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”

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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.

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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.

Signature: [Redacted]

Date: 5/4/16

Print Name: Amy Markezich

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.
Overlake Medical Clinics
1231-116th Ave NE, Suite 400
Bellevue, WA 98004-4623
Amy.markezich@overlakehospital.org
(425) 454-2671

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

                 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


9/1993 - 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 metalloproteinases 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


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
- 1996, 1997 Two-time NCAA All-American, Synchronized Swimming
- 1993-1997 Stanford University Varsity Synchronized Swim Team
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
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

Lung Areas Treated

www.txpulmonary.com/bronchial-thermoplasty/

Primary Ranking Criteria

- Safety: High
- Efficacy: High
- Cost: Medium
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
Current State Agency Policy

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

Bronchial Thermoplasty

Current State Agency Policy

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Unique Members by Year</th>
<th>Total Procedures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>2014</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Grand Total</td>
<td>12</td>
<td>26</td>
</tr>
</tbody>
</table>

Recommended: up to three procedures/lobe

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

<table>
<thead>
<tr>
<th>Primary Diagnoses Short Desc -</th>
<th>2013</th>
<th>2014</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute &amp; chronic Resp Fail</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthma NOS</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Asthma NOS w (as) Exac</td>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Bronchiectasis w/o AC Exac</td>
<td>4</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Chronic Obt Asthma NOS</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Grand Total</td>
<td>10</td>
<td>16</td>
<td>26</td>
</tr>
</tbody>
</table>
### 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

---

### Stepwise Approach for Asthma Therapy in Youth ≥ 12 years and Adults

#### Intermittent Asthma

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative: Cromolyn, LTPA, Mastcell degranulator or Thiosphingine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Each step:** Patient education, environmental control, and management of co-morbidities.

- Consider a step-up in therapy if the patient is experiencing any of the following: Symptoms >2 days/week, nighttime awakenings >3 times/week, limitation of normal activities, use of SABA >12 times/week, FEV₁ or peak flow <80% predicted/ personal best, or exacerbations requiring oral corticosteroids ≥3 per year.

- In the non-pregnant or lactating patient:
  - Steps 2-4: Consider substituting inhaled Immunotherapy for those with allergies.
  - Steps 5-6: Consider Omalizumab for those with persistent allergies.

#### Persistent Asthma: Daily Medication

Concur with asthma specialist if step 4 care or higher is required. Consider consultation at age 5.

- **Step 1:** SABA PPH
- **Step 2:** Low-dose ICS
- **Step 3:** Low-dose ICS + LABA
- **Step 4:** Medium-dose ICS + LABA
- **Step 5:** High-dose ICS + LABA
- **Step 6:** High-dose ICS + LABA + oral corticosteroid

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**Quick-Relief Medication for All Patients:**

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms - up to 2 treatments at maximum interval as needed. "One hour of use indicates controller failure."
- Use of SABA > 2 days/month or symptoms relief after prevention of EIB generally indicates inadequate control and the need to step up treatment.

(SABA - short acting beta agonist, ICS - inhaled corticosteroids, LTPA - leukotriene receptor antagonist, LABA - long acting beta agonist, ICS - inhaled corticosteroid)
### Components of Control

