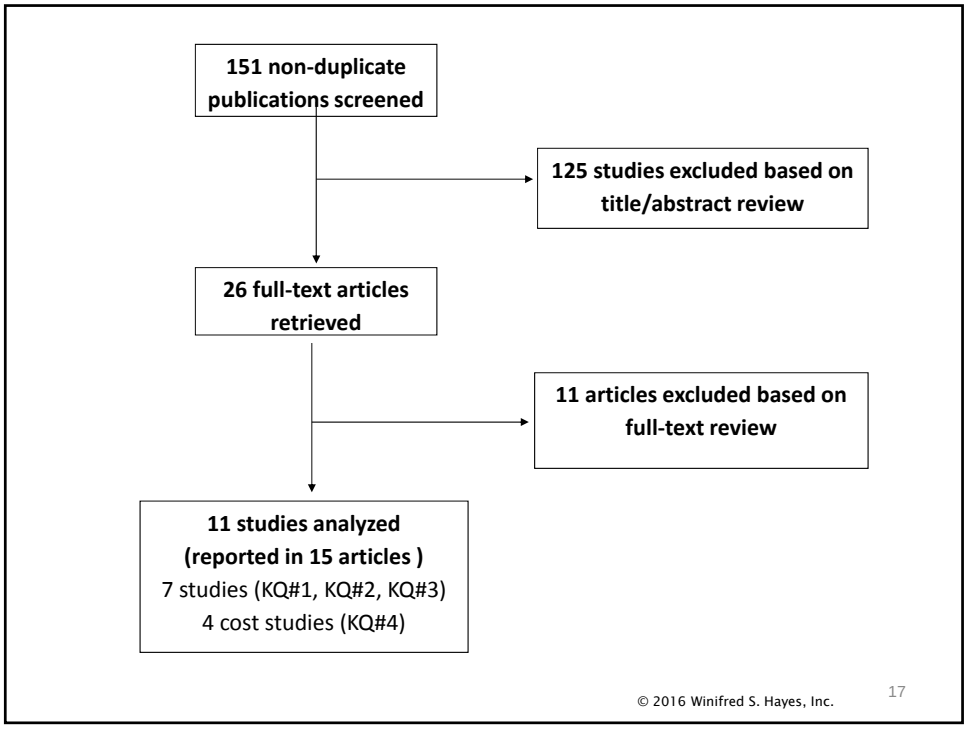

Quality Assessment Aligns with GRADE System (Appendix II)

- Individual **study** appraisal
  - *Are the study findings valid?*
    - Study design, execution, and analysis (checklist)
    - *Good — Fair — Poor — Very Poor*
- Evaluation of **body of evidence** for each outcome
  - *How confident are we that this evidence answers the KQs?*
    - –Applicability to PICO
    - –Quantity/Precision of data
    - –Consistency of findings across studies
    - –Publication bias
    - *High — Moderate — Low — Very Low*

Quality of the Body of Evidence

High

- Reliable evidence reflecting the true effect
- Unlikely to change with future studies

Moderate

- Reasonable confidence that the results represent the true direction of effect
- The effect estimate might change with future studies

Low

- Little confidence due to poor quality and/or mixed results and/or a paucity of studies
- Future studies are likely to change the estimates and possibly the direction

Very Low

- No confidence in any result found (e.g., paucity of data)
- Data are such that we cannot make a statement on the findings

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Findings

(See Summary of Findings Tables and Appendix IV for further detail)

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Overview: Studies Evaluating the Effectiveness of Bronchial Thermoplasty

Findings for KQ#1	# Studies, Overall Quality
KQ#1. Effectiveness of BT (n=480) • Studies demonstrated that BT was superior to sham tx or control tx with some inconsistency across outcome measures	7, low (1 GQ RCT, 2 FQ RCTs, 3 VPQ case series, 1 VPQ retrospective cohort study)
KQ#1a. Clinically meaningful improvement (n=439) • 2 of 3 studies demonstrated that BT was superior to sham tx or control tx for health-related QOL • 1 study demonstrated that 50% of pts met criteria for clinical improvement	4, very low (1 GQ RCT, 2 FQ RCTs, 1 VPQ retrospective cohort study)

