Asthma Heterogeneity, Phenotypes and Endotypes – Choosing the Right Biologic for your Patient

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DISCLOSURES

- **Speaker; Honorarium**
  - Boehinger Ingelheim  - Genentech
  - AstraZeneca  - Teva
  - Boston Scientific

- **Principal Investigator; Contracted Research**
  - Boehinger Ingelheim  - Vectura
  - Chiesi  - ALA
  - Sanofi-Aventis  - NIH
DISCLOSURES (cont.)

- Consultant; Consulting fee
  - Nuvaira
  - Aviragen
  - Genentech
  - Neutronic
  - Sanofi-Aventis
  - Teva
  - Theravance
  - Vectura

- Author; Royalties
  - Elsevier

- Co-Investigator; Contracted Research
  - NIH
  - NIH
  - PCORI
LEARNING OBJECTIVES

- Discuss the clinically relevant disease subtypes and molecular targets for new biologic medications in asthma
- Identify the impact of biomarkers on understanding future impairment and risk in our asthma patients
- Diagnose patients with symptoms of severe asthma to determine the level of disease control and uncover potential phenotypes that can guide ongoing therapy
Asthma is a Complex Heterogeneous Disease

- Asthma likely encompasses many different disease variants with different etiologies and pathophysiology.
  - Many phenotypes exist and are determined by clinical characteristics, physiology, triggers, and inflammatory parameters.
  - Multiple environmental and genetic factors contribute to the disease.

“Old School”

Categorizing Asthma by Endotype

Phenotype:
- Observable properties of an organism that are produced by the interactions of the genotype and the environment
- Encompasses the heterogeneity of clinical presentations but do not provide insight into the underlying pathophysiology

Endotype:
- A specific biologic pathway that explains the observable properties of a phenotype
- A subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism

Classification by Endotype May Identify Appropriately Targeted Treatment Approaches

- One of the major unmet needs in asthma lies with delivering mechanism-specific treatments that are highly effective in specific endotypes of asthma

- Understanding endotypes can identify those patients most likely to benefit from a particular type of therapy
  - This strategy can be advantageous both in clinical study design and for the development of future targeted therapies

Phenotypes based on TH2 vs non-TH2

Severity

Childhood
Adult
Age at onset

TH2

AERD
Late-onset, eosinophilic

Non-TH2

Very late-onset, (women)

EIA

Allergic asthma

Obesity-associated

Smoking-associated, neutrophilic

Smooth-muscle mediated, paucigranulocytic

Allergy/duration

Adult

# Potential Biomarkers for Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Sputum EOS</td>
<td>• Severe allergic and eosinophilic asthma</td>
</tr>
<tr>
<td></td>
<td>• Increased exacerbations and poor lung function</td>
</tr>
<tr>
<td>Blood EOS</td>
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<tr>
<td>IgE</td>
<td>• Severe allergic asthma</td>
</tr>
<tr>
<td>FeNO</td>
<td>• Indicator of oxidative and nitrative stress</td>
</tr>
<tr>
<td></td>
<td>• Severe allergic and eosinophilic asthma</td>
</tr>
<tr>
<td>Periostin</td>
<td>• Potentially allergic and eosinophilic asthma</td>
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EOS = eosinophil; FeNO = exhaled nitric oxide fraction; Ig = immunoglobulin.
40 Year Old African American Male was diagnosed with asthma shortly after birth. He has history of allergic rhinitis. Hospitalized 15 times with one additional burst of steroids in the last year. During one hospitalization for asthma was in the ICU, but never intubated. Medications albuterol PRN and fluticasone/salmeterol 500/50 1 puff BID. ACQ score today was 2.0. FEV1 1.93 L 50% predicted; post bronchodilator FEV1 increased to 2.50L 64% predicted (29% reversibility). 0.408 K/cu mm absolute blood eosinophils and total serum IgE 66 IU/ml.