<table>
<thead>
<tr>
<th></th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>(&lt; 2d/week)</td>
<td>(&gt; 2d/week)</td>
<td>Throughout the day</td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>(&lt; 2x/month)</td>
<td>1-3x/week</td>
<td>(&gt; 4x/week)</td>
</tr>
<tr>
<td><strong>SABA Use</strong></td>
<td>(&lt; 2d/week)</td>
<td>(&gt; 2d/week)</td>
<td>Several times per day</td>
</tr>
<tr>
<td><strong>Activity limitation</strong></td>
<td>None</td>
<td>Some</td>
<td>Extremely limited</td>
</tr>
<tr>
<td><strong>FEV1</strong></td>
<td>(&gt; 80%)</td>
<td>60-80%</td>
<td>(&lt; 60%)</td>
</tr>
<tr>
<td><strong>ATAQ</strong></td>
<td>(\leq 0.75)</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>ACQ</strong></td>
<td>(&gt; 20)</td>
<td>1.5</td>
<td>NA</td>
</tr>
<tr>
<td><strong>ACT</strong></td>
<td></td>
<td>16-19</td>
<td>(\leq 15)</td>
</tr>
<tr>
<td><strong>Exacerbation requiring systemic steroid</strong></td>
<td>0-1/year</td>
<td>(&gt; 2/year)</td>
<td>(&gt; 2/year)</td>
</tr>
<tr>
<td><strong>Adverse medication effects</strong></td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bronchial Thermoplasty</th>
<th>Control</th>
<th>Mean</th>
<th>Mean(SE)</th>
<th>Control</th>
<th>Mean</th>
<th>Mean(SE)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>H(mean% CI)</th>
<th>H(random% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial thermoplasty versus medical management</td>
<td>AR</td>
<td>15</td>
<td>1.22 (0.16)</td>
<td>54</td>
<td>1.69 (0.19)</td>
<td>4.07</td>
<td>0.22</td>
<td>4.07</td>
<td>0.22</td>
<td>0.27</td>
<td>0.27</td>
</tr>
<tr>
<td>RSA (1)</td>
<td>15</td>
<td>1.84 (1.00)</td>
<td>17</td>
<td>2.31 (0.18)</td>
<td>13.8</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.07</td>
<td>0.07</td>
</tr>
</tbody>
</table>

(1) final scores with imputed SE from baseline in each group.


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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bronchial Thermoplasty</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>455</td>
<td>354</td>
<td>37.8</td>
<td>1.53</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>AR 2</td>
<td>16/10</td>
<td>16/10</td>
<td>49.3</td>
<td>4.13</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>RSA</td>
<td>41%</td>
<td>10%</td>
<td>12.8</td>
<td>10.1</td>
<td>10.1</td>
<td>10.1</td>
<td>10.1</td>
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Total (95% CI) 260 | 169 | 100 | 3.50 | 1.26 | 9.68 |

Charisa Fotinos, Deputy Chief Medical Officer
WA – Health Care Authority

May 20, 2016

Bronchial Thermoplasty

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)

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
Bronchial Thermoplasty

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
**Order of Scheduled Presentations:**

**Bronchial Thermoplasty for Asthma**

<table>
<thead>
<tr>
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<td>Michael Wechsler, MD</td>
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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, Thoravance, Boston Scientific, and Vectura.

Boston Scientific made travel arrangements for my attendance at this meeting

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Michael Wechsler

Signature: X

Date: 5/6/2016

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

Phone Number: _____

conflict_of_interest_121814-FINAL.docx
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

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 minimize future risk

Preferred Controller Choice

- Step 1
  Low dose ICS
- Step 2
  Low dose ICS/LABA
- Step 3
  Medium dose ICS/LABA
- Step 4
  Refer for add-on treatment
- Step 5
  Bronchial Thermoplasty

Other Controller Options

- Consider low dose ICS
- Leukotriene receptor antagonists
- Low dose theophylline

Reliever

- As needed short acting beta2 – agonist (SABA)
- As needed SABA or low dose ICS / formoterol

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

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

- 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.

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

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

Comparison 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

**Durability of Efficacy - Reduction in ER Visits**
Maintained out to 5 years

- 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


---

**Safe - Long-Term Safety**
Maintained out to 5 Years

- 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)

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

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 $\beta_2$-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 $\beta_2$-agonist
- sx – symptom(s)
- tx – treatment/treat
- tx’d – treated
- VPQ – very-poor-quality
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

Bronchial Thermoplasty

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

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
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

The FDA warns caution in pts with the following conditions, as they were not studied in Castro (2010):

- Post-BD FEV₁ < 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?