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KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Evidence	Study results
7 studies (n=480) **Cox 2007** (n=109; RCT, FQ) **Pavord 2007** (n=32; RCT, FQ) **Castro 2010** (n=288; RCT, GQ) **Cox 2006** (n=16; case series, VPQ) **Doeing 2013** (n=8; case series, VPQ) **Bicknell 2015** (n=10; retrospective cohort, VPQ) **Chakir 2015** (n=17; case series, VPQ) **Low Overall Quality** (few studies, some with small sample sizes)	**Asthma-related QOL:** Improved compared with control in 2 of 3 RCTs **Severe exacerbations:** Decreased compared with control in 1 of 2 RCTs **Asthma sx:** Improved compared with control in 1 of 3 RCTs **Rescue medication use:** Decreased compared with control in 2 of 3 RCTs **FEV_1:** Did not improve in 3 RCTs No control or comparison grp (4 studies)

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KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Castro et al. (2010) 288 severe asthma pts BT: 190 pts Sham tx: 98 pts (mimicked BT tx but no RF energy delivered) Double-blind RCT (GQ) **Study strengths:** Randomized; placebo-controlled; sufficient sample size **Study limitations:** Lack of controlled f/u data after 1 yr; source of distribution data used in Bayesian model NR; some outcome measures collected via daily diaries **Funding source**: Ashthmatx Inc. and Boston Scientific Corp.	• Primary basis for FDA PMA of BT • Employed **Bayesian methods** rather than traditional statistical tools • Uses probabilities instead of hypothesis testing • Outcome statistic: PPS = posterior probability of superiority • Probabilities are revised when new evidence becomes available – posterior distribution • Controversial as they require use of a prior distribution for the tx effect • Castro did NR source of prior distribution or report the use of multiple priors • Calculations are complex

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

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KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Castro et al. (2010) 288 severe asthma pts BT: 190 pts Sham tx: 98 pts Double-blind RCT (GQ) **Study strengths:** Randomized; placebo-controlled; sufficient sample size **Study limitations:** Lack of controlled f/u data after 1 yr; source of distribution data used in Bayesian model NR; some outcome measures collected via daily diaries	**Secondary outcome measures (cont'd):** Meaningful improvements compared with sham tx grp at 1-yr f/u: • Severe exacerbations: 0.48 vs 0.70 per pt annually; PPS=0.96 • ED visits: 0.07 vs 0.43 per pt annually; PPS=0.999 • Days lost from work, school, or other activities due to asthma: 1.3 vs 3.9 per yr; PPS=0.993 No meaningful improvements were found for these measures at 1-yr f/u: • Morning PEF • Total sx scores; sx-free days • Rescue medication use • Unscheduled physician visits; hospitalizations • ACQ scores

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KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Castro et al. (2010) 288 severe asthma pts BT: 190 pts Sham tx: 98 pts Double-blind RCT (GQ) **Study strengths:** Randomized; placebo-controlled; sufficient sample size **Study limitations:** Lack of controlled f/u data after 1 yr; source of distribution data used in Bayesian model NR; some outcome measures collected via daily diaries	**2-yr f/u (Castro 2011):** • Uncontrolled f/u of 166 (87%) BT pts • No significant increases or decreases from 1 to 2 yrs f/u in severe exacerbations, asthma symptoms, ED visits, or hospitalizations **5-yr f/u (Wechsler 2013):** • Uncontrolled f/u of 162 (85%) BT pts • No significant increases in respiratory AEs or need for hospitalization

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KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Cox et al. (2007) 109 moderate to severe asthma pts BT: 55 pts Control tx (asthma medication): 54 pts RCT (FQ) **Study strengths:** Randomized; sufficiently powered **Study limitations:** Not blinded; not placebo-controlled; primary outcome measure collected via daily diaries; 5% of pts lost to f/u; only 1-yr f/u **Funding source**: Ashthmatx Inc.	**Primary outcome measure:** Improvement in mild exacerbations during 2-wk periods of LABA abstinence at 1-yr f/u: • Exacerbation = ≥20% reduction below BL in morning PEF; ≥3 additional puffs than BL of rescue medication; nocturnal awakening caused by asthma sx • Improvement was greater in BT grp than control grp (-0.16 vs +0.04); this **difference was significant (*P*<0.01)** **Secondary outcome measures:** Statistically significant improvements compared with control grp at 1-yr f/u: • Mild exacerbations with LABA: -0.17 vs +0.03 **(*P*<0.05)** • AQLQ: +1.3 vs +0.6 **(*P*<0.005)**