The best predictor of a subsequent exacerbation of asthma in this patient is:

A. Bronchodilator reversibility
B. Blood eosinophils
C. African American race
D. ACQ score
E. Atopic history
Severe Exacerbations are Associated with High EOS Levels¹

- Medical record data to identify primary care patients with asthma aged 12–80 years with 2 years of continuous records, including 1 year before (baseline) and 1 year after – 20,929 (16%) of 130 248 had blood eos >400/μL.

Adjusted rate ratios (RRs) for severe exacerbations and acute respiratory events, and odds ratios (ORs) for asthma control, for patients with peripheral blood eosinophil count greater than 400 cells per μL (vs 400 cells per μL or less) during 1 outcome year.

Role of Eosinophils in Severe Asthma

## Potential phenotype-targeted therapies in severe asthma

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<th>Associations</th>
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The best description of this patient’s asthma phenotype is:

A. Severe eosinophilic asthma
B. Severe neutrophilic asthma
C. Chronic airflow obstruction asthma
D. Severe allergic asthma
22 Year old female (BMI 33) diagnosed with asthma at age 2 has severe uncontrolled persistent asthma despite high dose fluticasone (1,000 mcg/day), salmeterol, and tiotropium with history of allergic rhinitis and urticaria. She has had 4 courses of corticosteroids in the past year and one hospitalization for asthma resulting in BiPAP therapy. Baseline FEV1 2.70 L 95% of predicted, post-bronchodilator FEV1 increased to 3.02L (107% predicted, 12% reversibility), 0.240 K/cu mm absolute blood eosinophils, FeNO 55 ppb and total serum IgE 660.

Which of the following currently available biologic therapy would be most appropriate for this patient?

A. Omalizumab  
B. Mepolizumab  
C. Dupilumab  
D. Reslizumab  
E. Epinephrine pen
Omalizumab: anti-IgE therapy for severe eosinophilic asthma?

EXTRA study: exacerbations reduced in severe asthma patients treated with high dose ICS+LABA: omalizumab vs. placebo RR 0.75 [0.61-0.92]¹

- Exploratory analysis revealed greatest effect in high biomarker subsets (median FeNO, Blood EOS, Periostin)²


CI, confidence interval; EOS, eosinophils; FeNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; ppb, parts per billion; RR, rate ratio.
Several (interdependent) determinants of anti-IL-5 clinical response in asthma

Exposure to drug
- Individual IL-5 drive
- Burden of disease in the airway

Blood eosinophil level
- OR
  - Demonstrable airway eosinophilia

Disease severity
- Based on background medication level

Level of baseline control
- Exacerbation history

Other patient factors
- e.g. Associated comorbidities (e.g. nasal polyps/sinus disease), allergy etc

- *Treating currently active tissue eosinophilia AND/OR*
- *Preventing the influx associated with a future exacerbation*
Mepolizumab: DREAM trial

Primary endpoint

- Placebo (exac=2.40/year, n=159)
- Mepolizumab 75 mg (exac=1.24/year, n=154)
- Mepolizumab 250 mg (exac=1.46/year, n=152)
- Mepolizumab 750 mg (exac=1.15/year, n=156)

Clinically significant exacerbations, n

Time from start of treatment (months)

Mepolizumab: DREAM trial

Secondary endpoints

- Change in blood eosinophil count
- Change in pre BD FEV1
- Change in sputum eosinophil count
- Change in ACQ

All mepolizum doses \( P < 0.001 \) vs placebo at 52 weeks

\( p = 0.0082 \) for mepolizumab 750 mg vs placebo at 52 weeks

Mepolizumab: MENSA study

Primary endpoint - asthma exacerbations

Mepolizumab 100 mg SC is licensed for the treatment of severe eosinophilic asthma.

Mepolizumab: MENSA study

Changes in SGRQ

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<th>Group</th>
<th>Change from baseline in SGRQ score</th>
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<tr>
<td>Placebo</td>
<td>9</td>
</tr>
<tr>
<td>75 mg IV</td>
<td>15.4</td>
</tr>
<tr>
<td>100 mg SC</td>
<td>16</td>
</tr>
</tbody>
</table>

6.4 points difference *  
7.0 points difference *

*p<0.001

IV, intravenous; SC, subcutaneous; SGRQ, St. George’s Respiratory Questionnaire. Mepolizumab 100 mg SC is licensed for the treatment of severe eosinophilic asthma.