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
151 non-duplicate publications screened

26 full-text articles retrieved

11 studies analyzed (reported in 15 articles)

125 studies excluded based on title/abstract review

11 articles excluded based on full-text review

11 studies analyzed (reported in 15 articles)

7 studies (KQ#1, KQ#2, KQ#3)
4 cost studies (KQ#4)

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

Findings

(See Summary of Findings Tables and Appendix IV for further detail)
Overview: Studies Evaluating the Effectiveness of Bronchial Thermoplasty

<table>
<thead>
<tr>
<th>Findings for KQ#1</th>
<th># Studies, Overall Quality</th>
</tr>
</thead>
</table>
| **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) |

### Evidence Study results
- **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<sub>1</sub>:** Did not improve in 3 RCTs

No control or comparison grp (4 studies)
### KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

#### Study details

<table>
<thead>
<tr>
<th>Castro et al. (2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>288 severe asthma pts</td>
</tr>
<tr>
<td>BT: 190 pts</td>
</tr>
<tr>
<td>Sham tx: 98 pts (mimicked BT tx but no RF energy delivered)</td>
</tr>
</tbody>
</table>

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**: Asthmatx Inc. and Boston Scientific Corp.

#### Study results

- **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

---

### Study results

- **Primary outcome measure**: Difference in integrated AQLQ score (average of 6, 9, 12 mos) between BT and sham grp
  - Meaningful improvement was defined as PPS >0.964 for AQLQ; all other outcomes PPS >0.95
  - Improvement was greater in BT grp than sham grp (1.35±1.10 vs 1.16±1.23); however, this difference did not reach its prespecified success criterion (PPS=0.96)

- **Secondary outcome measures**:
  - Proportion of pts that achieved MCID (≥0.5) in AQLQ scores: More BT pts achieved AQLQ MCID than sham pts (78.9% vs 64.3%; PPS=0.996)
### KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

<table>
<thead>
<tr>
<th>Study details</th>
<th>Study results</th>
</tr>
</thead>
</table>
| Castro et al. (2010) 288 severe asthma pts BT: 190 pts Sham tx: 98 pts Double-blind RCT (GQ) | **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 |
| Study strengths: Randomized; placebo-controlled; sufficient sample size | 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 |
| 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 | 5-yr f/u (Wechsler 2013):  
  - Uncontrolled f/u of 162 (85%) BT pts  
  - No significant increases in respiratory AEs or need for hospitalization |
KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

<table>
<thead>
<tr>
<th>Study details</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cox et al. (2007)</strong></td>
<td><strong>Primary outcome measure:</strong> Improvement in mild exacerbations during 2-wk periods of LABA abstinence at 1-yr f/u:</td>
</tr>
<tr>
<td>109 moderate to severe asthma pts</td>
<td>• Exacerbation = ≥20% reduction below BL in morning PEF; ≥3 additional puffs than BL of rescue medication; nocturnal awakening caused by asthma sx</td>
</tr>
<tr>
<td>BT: 55 pts</td>
<td>• Improvement was greater in BT grp than control grp (–0.16 vs +0.04); this difference was significant (P&lt;0.01)</td>
</tr>
<tr>
<td>Control tx (asthma medication): 54 pts</td>
<td><strong>Secondary outcome measures:</strong> Statistically significant improvements compared with control grp at 1-yr f/u:</td>
</tr>
<tr>
<td>RCT (FQ)</td>
<td>• Mild exacerbations with LABA: –0.17 vs +0.03 (P&lt;0.05)</td>
</tr>
<tr>
<td><strong>Study strengths:</strong> Randomized; sufficiently powered</td>
<td>• ACQ: –1.2 vs –0.5 (P&lt;0.005)</td>
</tr>
<tr>
<td><strong>Study limitations:</strong> Not blinded; not placebo-controlled; primary outcome measure collected via daily diaries; 5% of pts lost to f/u; only 1-yr f/u</td>
<td>• Sx-free days: +41% vs +17% (P&lt;0.01)</td>
</tr>
<tr>
<td><strong>Funding source:</strong> Ashthmatx Inc.</td>
<td>• Sx scores: –1.9 vs –0.7 (P&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>• Rescue BD use: –8.9 vs –1.2 puffs per wk (P&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>• Morning PEF: +39 vs +9 L/min (P&lt;0.005)</td>
</tr>
</tbody>
</table>