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Cox et al. (2007) 109 moderate to severe asthma pts BT: 55 pts Control tx (asthma medication): 54 pts RCT (FQ) **Study strengths:** Randomized; sufficiently powered **Study limitations:** Not blinded; not placebo-controlled; primary outcome measure collected via daily diaries; 5% of pts lost to f/u; only 1-yr f/u	**Secondary outcome measures (cont'd):** Statistically significant improvements compared with control grp at 1-yr f/u: • ACQ: -1.2 vs -0.5 **(*P*<0.005)** • Sx-free days: +41% vs +17% **(*P*<0.01)** • Sx scores: -1.9 vs -0.7 **(*P*<0.05)** • Rescue BD use: -8.9 vs -1.2 puffs per wk **(*P*<0.05)** • Morning PEF: +39 vs +9 L/min **(*P*<0.005)** No statistically significant improvements were found for these measures: • Severe exacerbations • Airway responsiveness • FEV_1

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results

Cox et al. (2007)
109 moderate to severe asthma pts
BT: 55 pts
Control tx (asthma medication): 54 pts
 	
RCT (FQ)
 	
Study strengths: Randomized; sufficiently powered
 	
Study limitations: Not blinded; not placebo-controlled; primary outcome measure collected via daily diaries; 5% of pts lost to f/u; only 1-yr f/u
	Long-term f/u (Thomson 2011):
	• F/u of 45 (82%) BT pts up to 5 yrs
	• 3-yr f/u of 24 (44%) control pts
	
	• Significant difference between grps for:
	  • Airway responsiveness: Increased 1.3 doublings for BT grp vs decrease of 0.4 doublings for control grp (*P*<0.05)
	
	• No significant differences between grps for:
	  • Other respiratory parameters
	  • Oral glucocorticoid use
	  • Worsening of asthma
	  • ED visits
	  • Hospitalizations

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Pavord et al. (2007) 32 severe asthma pts BT: 15 pts Control tx (asthma medication): 17 pts RCT (FQ) **Study strengths:** Randomized **Study limitations:** Not blinded; not placebo-controlled; small sample size; no power analysis; only 1 yr of controlled f/u; several efficacy outcomes were self-report data collected in daily diaries **Funding source**: Ashthmatx Inc.	**Primary outcome measure:** Safety measures (discussed in results for KQ#2: Safety) **Secondary outcome measures:** Statistically significant improvements compared with control grp at 1-yr f/u: • AQLQ (higher score better) (+1.5 vs +0.4) (*P*<0.05) • ACQ (lower score better) (-1.0 vs -0.2) (*P*<0.05) • Rescue bronchodilator use (-26% vs -6%) (*P*<0.05) The following measures were not statistically significant at 1-yr f/u: • FEV_1 • Morning or evening PEF • Sx-free days; sx scores • Airway responsiveness

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results

Pavord et al. (2007)
32 severe asthma pts
BT: 15 pts
Control tx (asthma medication): 17 pts
 	
RCT (FQ)
 	
Study strengths: Randomized
 	
Study limitations: Not blinded; not placebo-controlled; small sample size; no power analysis; only 1 yr of controlled f/u; several efficacy outcomes were self-report data collected in daily diaries
	5-yr f/u (Pavord 2013):
	• Uncontrolled f/u of 14 (93%) BT pts
	• No significant changes in yrs 2 through 5 in:
	  • Respiratory AEs
	  • Hospitalizations
	  • ED visits
	  • Asthma maintenance medication usage
	  • Respiratory parameters
	
	• Outcomes during f/u yrs 2 to 5 were collected once per yr and may be subject to recall bias

KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

Study details	Study results
Nonrandomized studies **Cox 2006** (n=16; case series, VPQ) **Doeing 2013** (n=8; case series, VPQ) **Bicknell 2015** (n=10; retrospective cohort, VPQ) **Chakir 2015** (n=17; case series, VPQ)	• 4 nonrandomized studies were included in the assessment • Results from these studies were mostly positive • Studies of very poor quality

KQ #1a: Is there clinically meaningful improvement for pts with severe asthma?