Mepolizumab: Oral Steroid Sparing

Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N = 66)</th>
<th>Mepolizumab (N = 69)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%) ( \dagger )</td>
<td>7 (11)</td>
<td>16 (23)</td>
<td>2.39 (1.25–4.56)</td>
<td>0.008</td>
</tr>
<tr>
<td>90 to 100%</td>
<td>5 (8)</td>
<td>12 (17)</td>
<td>5 (15)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment</td>
<td>37 (56)</td>
<td>25 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in daily oral glucocorticoid dose of ≤50% — no. (%) ( \dagger )</td>
<td>22 (33)</td>
<td>37 (54)</td>
<td>2.26 (1.10–4.65)</td>
<td>0.03</td>
</tr>
<tr>
<td>Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%) ( \dagger )</td>
<td>21 (32)</td>
<td>37 (54)</td>
<td>2.45 (1.12–5.37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reduction of 100% in oral glucocorticoid dose — no. (%) ( \dagger )</td>
<td>5 (8)</td>
<td>10 (15)</td>
<td>1.67 (0.49–5.75)</td>
<td>0.41</td>
</tr>
<tr>
<td>Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI) ( \dagger )</td>
<td>0.0 (–20.0 to 33.3)</td>
<td>50.0 (20.0 to 75.0)</td>
<td>NA</td>
<td>0.007</td>
</tr>
</tbody>
</table>

* Odds ratios are for the mepolizumab group as compared with the placebo group. NA denotes not applicable.
† Data for the primary outcome were analyzed with the use of a proportional-odds model (ordered multinomial logistic regression), with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 yr vs. ≥5 yr), and baseline oral glucocorticoid dose during the optimization phase.
‡ Data were analyzed with the use of a binary logistic-regression model with terms for study group, region, duration of oral glucocorticoid use at baseline (<5 yr vs. ≥5 yr), and baseline oral glucocorticoid dose during the optimization phase.
§ The median difference and associated confidence intervals were calculated with the use of the Hodges–lehman estimation. P values were calculated with the use of a Wilcoxon rank-sum test. For patients who withdrew from the study before the maintenance phase, a value equal to the minimum percent reduction in oral glucocorticoid use for all patients was imputed for the analysis.
Mepolizumab summary

- Mepolizumab significantly reduces the number of asthma exacerbations in patients with severe eosinophilic asthma compared with placebo.

- Treatment lowers blood and sputum eosinophil counts (750 mg IV) but SQ 100 mg Q4wks variable effects.

- There were small effects of mepolizumab on FEV$_1$ and AQLQ and ACQ scores, which generally did not differ significantly from those reported with placebo.

- Safety and tolerability profile for mepolizumab comparable to that for placebo.

Reslizumab* in asthma

- 106 patients with inadequately controlled asthma with elevated eosinophils counts were randomly assigned to reslizumab IV 3 mg/kg or placebo at baseline, and at weeks 4, 8, and 12

- 8% of reslizumab vs 19% of placebo group had an asthma exacerbation (p=0.083)

*Humanized anti-human IL-5 monoclonal antibody of the IgG4 isotype

The nasal polyp endotype

Change from baseline in ACQ score

Placebo
Reslizumab

With nasal polyps
n=22
n=16

Without nasal polyps
n=31
n=37

p=0.0119
p=0.7176

Reslizumab 3 mg/kg q 4 weeks over 52 weeks in exacerbation-prone, uncontrolled asthmatics with elevated blood eosinophils