No statistically significant improvements were found for these measures:
- Severe exacerbations
- Airway responsiveness
- FEV₁
### KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

<table>
<thead>
<tr>
<th>Study details</th>
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<tbody>
<tr>
<td><strong>Cox et al. (2007)</strong>&lt;br&gt;109 moderate to severe asthma pts&lt;br&gt;BT: 55 pts&lt;br&gt;Control tx (asthma medication): 54 pts&lt;br&gt;RCT (FQ)</td>
<td><strong>Long-term f/u (Thomson 2011):</strong>&lt;br&gt;• F/u of 45 (82%) BT pts up to 5 yrs&lt;br&gt;• 3-yr f/u of 24 (44%) control pts&lt;br&gt;<strong>Significant difference</strong> between grps for:&lt;br&gt;• Airway responsiveness: Increased 1.3 doublings for BT grp vs decrease of 0.4 doublings for control grp <em>(P&lt;0.05)</em>&lt;br&gt;<strong>No significant differences</strong> between grps for:&lt;br&gt;• Other respiratory parameters&lt;br&gt;• Oral glucocorticoid use&lt;br&gt;• Worsening of asthma&lt;br&gt;• ED visits&lt;br&gt;• Hospitalizations</td>
</tr>
<tr>
<td>Study strengths: Randomized; sufficiently powered&lt;br&gt;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</td>
<td></td>
</tr>
</tbody>
</table>

**Pavord et al. (2007)**<br>32 severe asthma pts<br>BT: 15 pts<br>Control tx (asthma medication): 17 pts<br>RCT (FQ) | **Primary outcome measure:** Safety measures (discussed in results for KQ#2: Safety)<br>**Secondary outcome measures:**<br>Statistically significant improvements compared with control grp at 1-yr f/u:<br>• AQLQ (higher score better) (+1.5 vs +0.4) *(P<0.05)*<br>• ACQ (lower score better) (–1.0 vs –0.2) *(P<0.05)*<br>• Rescue bronchodilator use (–26% vs –6%) *(P<0.05)*<br>The following measures were not statistically significant at 1-yr f/u:<br>• FEV₁<br>• Morning or evening PEF<br>• Sx-free days; sx scores<br>• Airway responsiveness |
| Study strengths: Randomized<br>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<br>Funding source: Ashthmatx Inc. | |

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### KQ#1: Effectiveness of Bronchial Thermoplasty for Asthma

<table>
<thead>
<tr>
<th>Study details</th>
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</thead>
<tbody>
<tr>
<td><strong>Pavord et al. (2007)</strong>&lt;br&gt;32 severe asthma pts&lt;br&gt;BT: 15 pts&lt;br&gt;Control tx (asthma medication): 17 pts</td>
<td>5-yr f/u (Pavord 2013):&lt;br&gt;• Uncontrolled f/u of 14 (93%) BT pts&lt;br&gt;• No significant changes in yrs 2 through 5 in:&lt;br&gt;  • Respiratory AEs&lt;br&gt;  • Hospitalizations&lt;br&gt;  • ED visits&lt;br&gt;  • Asthma maintenance medication usage&lt;br&gt;  • Respiratory parameters&lt;br&gt;• Outcomes during f/u yrs 2 to 5 were collected once per yr and may be subject to recall bias</td>
</tr>
<tr>
<td><strong>RCT (FQ)</strong></td>
<td><strong>Study strengths:</strong>&lt;br&gt;Randomized</td>
</tr>
</tbody>
</table>
| **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 | **Study results**