- 3 RCTs and 1 retrospective cohort study included definition for clinically meaningful improvement
  - AQLQ: Change of >0.5 is MCID (Juniper 1994)
- RCTs: AQLQ MCID
  - Cox (2007): Btwn-grp difference of 0.69 (+1.3 BT vs +0.6 control; ***P*<0.005**) at 12 mos
  - Pavord (2007): Btwn-grp difference of 1.1 (+1.5 BT vs +0.4 control; ***P*<0.05**) at 12 mos
  - Castro (2010): Btwn-grp difference of 0.19 (+1.35 BT vs +1.16 sham; PPS=0.96); did not reach PPS planned 0.964
    - 78.9% of BT pts vs 64.3% sham pts met MCID (PPS=0.996)

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KQ #1a: Is there clinically meaningful improvement for pts with severe asthma?

- Retrospective cohort study (Bicknell 2015)
  - Clinical improvement defined as achieving ≥ 1 of the following at 1-yr f/u:
    - Reduction by ≥ 1 severe exacerbation or hospitalization
    - Improvement by MCID in ACQ (decrease by ≥ 0.5) or AQLQ (increase by ≥ 0.5)
    - Reduction in asthma medication without a loss of asthma control
  - 5 (50%) of 10 clinic pts and 11 (73%) of 15 RCT pts met the criteria for clinical improvement

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KQ #2: What harms are associated with bronchial thermoplasty?

- Statistically significant increase in AEs during BT tx period (BT + 6 wks) (Cox 2006; Cox 2007; Pavord 2007)
  - Dyspnea
  - Wheezing
  - Chest discomfort
  - Night awakenings
  - Sputum discoloration
  - Cough
  - Productive cough
  - Bronchial irritation
  - Nasal congestion

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KQ #2: What harms are associated with bronchial thermoplasty?

- Hospitalizations during BT tx period
  - 1 of 3 RCTs found significant increase in BT grp
    - 5.5% BT grp vs 3.7% control grp (NS) (Cox 2007)
    - 27% BT grp vs 0% control grp ($P<0.05$) (Pavord 2007)
    - 5% BT grp vs 4% sham tx grp (NS) (Castro 2010)
  - Nonrandomized studies: Hospitalization ranged from 0% to 62.5% (Cox 2006; Doeing 2013; Bicknell 2015; Chakir 2015)
  - Appeared to be higher in studies that enrolled pts with more severe asthma
    - Mild/moderate asthma: 0% to 5.5% (Cox 2006; Cox 2007)
    - Severe asthma: 5% to 62.5% (Castro 2010; Doeing 2013; Bicknell 2015; Chakir 2015)

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KQ #2: What harms are associated with bronchial thermoplasty?

- Complications during long-term f/u
  - Thomson (2011) f/u of pts in Cox (2007):
    - 45 (82%) BT pts for 5 yrs and 24 (44%) control pts for 3 yrs
    - Btwn-grp differences in worsening of asthma, hospitalizations, and ED visits were NS
    - No serious AEs due to BT occurred in 5 yrs
  - Pavord (2013) f/u of Pavord (2007):
    - Uncontrolled f/u of 14 (93%) BT pts
    - In yrs 2 to 5, rates of respiratory AEs, hospitalizations, and ED visits were essentially unchanged
    - No serious AEs due to BT occurred in 5 yrs

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KQ #2: What harms are associated with bronchial thermoplasty?

- Complications during long-term f/u
  - Wechsler (2013) f/u of Castro (2010):
    - Uncontrolled f/u of 162 (85%) BT pts
    - No significant increases in respiratory AEs or hospitalization
    - Computed tomography findings were unchanged except for development of bronchiectasis in 3 (2%) pts

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KQ #3: Differential performance or impact according to clinical hx, pt characteristics?

- No studies were specifically designed to assess differential effects of BT
- Pt selection criteria varied
- Several post hoc analyses investigating pt characteristics or prognostic factors
- Data are preliminary

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Patient Selection Criteria

Author (year)	Asthma severity	Medications	FEV_1	Other
Castro (2010) RCT	Severe	ICS (≥1000 µg/day), LABA (≥100 µg/day); daily need <8 puffs short-acting BD, <4 puffs long-acting BD, <2 nebulizer tx Exclude: Oral corticosteroids (OCS) ≥10 mg/day	Pre-BD ≥60% Actual mean 78%	≥2 days of asthma sx/wk Low AQLQ score (≤6.25)
Pavord (2007) RCT	Severe	ICS (≥750 µg/day); LABA (≥100 µg/day)	Pre-BD ≥50% Actual mean 63%	--
Cox (2007) RCT	Moderate or severe	ICS (≥200 µg/day); LABA (≥100 µg/day); daily need ≤4 puffs short-acting BD; stable asthma medication	Pre-BD 60% to 85% Actual mean 73%	No unscheduled physical visits for asthma