<table>
<thead>
<tr>
<th>Pooled results (Studies 3082/3083)</th>
<th>PBO n=476</th>
<th>Reslizumab 3 mg/kg n=477</th>
<th>RR (95% CI)</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAE*</td>
<td>1.81</td>
<td>0.84</td>
<td>0.46 (0.37, 0.58)</td>
<td>54%</td>
</tr>
<tr>
<td>CAE requiring systemic corticosteroid</td>
<td>1.54</td>
<td>0.66</td>
<td>0.42 (0.33, 0.55)</td>
<td>58%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from baseline over 52 weeks</th>
<th>ΔResli-PBO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>0.12</td>
</tr>
<tr>
<td>AQLQ</td>
<td>0.81</td>
</tr>
<tr>
<td>ACQ</td>
<td>−0.77</td>
</tr>
<tr>
<td>ASUI</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*CAE defined as a worsening requiring additional corticosteroid and/or other urgent treatment including ER/hospital

Influence of background therapy on asthma exacerbations with reslizumab

- Reslizumab was efficacious in reducing CAE regardless of the treatments patients were receiving at baseline

*Reslizumab relative to placebo

<table>
<thead>
<tr>
<th>Background Therapy</th>
<th>Rate-Ratio* (95% CI)</th>
<th>n Reslizumab</th>
<th>n Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.46 (0.37–0.58)</td>
<td>477</td>
<td>476</td>
</tr>
<tr>
<td>OCS at baseline</td>
<td>0.32 (0.18–0.55)</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>ICS plus LABA</td>
<td>0.45 (0.35–0.58)</td>
<td>397</td>
<td>383</td>
</tr>
<tr>
<td>ICS no LABA</td>
<td>0.51 (0.29–0.89)</td>
<td>80</td>
<td>93</td>
</tr>
</tbody>
</table>

Reslizumab effect on lung function

- Change from baseline to each visit in FEV1 by treatment group: pooled results for studies 3082/3083

** p<0.01

Predicting response to Reslizumab

Percent CAE reduction

*Castro et al ATS 2016 Late Breaking Abstract (Pooled study 3082/3083)
Reslizumab summary

- Patients receiving reslizumab (3 mg/kg IV Q 4wks) showed significantly greater reductions in sputum eosinophils, asthma exacerbations, improvements in airway function, and greater asthma control than those receiving placebo.

- Reslizumab can be targeted to the patients most likely to benefit by applying fairly simple blood eosinophil, asthma control, lung function, and disease severity criteria.

- Reslizumab was generally well-tolerated.
Question 4

- 42 Year old female (BMI 33), diagnosed asthma age 32, has severe uncontrolled persistent asthma despite high dose fluticasone (1,000 mcg/day), salmeterol, and tiotropium. She has had 4 courses of corticosteroids in the past year and one hospitalization for asthma resulting in BiPAP therapy. Baseline FEV1 of 1.60 L 65% of predicted, post-bronchodilator FEV1 increased to 2.02L. 0.440 K/cu mm absolute blood eosinophils and total serum IgE 660.

Which of the following currently available biologic therapy would be most appropriate for this patient?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Reslizumab
E. Epinephrine pen
Benralizumab (anti-IL-5Rα)

- A targeted, anti-eosinophil therapy under investigation

Benralizumab is a humanized, afucosylated monoclonal antibody (IgG1k) that binds with high affinity to IL-5Rα and efficiently depletes eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC)

- Eosinophils are thought to play a critical role in the pathogenesis and severity of asthma
- ~40–60% of people with severe asthma have eosinophilic inflammation
- Increased eosinophil count is associated with an increased frequency of exacerbations
- IL-5R is important in mediating the differentiation, proliferation, and activation of eosinophils by IL-5

**Benralizumab**

**Primary endpoint:** AER

**Secondary endpoints:** FEV\(_1\), ACQ-6

ACQ-6; Asthma Control Questionnaire-6; AER, annual exacerbation rate (total observed exacerbations to week 52 divided by total duration of person-year follow-up); CBC, complete blood count with differential; Fe\(_{NO}\), fraction of exhaled nitric oxide; FEV\(_1\), forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ppb, parts per billion