#### Nonrandomized studies

- **Cox 2006** (n=16; case series, VPQ)<br>• 4 nonrandomized studies were included in the assessment<br>• Results from these studies were mostly positive<br>• Studies of very poor quality
- **Doeing 2013** (n=8; case series, VPQ)
- **Bicknell 2015** (n=10; retrospective cohort, VPQ)
- **Chakir 2015** (n=17; case series, VPQ)
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): Between-grp difference of 0.69 (+1.3 BT vs +0.6 control; \( P<0.005 \)) at 12 mos
  - Pavord (2007): Between-grp difference of 1.1 (+1.5 BT vs +0.4 control; \( P<0.05 \)) at 12 mos
  - Castro (2010): Between-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)

- 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
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

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

- Complications during long-term f/u
    - 45 (82%) BT pts for 5 yrs and 24 (44%) control pts for 3 yrs
    - Btw-grp differences in worsening of asthma, hospitalizations, and ED visits were NS
    - No serious AEs due to BT occurred in 5 yrs
    - 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

  - 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
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

### Patient Selection Criteria

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Asthma severity</th>
<th>Medications</th>
<th>FEV₁</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castro (2010)</td>
<td>Severe</td>
<td>ICS (≥1000 µg/day), LABA (≥100 µg/day); daily need &lt;8 puffs short-acting BD, &lt;4 puffs long-acting BD, &lt;2 nebulizer tx</td>
<td>Pre-BD ≥60% Actual mean 78%</td>
<td>≥2 days of asthma sx/wk Low AQLQ score (≤6.25)</td>
</tr>
<tr>
<td>Pavord (2007)</td>
<td>Severe</td>
<td>ICS (≥750 µg/day); LABA (≥100 µg/day)</td>
<td>Pre-BD ≥50% Actual mean 63%</td>
<td>--</td>
</tr>
<tr>
<td>Cox (2007)</td>
<td>Moderate or severe</td>
<td>ICS (≥200 µg/day); LABA (≥100 µg/day); daily need ≤4 puffs short-acting BD; stable asthma medication</td>
<td>Pre-BD 60% to 85% Actual mean 73%</td>
<td>No unscheduled physical visits for asthma</td>
</tr>
</tbody>
</table>
### Patient Selection Criteria

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Asthma severity</th>
<th>Medications</th>
<th>FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox (2006)</td>
<td>Mild to moderate</td>
<td><strong>Exclude:</strong> &gt;4 puffs per day SABA</td>
<td>Actual mean Pre–BD 82%</td>
</tr>
<tr>
<td>Doeing (2013)</td>
<td>Severe</td>
<td>ICS (≥1000 µg/day); LABA (≥100 µg/day)</td>
<td>Actual mean Pre–BD 52%</td>
</tr>
<tr>
<td>Bicknell (2015)</td>
<td>Severe</td>
<td>ICS (≥1000 µg/day)</td>
<td>Actual mean Pre–BD 72%</td>
</tr>
<tr>
<td>Chakir (2015)</td>
<td>Severe</td>
<td>ICS (≥500 µg/day); LABA (≥100 µg/day)</td>
<td>Pre–BD ≥50%</td>
</tr>
</tbody>
</table>

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### 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

- 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$_1$ ≥ 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)

- 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

Practice Guidelines and Payer Policies
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

<table>
<thead>
<tr>
<th>Quantity/quality of guidelines</th>
<th>Tx recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 guidelines (1 good, 3 fair)</td>
<td><strong>BTS (2011):</strong> BT is a possible tx option in select pts with severe asthma; should be limited to few specialist centers</td>
</tr>
<tr>
<td><strong>ATS, American Thoracic Society</strong></td>
<td><strong>ERS/ATS (2014):</strong> BT for severe asthma only in clinical trial or systematic registry; available evidence is considered to be of very low quality</td>
</tr>
<tr>
<td><strong>BTS, British Thoracic Society</strong></td>
<td><strong>GINA (2015):</strong> BT is a possible tx option in select pts with severe asthma; long-term safety and efficacy unknown; large placebo effect in current studies</td>
</tr>
<tr>
<td><strong>ERS, European Respiratory Society</strong></td>
<td><strong>NICE (2012):</strong> 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</td>
</tr>
<tr>
<td><strong>GINA, Global Initiative for Asthma</strong></td>
<td></td>
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<td><strong>NICE, National Institute for Health and Care Excellence</strong></td>
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</table>
Overall Summary and Discussion

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?
**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 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.