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Patient Selection Criteria

Author (year)	Asthma severity	Medications	FEV_1
Cox (2006) Case series	Mild to moderate	Exclude: >4 puffs per day SABA	Actual mean Pre-BD 82%
Doeing (2013) Case series	Severe	ICS (≥1000 µg/day); LABA (≥100 µg/day)	Actual mean Pre-BD 52%
Bicknell (2015) Cohort study	Severe	ICS (≥1000 µg/day)	Actual mean Pre-BD 72%
Chakir (2015) Case series	Severe	ICS (≥500 µg/day); LABA (≥100 µg/day)	Pre-BD ≥50% Actual mean 64%

KQ #3: Differential performance or impact according to clinical hx, pt characteristics?

- Other prognostic variables that may have affected clinical outcomes
  - Pts who required daily doses of > 1000 µg/day beclomethasone exhibited greater improvements in respiratory parameters and ACQ (Cox 2007)
  - Less favorable BL AQLQ scores were more likely to meet MCID in AQLQ score following BT (Castro 2010)
  - Those that met MCID in AQLQ have fewer asthma-related AEs and medical utilization during yrs 2 to 5 f/u (Wechsler 2013)

KQ #4: Cost Implications

- 4 studies assessed cost comparison of BT vs usual care or cost-effectiveness of BT
  - 3 conducted in U.S.; 1 in Italy (Menzella 2014)
  - 2 studies financially supported by Boston Scientific (Menzella 2014; Cangelosi 2015)
  - 1 study received funding from pharmaceutical companies (Zafari 2016)
  - 1 study did NR funding source; Castro an author (Zein 2015)
  - All studies were based in part on clinical data from Castro 2010 (Menzella 2014; Cangelosi 2015; Zafari 2015; Zein 2015)
  - BT ⇧ costs in the short term; ⇧ savings/QALYs in longer term

KQ #4: Cost Implications

- Budget impact analysis of usual care vs BT (Menzella 2014)
  - Yr 1: BT ⇧ costs €20,000 (USD $24,012.77, yr 2015) per pt
  - Yr 3: BT ⇧ savings €1 million for the regional healthcare system (USD $1.2 million, yr 2015)
  - Yr 5: BT ⇧ savings €19.2 million (USD $23.1 million, yr 2015)
  - Study limitations
    - Imputed data were derived from multiple sources
    - Hypothetical BT pts ($FEV_1 < 60\%$) differed from those included in the Castro (2010) study ($FEV_1 \geq 60\%$)
    - Results may not be applicable to U.S. settings

KQ #4: Cost-Effectiveness

- 3 studies estimated the cost-effectiveness of BT from a payer perspective
- Cangelosi et al. (2015)
  - BT vs high-dose combination tx in poorly controlled severe asthma pts (high-dose tx and ≥ 1 ED visit in last yr)
  - Over a 5-yr period, BT ⇧ 0.18 QALYs (3.14 vs 2.96) driven primarily by ⇩ exacerbations
  - These findings resulted in an incremental cost-effectiveness ratio (ICER) of $5495 ($5699.28, yr 2015*) per QALY
  - Study limitations
    - Imputed data were derived from multiple sources
    - Castro (2010) study did not limit to population of interest (≥ 1 ED visit in last yr)

KQ #4: Cost-Effectiveness

- Zein et al. (2015)
  - BT vs usual care in poorly controlled severe asthma pts
  - BT ⇧ 0.19 QALYs (6.40 vs 6.21)
  - ICER of $45,300 ($46,984.04, yr 2015) per QALY (5 yrs) and $29,821 ($30,929.60, yr 2015) per QALY (10 yrs)
  - Study limitations
    - Imputed data were derived from multiple sources
    - Published clinical trials limited to 5 yrs f/u

