



### Moderate - Severe Asthma

- **Definition:** Asthma treated with high-dose inhaled corticosteroid and an additional controller medication or systemic corticosteroids with or without other controllers, or remains uncontrolled despite these therapies
- Despite recent advances in asthma management, ~ 50% of patients with moderate-to-severe disease have uncontrolled symptoms despite adherence to ICS or LABA therapy
- Associated with increased morbidity, mortality and increased consumption of health care resources
- Over next 2 decades, asthma management predicted to cost ~ \$1 trillion in US

1. Sassi et al. / Ann Allergy Asthma Immunol 127 (2021) 423-427  
 2. Opatowski et al. / Ann Allergy Asthma Immunol 126 (2021) 1-10

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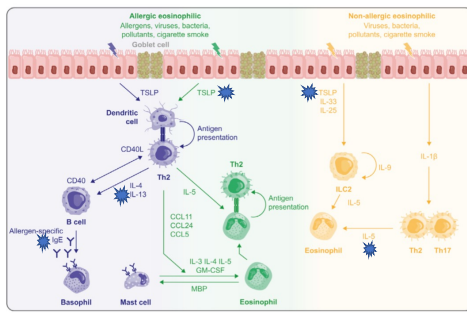
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### Asthma endotypes

- Type 2-high – suggests presence of TH2 CD4 + lymphocytes that secrete IL-4, IL-5, IL-9, IL-13
  - IgE- mediated hypersensitivity → secretion of these cytokines in a subset of T2-high asthma
- Diversity within the Th2 high endotype, some patients may have dominance of only 1 biomarker:
  - Allergic
  - Eosinophilic
  - FeNO predominant
- Non-T2 (or T2-low, or neutrophilic asthma)
  - Associated with oxidative stress, chronic infection, smoking, obesity, high fat diet
  - Associated with poor response to corticosteroids

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## Biologics for Asthma

The US FDA currently has 6 biologics approved for the treatment of patients with moderate-severe asthma

- 5 for type 2-high
  - Anti-IgE
  - Anti-IL-5 or IL-5 receptor
  - Anti-IL-4 receptor alpha
- 1 for both
  - Anti-TSLP (most recently approved)

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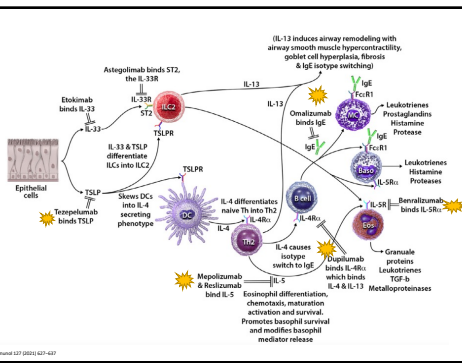
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Variable	Omalizumab	Mepolizumab	Reslizumab	Dupilumab	Benralizumab
FDA approval status	Yes	Yes	Yes	Yes	Yes
Age approved	≥6 y	≥6 y	≥18 y	≥12 y	≥12 y
Mechanism of action	Anti-IgE	Anti-IL-5	Anti-IL-5	Anti-IL-4/13Ra	Anti-IL-5Ra
Route	SC	SC	IV	SC	SC
Frequency	Every 2-4 wk (weight-based and pretreatment IgE)	Every 4 wk	Every 4 wk	Every 2 wk	Every 4 wk for 3 doses and then every 8 wk
Dose	150-375 mg	40-100 mg (on the basis of age)	3 mg/kg infusion	400-600 mg initial dose followed by 200-300 mg	30 mg
High level of evidence for measured outcomes <sup>28</sup>	Reduced exacerbations, daily OCS dose	Reduced exacerbations, daily OCS dose, and rescue medication use	Reduced exacerbations, controller, and rescue medication use, improved QOL	Reduced exacerbations, daily OCS dose, and improved FEV1	Reduced exacerbations, daily OCS dose, and controller medications, and improved QOL

Abbreviations: FDA, Food and Drug Authority; FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; IV, intravenous; OCS, oral corticosteroid; QOL, quality of life; SC, subcutaneous.