ELEN Index: mathematical algorithm to predict sputum eosinophils from CBC data

Benralizumab: primary efficacy endpoint: AER (mITT)

- Benralizumab 20 mg significantly reduced AER relative to placebo in patients with baseline blood eosinophils ≥300 cells/µL
- Benralizumab 100 mg significantly reduced AER relative to placebo in eosinophilic patients and in patients with baseline blood eosinophils ≥300 and ≥400 cells/µL

*Statistically significant (p<0.169)
†Data are expressed as mean (80% CI)

AERR, annual exacerbation rate reduction; RR, rate reduction

Benralizumab: conclusions

◆ In patients with uncontrolled eosinophilic asthma, benralizumab 20 mg and 100 mg may have an effect on exacerbations, lung function, and asthma control, compared with placebo
  – Positive correlation between degree of benefit and baseline blood eosinophil counts

◆ Benralizumab 30 mg SC is effective in reducing exacerbations and improving lung function

◆ Benralizumab had an acceptable safety profile at all doses
Dupilumab, a fully human monoclonal antibody against the IL-4 receptor alpha subunit, inhibits IL-4 and IL-13 signaling

Multinational, 24-week, randomized, double-blind, placebo-controlled, dose-ranging study in patients with persistent, uncontrolled asthma despite use of medium-to-high dose ICS/LABA

To ensure a balanced distribution of blood eosinophil (Eos) counts in patients across treatment regimens, randomization was stratified by blood Eos count at screening: ≥ 300 cells/μL, 200–299 cells/μL, and < 200 cells/μL

Screening period (14–21 days)

Randomization (1:1:1:1:1)

- n = 150 Dupilumab 300 mg q2w with loading dose (600 mg)
- n = 150 Dupilumab 300 mg q4w with loading dose (600 mg)
- n = 150 Dupilumab 200 mg q2w with loading dose (400 mg)
- n = 150 Dupilumab 200 mg q4w with loading dose (400 mg)
- n = 150 Placebo

Dupilumab or placebo was added on to therapy with ICS/LABA

24-week treatment period

q2w, every 2 weeks; q4w, every 4 weeks.

### Dupilumab: Severe Exacerbation Rate

**Eos ≥ 300 cells/µL**

- Placebo (n = 68) 0.08, 0.52
- 200 mg q4w (n = 59) 95% CI 0.36, 1.29
- 300 mg q4w (n = 66) 95% CI 0.36, 1.29
- 200 mg q2w (n = 64) 95% CI 0.13, 0.68
- 300 mg q2w (n = 64) 95% CI 0.13, 0.68

**Eos < 300 cells/µL**

- Placebo (n = 90) 0.08, 0.52
- 200 mg q4w (n = 91) 95% CI 0.29, 0.84
- 300 mg q4w (n = 91) 95% CI 0.29, 0.84
- 200 mg q2w (n = 84) 95% CI 0.25, 0.79
- 300 mg q2w (n = 92) 95% CI 0.25, 0.79

- **At Week 24, the q2w regimens showed a significant decrease in severe asthma exacerbation rates in patients with Eos ≥ 300 cells/µL, patients with Eos < 300 cells/µL, and the overall population**

The annualized exacerbation rate was adjusted for treatment duration in patients who discontinued prematurely. Arrows represent percent change relative to placebo. *P < 0.05, **P < 0.01, ***P < 0.001 vs placebo. CI, confidence interval.
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Bronchial Thermoplasty

- The catheter is a flexible tube with an expandable wire array at the tip
- The Radiofrequency Controller supplies energy that is converted to heat in the airway wall

- Monopolar radiofrequency (RF) energy
- Temperature controlled: 65 °C
- 10 seconds
- Multiple safety algorithms to ensure controlled energy delivery
The reduction in severe exacerbations requiring systemic corticosteroids at 1 year (vs. sham-treated patients) was maintained out to at least 5 years.
Predictors of Bronchial Thermoplasty response

- 40 severe asthma pts characterized pre BT at Wash Univ:
  - Post-BD FEV₁ 70%, range 44-121%, AQLQ score 3.4±1.2, ICS dose 2,185±621 mcg/d, 2.9±3.0 exacerbations requiring pred bursts prior yr.

