Unmasking Asthma: A Guide to Phenotypes and Targeted Care

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Objectives

- Understanding clinical heterogeneity
- Differentiate fetal types and endo types
- Trace the evolution of asthma models
- Analyzed specific asthma phenotypes
- Explore biological inflammatory mechanisms
- Utilize actionable biomarkers
- Implement precision targeted care

01. Defining Heterogeneity

Why modern respiratory medicine classifies asthma as a cluster of distinct pathophysiological syndromes rather than a singular chronic disease.

What is an asthma phenotype?

- Clinical phenotypes categorize patients by what can be observed on the outside: when the disease started, what triggers it, comorbidities, and how the patient responds to standard medications.
- Early onset allergic asthma
- Late onset eosinophilic asthma
- Obesity related asthma
- Exercise induced bronchoconstriction
- Occupational asthma
- Fixed airway limitation asthma

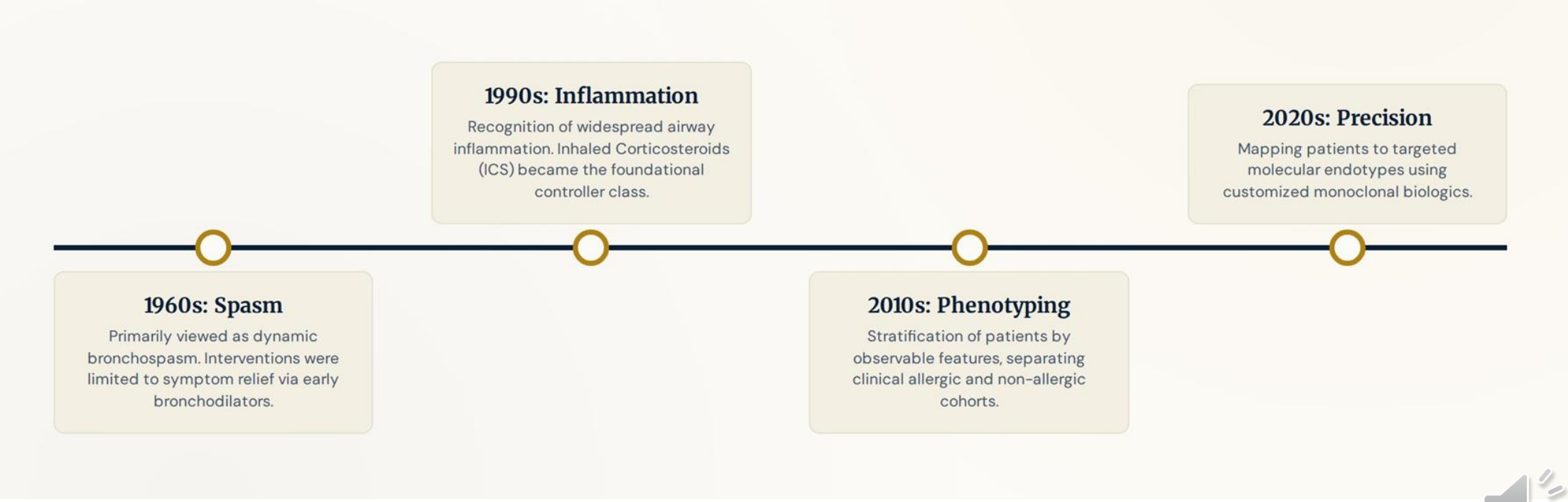
Phenotypes and endotypes

- To treat asthma effectively, medical professionals look at it through two different lenses: phenotypes and endotypes.
- Asthma Phenotype:
  - This is *what you see* on the outside. It describes the observable characteristics, triggers, and clinical presentation—like adult-onset asthma, exercise-induced asthma, or obesity-related asthma.
- Asthma Endotype:
  - This is *what is happening* on the inside. It describes the specific, distinct functional or pathological mechanism at the cellular and molecular level that drives the disease.

Asthma endotypes and inflammatory pathways

- Biological diversity focuses on what is happening at the cellular level. Medicine primarily splits this into two major immunologic categories:
- Type 2-High
  - Eosinophilic Pathway
  - Allergic/IgE Pathway
  - Key Biomarkers tracked by blood test and FeNO
- Type 2-Low
  - Neutrophilic Pathway
  - Paucigranulocytic Pathway
  - Epithelial Dysfunction

Evolution of asthma models



Cellular drivers of disease

- Key cellular mediators T2 High Asthma (Overactive Immune response)
  - Eosinophils
    - T2-High Asthma
    - Respond well to corticosteroids
  - Th2 cells and ILC2s (Innate Lymphoid Cells)
    - T2- High Asthma
    - Respond well to corticosteroids
- Neutrophils
    - T2-Low Asthma (Obesity, Late Onset Asthma)
    - Corticosteroids **do not** induce apoptosis in neutrophils. In fact, they prolong neutrophil survival by delaying their natural cell death and promoting their release from bone marrow

02. The Phenotypic Spectrum

A rigorous examination of clinical, demographic, and observable physiological patterns that segment major asthmatic populations.