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### Anti-IgE Biologics

- Omalizumab
- Ligelizumab - a high-affinity anti-IgE mAb (remains under active investigation for CSU but not asthma)
- Investigation into other anti-IgE agents has been discontinued - failures to achieve primary end points

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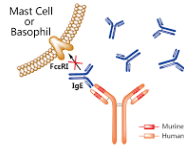
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### Omalizumab (Xolair, Genentech, San Francisco, CA)

- June 2003 - first biologic approved by FDA for use in patients with moderate-to-severe persistent allergic asthma
- A monoclonal antibody - targets free IgE, prevents its binding to the high-affinity IgE receptor (FcεR1)
- Causes down-regulation of the receptor on these cells
- ↓ pro-asthmatic mediator release
- ↑ IFN production by plasmacytoid dendritic cells



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### Omalizumab

Comorbid conditions that favor the use of omalizumab include:

- Chronic rhinosinusitis with nasal polyposis (CRSwNP) (FDA-approved indication 2020)
- Chronic urticaria (FDA-approved indication 2016)
- Allergic rhinitis
- Food allergies
- Allergic bronchopulmonary aspergillosis (ABPA)
- Eosinophilic granulomatosis with polyangiitis
- Asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS)

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### Omalizumab – Important Endpoints

- In a phase III trial of patients with severe allergic asthma, addition of omalizumab decreased average **number of asthma exacerbations** by 48%
  - Subset of patients with peripheral eosinophil levels  $\geq 400/\text{mL}$ , 74% reduction
  - Baseline IgE levels, number/type of allergen sensitizations – did not predict response
- Open-label pragmatic trial - 39% **reduction in daily OCS use** more than 52 weeks, and improvement in **quality-of-life questionnaire scores**
- Real-world study of omalizumab - half of the 85% of patients with uncontrolled symptoms at baseline achieved good asthma control using the **asthma control test**

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### Omalizumab

- Approved for asthma  $\geq 6$  yo
- Recommended SQ dose administered either in a health care setting or at home every 2 or 4 weeks
- Dosing depends on body weight and total serum IgE levels
- Typical scenario - Patient with allergic asthma w/ worsening symptoms when exposed to aeroallergens; serum IgE level  $> 30 \text{ IU/mL}$

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### Omalizumab – Adverse Events

- Most common treatment-related adverse events
  - Nasopharyngitis
  - Headache
  - Sinusitis
  - Upper respiratory tract infections
- Anaphylaxis - 0.14% with therapy vs. 0.07% in controls
- Malignancies
  - In 2003 - 0.5% treated patients vs. 0.2% controls
  - In 2010 - 4.14 per 1000 patient-years of observation vs. 4.45 controls

Wang G, Wechter MB. A rational approach to omalizumab and other biologic therapies in asthma. Annals 2022; 136(6): 376

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### Anti-IL-5/5R

3 FDA - approved biologics targeting the IL-5/5R pathway:

- Mepolizumab - subcutaneous anti-IL-5
- Benralizumab - subcutaneous anti -IL-5Ra
- Reslizumab - intravenous anti-IL-5

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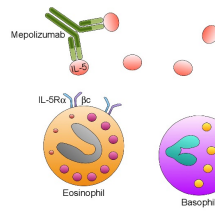
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### Mepolizumab (Nucala, GalxoSmithKline, Philadelphia, PA)

- More than 10 years until next biologic approved for asthma
- November 2015 - FDA- approved for use as an add-on maintenance treatment for patients with severe eosinophilic asthma
- IgG 1 kappa monoclonal antibody - targets IL-5 and prevents it from binding to IL-5 receptors
- Inhibits eosinophil production and survival



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### Mepolizumab

- Other *FDA-approved indications* for mepolizumab include:
  - Eosinophilic granulomatosis with polyangiitis (2017)
  - Hypereosinophilic syndromes (2020)
  - CRSwNP (2021)
- Positive effects seen in allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic COPD

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### Mepolizumab – Endpoints

- In phase III clinical trials, mepolizumab reduced **relative exacerbation rates** by 53%
- The Steroid Reduction with Mepolizumab Study (SIRIUS) trial
  - 63% of mepolizumab users were able to **reduce their OCS use** by 50% - 100%

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### Mepolizumab

- Approved for children ages 6 years and older
- Dosing:
  - 100-mg SQ injection for patients 12 years and older every 4 weeks
  - 40-mg SQ injection for patients 6 to 11 years old every 4 weeks
- Available as an auto-injector - can be dosed at home or in clinic
- No significant adverse events

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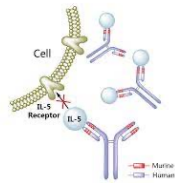
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### Reslizumab (Cinqair, Teva Pharmaceutical Industries, Frazer, PA)