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

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Safety Evidence</th>
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<tbody>
<tr>
<td>Infection</td>
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<td>Hospitalization</td>
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<td>Wheezing</td>
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<td>Discomfort</td>
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<td>Bronchial irritation</td>
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<td>Nasal congestion</td>
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<td>Bronchiectasis</td>
<td></td>
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<tr>
<td>Efficacy – Effectiveness Outcomes</td>
<td>Efficacy / Effectiveness Evidence</td>
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<td>----------------------------------</td>
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<td>Quality of life- asthma QoL scores</td>
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<td>Asthma control</td>
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<td>Severe exacerbations</td>
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<td>Medication use</td>
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<td>Lung function</td>
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<tr>
<td>Emergency department visits</td>
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<tr>
<td>Mortality</td>
<td></td>
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<tr>
<td>Days lost from work/school/activities</td>
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<tr>
<td>Symptom-free days</td>
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</table>

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<thead>
<tr>
<th>Special Population / Considerations Outcomes</th>
<th>Special Populations/ Considerations Evidence</th>
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<tbody>
<tr>
<td>Asthma severity</td>
<td></td>
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<tr>
<td>Daily medication dose level</td>
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<tr>
<td>Asthma QoL score</td>
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<th>Cost Outcomes</th>
<th>Cost Evidence</th>
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<tr>
<td>Cost</td>
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<tr>
<td>Cost effectiveness</td>
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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; 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)

<table>
<thead>
<tr>
<th>Quantity of Individual GLs</th>
<th>Individual GL Quality</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (BTS, ERS/ATS, GINA, NICE)</td>
<td>1 Good 3 Fair</td>
<td><strong>BTS (Good Quality):</strong> 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.</td>
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<td><strong>ERS/ATS (Fair Quality):</strong> 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).</td>
</tr>
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<td><strong>GINA (Fair Quality):</strong> 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.</td>
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<tr>
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<td><strong>NICE (Fair Quality):</strong> 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.</td>
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</tbody>
</table>

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; FEV₁, forced expiratory volume in 1 second; f/u, follow-up; GINA, Global Initiative for Asthma; LABA, long-acting β₂-agonist; NICE, National
### Sponsor, Title

<table>
<thead>
<tr>
<th>Sponsor, Title</th>
<th>Relevant Recommendations</th>
<th>Quality*/Main Limitations</th>
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<tbody>
<tr>
<td>British Thoracic Society (BTS)</td>
<td>Pt selection: Pts w/ severe persistent asthma receiving high-dose combination inhalers (&gt;1000 µg beclomethasone equivalent) plus long-acting bronchodilators or long-term oral corticosteroids. The FEV₁ should be &gt;50% predicted.</td>
<td>6 – Good (keywords and search strings not specified, funding source not stated, some members have potential conflicts of interest)</td>
</tr>
<tr>
<td>British Thoracic Society Guideline for Advanced Diagnostic and Therapeutic Flexible Bronchoscopy in Adults</td>
<td>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).&lt;br&gt;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.</td>
<td>5 – Fair (strengths and limitations of body of evidence not clearly described, whether guideline reviewed by external experts not stated, funding source not reported)</td>
</tr>
<tr>
<td>European Respiratory Society (ERS); American Thoracic Society (ATS)</td>
<td>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.</td>
<td>4 – Fair (strengths and limitations of body of evidence not clearly described, guideline not reviewed by external experts)</td>
</tr>
<tr>
<td>International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.</td>
<td>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.</td>
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</table>
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.

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.

**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:

<table>
<thead>
<tr>
<th></th>
<th>Unproven (no)</th>
<th>Equivalent (yes)</th>
<th>Less (yes)</th>
<th>More (yes)</th>
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<tr>
<td>Effective</td>
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<td>Safe</td>
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<tr>
<td>Cost-effective</td>
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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.