KQ #4: Cost-Effectiveness

- Zafari et al. (2016)
  - BT vs usual care vs omalizumab tx for moderate-to-severe allergic asthma pts
  - BT ⇧ 0.16 QALYs vs usual care (3.24 vs 3.08) and BT ⇩ 0.02 QALYs vs omalizumab (3.24 vs 3.26)
  - ICER of BT vs usual care $12,500/QALY ($12,964.69/QALY, yr 2015); ICER of BT vs omalizumab $3.15 million/QALY ($3.27 million/QALY, yr 2015); ICER of omalizumab vs usual care $529,000/QALY ($548,665.67/QALY, yr 2015)
  - Study limitations
    - Imputed data were derived from multiple sources
    - No published clinical trials have studied the effect of BT on allergic asthma pts

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Practice Guidelines and Payer Policies

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Payer Policies

- No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified
- Aetna and Regence Group
  - BT is investigational for the treatment of asthma
- GroupHealth
  - BT does not meet the Group Health Medical Technology Assessment Criteria

Practice Guidelines

Quantity/quality of guidelines	Tx recommendations
4 guidelines (1 good, 3 fair)	BTS (2011): BT is a possible tx option in select pts with severe asthma; should be limited to few specialist centers
ATS, American Thoracic Society **BTS**, British Thoracic Society	ERS/ATS (2014): BT for severe asthma only in clinical trial or systematic registry; available evidence is considered to be of very low quality
ERS, European Respiratory Society **GINA**, Global Initiative for Asthma	GINA (2015): BT is a possible tx option in select pts with severe asthma; long-term safety and efficacy unknown; large placebo effect in current studies
NICE, National Institute for Health and Care Excellence	NICE (2012): BT has been shown to provide improvements in sx/QOL and reductions in exacerbations/hospitalizations; long-term safety unknown; context of clinical trial/registry only

Overall Summary and Discussion

Final Summary

- Overall, low-quality evidence suggests that BT may provide some benefits in the short term, with some inconsistent results across studies
  - 2 of 3 RCTs demonstrated that asthma-related QOL improved to an extent that was clinically meaningful relative to control
  - Low-quality evidence (small quantity of data, small sample sizes, inconsistency across outcome measures, varied pt selection criteria; insufficient long-term efficacy data)
- Current evidence suggests that BT does not pose major safety concerns in the short term
  - Evidence of safety is of low quality (small quantity of data, small sample sizes, and insufficient evidence for long-term safety)
  - Labeling information by the FDA warns that pneumothorax and respiratory failure are potential AEs

Final Summary

- Study methodology varied among RCTs
  - Pt selection criteria varied considerably
  - Different primary outcome measures
- Although BT is indicated in pts with severe asthma, 1 RCT included pts with moderate and severe asthma
- Data on differential effects of pt characteristics or tx hx are preliminary in nature
  - More research is needed to better identify pts that may most benefit from BT
- Cost-effectiveness studies found that BT increased costs in the short term but increased QALYs in the longer term

Additional Research Needed for All Key Questions

- RCTs and long-term cohort studies of sufficient size and design to further investigate the safety and efficacy of BT in pts with severe asthma
- Studies designed to systematically investigate differential effectiveness and safety according to pt characteristics and previous tx hx
- Studies investigating the impact of BT on QOL and functional status


Thank you!
QUESTIONS?
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Washington State Health Care Authority
Health Technology Assessment

FINAL Key Questions and Background

Bronchial Thermoplasty

Medical Background

The National Asthma and Education and Prevention Program Expert Panel Report recommends add-on therapy with long-acting beta agonists, leukotriene modifiers, theophylline, and omalizumab in patients with difficult-to-treat asthma who take inhaled corticosteroids. These therapies reduce inflammation or decrease airway narrowing by relaxing airway smooth muscles. Unfortunately, therapeutic options for patients with severe asthma remain limited and adjunctive therapies (like those listed above) targeting other mediators of the inflammatory pathway have yielded variable results.

Bronchial thermoplasty is designed to reduce the smooth muscle that constricts the airway during asthma attacks. This procedure relies on a catheter that has an expandable array of electrodes that is delivered to the airway via a bronchoscope, which allows the physician to see inside the lung. After the catheter is threaded into the airway, a wire leading out of the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to curl into a ball shape around the front end of the catheter. The curved electrodes are held against the bronchial walls and an electrical current is applied to generate heat that destroys the smooth muscle underneath the lining of the bronchial passages. Bronchial thermoplasty is performed in 3 separate procedures in which all accessible airways located beyond the mainstream bronchi (average of 3-10 mm in diameter) except for the right middle lobe are treated. The delivery of energy during bronchial thermoplasty uses continuous feedback to tightly control the degree and time of tissue heating to decrease airway smooth muscle mass without airway perforation or stenosis. Dividing the treatment into three procedures allows shorter procedure times and obviates the risks associated with widespread irritation of the airways in patients with severe asthma. Bronchial thermoplasty is typically performed by a pulmonologist with the patient under moderate sedation or general anesthesia.