- March 2016 - Approved by FDA for use as add-on maintenance treatment of patients with severe eosinophilic asthma
- A monoclonal antibody - binds IL-5 (but is an IgG4-kappa molecule)



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### Reslizumab – Endpoints

- Found to reduce **frequency of asthma exacerbations** at 1 year in a phase III pooled data analysis by 54% compared with placebo when blood eosinophil levels were greater than or equal to 400 cells/mL
- Also markedly **reduces blood eosinophil counts**
- Elevated pretreatment blood eosinophil counts predict greater **improvements in lung function and asthma control**
- In prednisone-dependent patients with severe asthma, weight-adjusted reslizumab was superior to fixed-dose mepolizumab in achieving asthma control

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### Reslizumab

- Approved for adults 18 and over
- Weight-based dosing - may help patients with higher BMI
- May also be efficacious in CRSwNP
- Administered as a 3 mg/kg IV infusion Q4 weeks over 20-50 min.
- No significant adverse events

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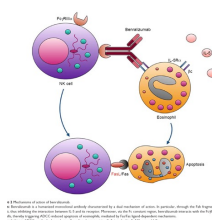
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### Benralizumab (Fasenra, AstraZeneca, So€dert€alje, Sweden)

- November 2017 - FDA-approved for asthma
- A monoclonal IgG1 kappa antibody – targets the IL-5a receptor → antibody-dependent cell-mediated cytotoxicity of cells expressing these receptors
- Targets the receptor vs. the ligand itself (i.e. mepolizumab/ reslizumab)
- More effective at depleting tissue-dwelling eosinophils and basophils, which also express this receptor



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### Benralizumab – Endpoints

- In its phase 3 trials, benralizumab decreased **annual asthma exacerbation rates** by 45%
- Improved levels of **prebronchodilator forced expiratory volume in 1 second** by 159 mL
- Also found to **reduce OCS use** by at least 50% in 2/3 of patients

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### Benralizumab

- Approved for patients 12 years and older with severe eosinophilic asthma
- Administered as a 30-mg subcutaneous injection Q4 weeks for the first 3 doses and then Q8 weeks
- No significant adverse events

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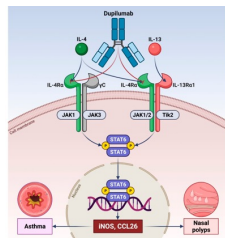
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### Dupilumab (Dupixent, Regeneron Pharmaceuticals, Tarrytown, NY)

- March 2017 - approved by FDA for use in patients with eosinophilic or OCS-dependent (regardless of eosinophil counts) moderate-to-severe asthma
- 2021 - approved for children (6-11)
- Dupilumab - a fully human monoclonal antibody targeting the IL-4Ra, resulting in blockade of both IL-4 and IL-13




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### Dupilimab

- Elevated FeNO (fractional exhaled nitric oxide level) - most favorable predictor for responses to dupilumab independently and additively to blood eosinophils
- Higher baseline peripheral eosinophil counts predict better response
- FDA-approved for AD (2017, now down to 6 months of age - 2022), CRSwNP (2019), and EoE (2022)
- Exhibited favorable outcomes for aspirin-exacerbated respiratory disease (AERD)

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### Dupilimab

#### Adverse effects

- Blood eosinophilia – observed in 14% of patients
  - Tends to resolve in many patients with time
- Associated with the development of conjunctivitis in 9% to 28% of patients with concomitant AD

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### Dupilimab – Endpoints

- In the Liberty QUEST trial, decreased **severe asthma exacerbations** in patients with moderate-to-severe asthma by 48% vs. placebo
  - Also showed a significant improvement in the **levels of forced expiratory volume in 1 second** by 320 mL
- OCS dependent patients in the phase III Liberty Asthma VENTURE trial were able to **decrease their daily dose of OCS** by 70% while on dupilumab vs. placebo and approximately 50% were able to completely **discontinue OCS use**

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### Dupilimab

- Indicated as an add-on maintenance treatment of adult and pediatric patients aged **6 years and older** with moderate-to-severe asthma characterized by an eosinophilic phenotype or with OCS dependent asthma
- For eosinophilic moderate-to-severe asthma, initial dose is a 400-mg subcutaneous injection followed by a 200-mg prefilled injection administered Q2 weeks
- For OCS-dependent moderate-to-severe asthma, recommended dose is an initial 600-mg injection followed by a 300-mg prefilled injection given every 2 weeks
- For pediatric patients (ages 6-11) – weight based, given Q2 or Q4 weeks