- Increase AQLQ/ACT 1 yr post BT predicted by:
  - 30 (79%) responders, 8 (21%) non-responders
  - Shorter duration asthma (19±15 vs. 40±12 yrs, p=0.006)

*increase in AQLQ≥0.5 or ACT ≥3; Decrease in ICS, ≥240 mcg/d or OCS, ≥2.5 mg/d

Sarikonda, Sheshadri et al ATS 2014
Predictors of Bronchial Thermoplasty response

- ICS/OCS dose reduction* 1 yr post BT predicted by:
  - Lower AQLQ score (2.9±1.1 vs. 3.9±1.1, p=0.026),
  - Higher OCS dose (13.3±16.4 vs. 1.8±6.1 mg/d, p=0.01)
  - More exacerbations requiring pred burst prior yr 4.8±2.7 vs. 2.3±2.8 (p=0.04)
  - Higher residual volume/TLC on plethysmography (38.7±11.8 vs. 32.4±6.9 L, p=0.09) and resistance (Raw 4.0±1.7 vs. 1.9±1.1, p=0.03)

*increase in AQLQ≥0.5 or ACT ≥3; Decrease in ICS, ≥240 mcg/d or OCS, ≥2.5 mg/d

Sarikonda, Sheshadri et al ATS 2014
He Images for our Severe Asthma Patient
Pre-Bronchial Thermoplasty
$^3$He Images for our Severe Asthma Patient Post Bronchial Thermoplasty
Single-session bronchial thermoplasty for severe asthmatics guided by HXe MRI

A double-blind pilot study of 30 severe asthma pts with image-guided BT compared to traditional treatment:

- **Specific Aim 1:** To determine to what extent the single-session guided treatment is not inferior in benefit to the standard full three session treatment course (revealed by unblinding the analysis).
- **Specific Aim 2:** To assess HXe MRI as an imaging biomarker of asthma disease severity in the context of BT and evaluate our proposed image guided airway treatment prioritizing scheme.
Site of action of targeted therapies for severe asthma.

*Trivedi A et al Lancet Resp 2016 In press*
Targeted therapies based on severe asthma phenotypes with associated biomarkers

### Phenotypes
- Aspirin-sensitive asthma/AERD
- Severe T2 Allergic Asthma
- Severe Eosinophilic asthma
- Chronic airflow obstruction

### Biomarkers
- Elevated FeNO
- Elevated uLTE4
- High serum eosinophils
- High serum IgE
- High FeNO
- Recurrent exacerbations
- High serum IgE
- High FeNO
- Airway remodeling
- Increased airway wall thickness

### Targeted Therapies
- Leukotriene modifier
- Anti-IgE
- Anti-IL 5/α
- Anti-IgE
- Anti-IL-13
- IL -4α
- Anti-IL-5/α
- Anti IL-4α
- Bronchial thermoplasty
- Other biologics

*Trivedi A et al Lancet Resp 2016 In press*
Phenotype-guided approach in asthma

- Many phenotypes exist in asthma though the biologic pathway (endotype) is unclear for most.
- Ongoing studies of large-scale, molecularly and genetically focused and extensively clinically characterized cohorts of asthma should enhance our ability to molecularly understand these phenotypes.
- Biologic therapy with anti-IL 5 for the eosinophilic uncontrolled asthma is a well-established endotype but likely represents less 40% of uncontrolled asthma.
Phenotype-guided approach in asthma

- Targeted phenotype therapy can lead to personalized medical therapy for asthma

- Many questions remain
  - Are there better biomarkers than the blood EOS?
  - Is anti-IL-4 and anti-IL-13 therapy as effective as anti-IL-5?
  - Will other biologic targets work?
    - Anti-IL-17, anti-IL-33, TSLP, and more
  - Is chronic airflow obstruction and airway remodeling a phenotype or an end-result from many different pathways?