Policy Context

Bronchial thermoplasty is a procedure used to treat asthma that is not well-controlled by medication. Smooth muscle in the lungs is altered by placement of a radiofrequency catheter that heats the muscle tissue, reducing the likelihood of bronchoconstriction during an asthma reaction. The specific catheter for the procedure was approved for marketing by the FDA in 2010. There are high concerns related to the safety and efficacy of bronchial thermoplasty, and medium concerns for the cost-effectiveness of the procedure.

Scope of This HTA

Population: Adults diagnosed with moderate or severe asthma

Interventions*:* Bronchial thermoplasty

Comparators: Medical management; sham treatment; no comparator

Outcomes: Quality of life; asthma control including medication use; asthma exacerbations; lung function; safety; emergency department visits; hospitalizations; mortality; cost and cost-effectiveness .

Key Questions

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?
    a. Is there clinically meaningful improvement for patients with severe asthma?
2. What are the harms associated with bronchial thermoplasty?
3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?
4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

Public Comment & Response

See ***Draft Key Questions: Public Comment & Response*** document published separately.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.**Using evidence as the basis for a coverage decision**

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document:

What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Infection	
Hospitalization	
Wheezing	
Discomfort	
Bronchial irritation	
Nasal congestion	
Bronchiectasis	

Efficacy – Effectiveness Outcomes	Efficacy / Effectiveness Evidence
Quality of life- asthma QoL scores	
Asthma control	
Severe exacerbations	
Medication use	
Lung function	
Emergency department visits	
Mortality	
Days lost from work/school/activities	
Symptom-free days	
Special Population / Considerations Outcomes	**Special Populations/ Considerations Evidence**
Asthma severity	
Daily medication dose level	
Asthma QoL score	
Cost Outcomes	**Cost Evidence**
Cost	
Cost effectiveness	

Medicare Coverage and Guidelines

From page 22 of the Final Evidence Report

No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified for bronchial thermoplasty.

From page 21 of the Final Evidence Report

Table 2. Summary of Practice Guideline Recommendations

Key: ATS, American Thoracic Society; BT, bronchial thermoplasty; BTS, British Thoracic Society;; BTS, British Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; GL(s), guidelines(s); NICE, National Institute for Health and Clinical Excellence; pt(s), patient(s); QOL, quality of life; sx, symptoms; tx, treatment (or therapy)

Quantity of Individual GLs	Individual GL Quality	Recommendations
4 (BTS, ERS/ATS, GINA, NICE)	1 Good 3 Fair	BTS (Good Quality): BT is a possible tx option in selected pts w/ severe persistent asthma already on maximal tx, although its place in the tx of asthma remains to be established (Grade A). Long-term safety and efficacy of BT remain unclear and BT should be limited to a few specialist centers in carefully selected pts. ERS/ATS (Fair Quality): The available evidence concerning this procedure is considered to be of very low quality. ERS/ATS strongly recommend that BT be performed only in adults with severe asthma and only in the context of a clinical trial or systematic registry (strong recommendation). GINA (Fair Quality): BT is a potential option for highly selected adult pts who have uncontrolled asthma despite use of recommended tx regimens and referral to an asthma specialty center (Evidence B). The long-term safety and efficacy of BT are unknown. Carefully controlled trials are important as a large placebo effect has been seen in studies to date. NICE (Fair Quality): For pts w/ severe asthma, BT has been shown to provide some improvements in sx and QOL and reductions in exacerbations and hospitalizations. Although evidence of safety is adequate in the short and medium term, more evidence of long-term safety is needed; therefore, BT should only be used after establishment of special arrangements for clinical governance, including pt consent and research or audit. The NICE encourages additional research to evaluate the long-term safety and efficacy of BT.