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- The pivotal studies for the 4 latter biologics enrolled patients with severe T2 asthma, even if they varied in their eligibility criteria and definitions for eosinophilic disease
- T2-high disease has been defined:
  - Sputum eosinophil levels greater than or equal to 1%
  - Blood eosinophil levels greater than or equal to 150 cells/mL  
OR
  - FeNO levels  $\geq$  20 parts per billion

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### Despite the T2-high targeted biologics...

- Approximately 30% of patients with severe asthma receiving biologics tailored to their specific downstream type 2 biomarkers (including total IgE, peripheral blood eos, and FeNO) do not experience meaningful improvements in their asthma exacerbation rates
- Perhaps targeting upstream epithelial alarmins (i.e., IL-33, TSLP, IL-25) has been proposed to tackle the immunologic heterogeneity of asthma

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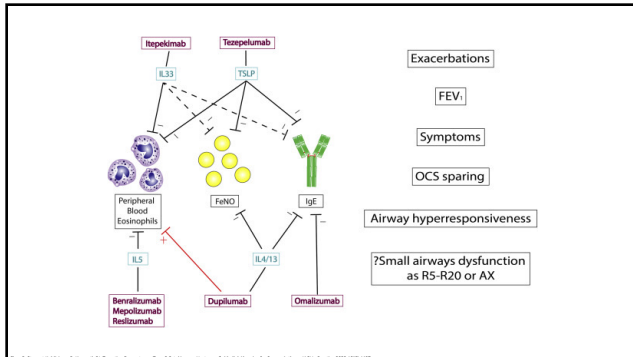
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### Anti-Thymic Stromal Lymphopoeitin (TSLP)

- Tezepelumab - a human mAb that binds TSLP
- TSLP - an epithelial cell-derived cytokine released in response to multiple triggers (allergens, viruses, pollutants)
- Driver of eosinophilic and neutrophilic inflammation in addition to structural changes to the airway
- Approved December 2021
- First biologic with at least some degree of activity in T2 low refractory severe asthma that is at present an unmet need

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### Tezepelumab

- Taken together results from phase 2/3 trials suggest that blocking the upstream alarmin TSLP with Tezepelumab results in clinically meaningful improvements in asthma control in patients with T2 high asthma with regards to **exacerbations, ACQ, and FEV<sub>1</sub>**
- Lesser degrees of improvements in T2-low asthma in relation to exacerbation reductions but not for FEV<sub>1</sub> or ACQ
- There is a lack of apparent efficacy in OCS-dependent patients

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### Which to Choose?

Depends on:

- Asthma phenotype
- Age
- Comorbidities
- Goals of therapy
- Triggers of exacerbations
- Adverse effect profile

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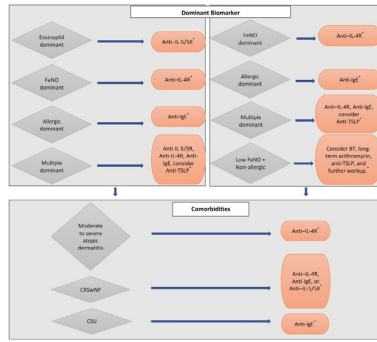
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1. Determine dominant biomarker
2. Consider comorbidities




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### CASE 1

- 35-year-old male
- Allergic sensitization to outdoor environmental aeroallergens
- Asthma flares in springtime especially
- Total serum IgE level = 500 IU/mL
- Absolute eosinophil count (AEC) of 200 cells/mcL
- FeNO 22 ppb

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- Allergic sensitization seems to be the dominant biomarker
- **OMALIZUMAB**

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**CASE 2**

- 50-year-old female
- AEC 800 cells/mcL
- 5% sputum eosinophils
- FeNO 35ppb
- Total serum IgE 300 IU/mL
- Allergic sensitization to a few trees, no seasonal variation in respiratory symptoms

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- Eosinophilia seems to be the dominant biomarker
- **ANTI-IL5/5R**
- **No compelling data suggesting any anti-IL-5/5R therapy is better than another**