From page 81 of the Final Evidence Report

APPENDIX V. Summary of Practice Guidelines

Key: AE(s), adverse event(s); ATS, American Thoracic Society; BT, bronchial thermoplasty; BTS, British Thoracic Society; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; f/u, follow-up; GINA, Global Initiative for Asthma; LABA, long-acting β_2-agonist; NICE, National

Institute for Health and Clinical Excellence; pt(s), patient(s); RCT, randomized controlled trial; QOL, quality of life; tx, treatment (or therapy); tx'd, treated

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
British Thoracic Society (BTS) (Du Rand et al., 2011) *British Thoracic Society Guideline for Advanced Diagnostic and Therapeutic Flexible Bronchoscopy in Adults*	Pt selection: Pts w/ severe persistent asthma receiving high-dose combination inhalers (>1000 µg beclomethasone equivalent) plus long-acting bronchodilators or long-term oral corticosteroids. The FEV_1 should be >50% predicted. Available Evidence: 3 RCTs have consistently demonstrated a transient increase in asthma-related AEs in the short term during BT, but are associated w/ a significant reduction in AEs, asthma-related symptoms, and hospitalizations in the longer term. However, the studies are selective and the outcomes are only positive in some aspects. (Evidence level 1). Recommendation: BT is a possible tx option in selected pts w/ severe persistent asthma already on maximal tx, although its place in the tx of asthma remains to be established (Grade A). Long-term safety and efficacy of BT remain unclear. Because of this, tx should be limited to a few specialist centers in carefully selected pts. Longer-term f/u of tx'd pts is recommended.	6 – Good (keywords and search strings not specified, funding source not stated, some members have potential conflicts of interest)
European Respiratory Society (ERS); American Thoracic Society (ATS) (Chung et al., 2014) *International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.*	Pt selection: Pts w/ severe asthma. Severe asthma is defined as asthma which requires tx w/ guidelines suggested medications for GINA steps 4-5 asthma (high-dose inhaled corticosteroid and LABA or leukotriene modifier/theophylline) for the previous yr or systemic corticosteroids for ≥50% of the previous yr to prevent it from becoming "uncontrolled" or which remains uncontrolled despite this tx. Available Evidence: The available evidence concerning this procedure is considered to be of very low quality. The ERS/ATS have very low confidence in the reported efficacy of BT. Both potential benefits and harms may be large and the long-term consequences of this new approach to asthma tx utilizing an invasive physical intervention is unknown. Additional studies are needed to assess its long-term benefits and safety, including asthma exacerbation rates and lung function, determining the phenotypes of pts who respond to BT, and evaluating its effects on pts who require systemic steroid tx or who have severe obstructive asthma. Recommendation: ERS and ATS strongly recommend that BT be performed only in adults w/ severe asthma and only in the context of a clinical trial or systematic registry (strong recommendation). Further research is likely to have an important impact on this recommendation.	5 – Fair (strengths and limitations of body of evidence not clearly described, whether guideline reviewed by external experts not stated, funding source not reported)
Global Initiative for Asthma (GINA) (GINA, 2015) *Global Strategy for Asthma Management and Prevention*	Pt selection: Caution should be used in selecting pts for this procedure, as the number of published clinical trials assessing this procedure is small, and excluded pts w/ chronic sinus disease, frequent chest infections, and FEV_1 <60% predicted (Evidence D).	4 – Fair (strengths and limitations of body of evidence not clearly described, guideline not reviewed by external

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
	Recommendation: BT is a potential option for highly selected adult pts who have uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Evidence B). The long-term safety and efficacy of BT are unknown. Carefully controlled trials are important as a large placebo effect has been seen in studies to date.	experts, funding source and conflict of interest not stated)
National Institute for Health and Care Excellence (NICE) (NICE, 2012) *Bronchial thermoplasty for severe asthma*	For pts w/ severe asthma, BT has been shown to provide some improvements in symptoms and QOL and reductions in exacerbations and hospitalizations. Although evidence of safety is adequate in the short and medium term, more evidence of long-term safety is needed; therefore, BT should only be used after establishment of special arrangements for clinical governance, including pt consent and research or audit. The NICE encourages additional research to evaluate the long-term safety and efficacy of BT.	4 –Fair (methods for formulating the recommendations not clearly described, guideline not reviewed by external experts, procedure for updating guideline not stated, funding source and conflict of interests not stated)

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?

- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
    - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
    - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ;

additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective				
Safe				
Cost-effective				

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____ Not Covered ____ Covered Unconditionally ____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.