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**CASE 3**

- 22-year-old male
- AEC 300 cells/mcL
- FeNO 85 ppb
- Total serum IgE 500 IU/mL
- Sensitization to pollens and animal dander, notes perennial respiratory issues
- History of great response to OCS bursts

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- Elevated FeNO level - high activity of the IL-13 pathway
- Milder eosinophilic inflammation and allergic sensitization without clinical dominance
  
- DUPILIMAB

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**CASE 4**

- 67-year-old female
- On maintenance OCS for years with inability to taper
- A previous taper led to an exacerbation requiring hospitalization
- AEC is 0 BAL (remember she is on prednisone)
- Eosinophils are 0%
- FeNO is 20 ppb
- Total serum IgE is 130 IU/mL
- No history of atopy or allergic sensitization

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- Difficulty tapering down maintenance OCS
- Indication of **DUPILIMAB** for corticosteroid-dependent asthma
- Data from OCS studies with mepolizumab and benralizumab suggest that either of these could be effective if there were any history of systemic eosinophilia

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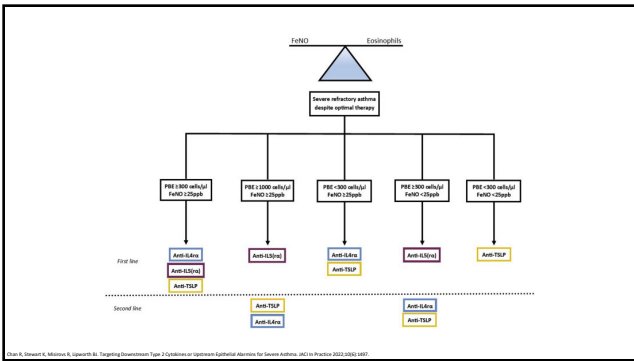
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- ### Future of Biologics and Asthma
- Which biologic should we chose for our patient?
    - Especially when the agents target similar pathways?
  - Are there predictors of which patient will respond best to each therapy?
  - How do you define a responder?
  - At what point should a switch be considered?
  - How long should use of a biologic be continued?
  - What are the long-term adverse effects?

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### Future of Biologics and Asthma

Other biologic and small-molecule therapeutics under various stages of development

- Anti-IL-33 agents – astegolimab and itepekimab
- Anti-IL-13
- Anti-IL-23p19
- Chemoattractant receptor–homologous molecule expressed on T-helper type 2 cells or prostaglandin D2 antagonists
- Anti-GATA3 DNzyme
- Toll-like receptor 9 agonists

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### Limitations/Considerations – Adherence

- Lower/worse adherence
  - Clinic- administered biologics
  - Black race
  - Hispanic ethnicity
  - Lower education
  - Medicare only insurance
  - Higher patient out-of-pocket cost
- Higher/better adherence
  - At home or hybrid administered biologics
  - Specialist access

Delavue P, et al. Factors Related to Biologic Adherence and Outcomes Among Moderate-to-Severe Asthma Patients. JGIM in Practice 2022. In press.

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### Limitations/Considerations – Costs

- Very high-cost medications
- According to data provided by pharmaceutical manufacturers, wholesale acquisition cost of an individual unit of these biologics can range from \$879 to >\$4750 (2018 US dollars)
  - Does not capture associated fees by practitioners for administration and indirect costs to patients for administration time
- More cost-effective
  - When used as part of a precision medicine strategy
  - When used in the context of an ongoing care partnership
  - Limit biologic treatment to responders
  - Use readily available biomarkers
  - Reevaluate therapy to ensure effectiveness

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### Conclusions

- Use of biomarkers can help guide biologic selection (and increase cost-effectiveness)
  - Eosinophils (blood, sputum, BAL)
  - Total serum IgE
  - FeNO
  - Evidence of allergic sensitization to environmental aeroallergens (skin testing or serum-specific IgE)
  - Atopy/ comorbidities
- Biomarkers allow for better estimation of whether people with type 2 asthma have IL-5 vs IL-4 or IL-13 predominance
- Biologics may be able to address not only asthma but also uncontrolled comorbidities

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### Conclusions

- Shared decision-making is pivotal for success and ensuring adherence to biologic therapeutics
- Provide education on risks, benefits, and logistics in the administration of these injected therapeutics
- In the future, it is expected that novel therapies, including those that target upstream cytokines and work more broadly, or ones that have more sustained durability, will be able to offer greater outcomes to many of our patients with severe asthma

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### QUESTIONS?




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