Allergic (atopic) phenotype

- Early-onset
- IgE mediated
- Steroid responsiveness
- Closely associated with other atopic comorbidities such as allergic rhinitis, eczema, and food allergies

Non-allergic phenotypes

- Etiological profiles
  - Adult/Late Onset
  - Neutrophilic inflammation
  - Non- IgE Mediated pathways
  - Environmental host triggers
- Therapeutic realities
  - Poor corticosteroid responsiveness
  - Limited biologic targets
  - Focus on comorbidity and trigger management

Exploring asthma phenotypes

- Unlike childhood asthma, which is overwhelmingly driven by allergies (atopy), adult-onset asthma is highly heterogeneous and splits into several distinct phenotypes
  - Late-Onset Eosinophilic (T2-High) Phenotype
  - Aspirin-Exacerbated Respiratory Disease (AERD / Samter's Triad)
  - Obesity-Associated (T2-Low) Phenotype
  - Neutrophilic or Paucigranulocytic (T2-Low) Phenotype
- General Characteristics & Clinical Distinctions
  - Gender bias
  - Triggers
  - Steroid sensitivity
  - Role of biologics

Persistent air flow limitation (fixed airway obstruction)

- Structural airway remodeling
  - Airway remodeling
  - Subepithelial fibrosis
  - Smooth muscle hyperplasia
  - Loss of elastic recoil
- Diagnostic criteria
  - Spirometry (FEV1/FVC less than 0.70)
  - Incomplete reversibility with bronchodilators
  - Resistance to corticosteroid trials

Obesity associated asthma

- Mechanistic drivers
  - Mechanical restriction
    - Reduced FRC
    - Airway narrowing
    - Tidal breath changes
  - Metabolic signaling
    - Leptin Pro-inflammatory shift
    - Loss of adiponectin protection
    - System local inflammation
  - Steroid resistance
    - Non-Eosinophilic Target Mismatch
    - Impaired Glucocorticoid Receptor Function

03. Endotypic Mechanisms

Translating clinical phenotypes into cellular and molecular endotypes to drive biomarker-led precision decisions.

Type 2 high inflammation (Early onset asthma, Aspirin induced)

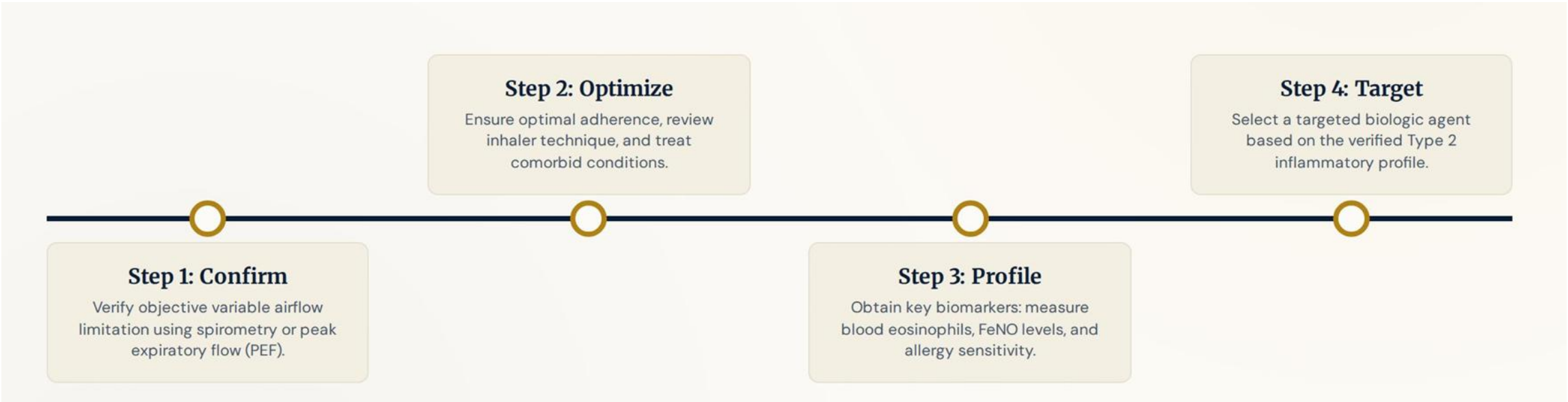
- Type 2 high (T2-high) inflammatory cascade begins at the airway lining with the release of Epithelial Alarmins.
- These proteins are rapidly secreted by airway epithelial cells when they encounter environmental triggers like viruses, bacteria, allergens, or physical pollutants
- Epithelial Alarmins
  - TSLP
  - IL-25
  - IL-33
- Interleukin cascade
  - IL-4
  - IL-13
  - IL- 5

Type 2- Low Mechanisms (Neutrophilic Asthma, Obesity Related Asthma)

- Type 2-low (T2-low) mechanism refers to a specific biological pathway in asthma that is entirely distinct from classic, allergic asthma.
- While classic asthma is driven by Type 2 helper T cells and eosinophils, T2-low asthma is characterized by an absence of typical allergic pathways and eosinophilic inflammation
- Neutrophilic drive
- Paucigranulocytic
- Corticosteroid resistant

04. Precision Targeted Care

A structured clinical framework for matching severe asthma patients with specific biologic interventions according to verified biomarker profiles.


Step 1: Confirm
Verify objective variable airflow limitation using spirometry or peak expiratory flow (PEF).
Step 2: Optimize
Ensure optimal adherence, review inhaler technique, and treat comorbid conditions.
Step 3: Profile
Obtain key biomarkers: measure blood eosinophils, FeNO levels, and allergy sensitivity.
Step 4: Target
Select a targeted biologic agent based on the verified Type 2 inflammatory profile.

Biologic therapy categories

Biologic Therapy Category	Targeted Biological Mechanism
Anti-IgE therapy	* Targets and neutralizes Immunoglobulin E (IgE) antibodies to block the root cascade of allergic hypersensitivity.
Anti-IL-5 pathways	* Inhibits Interleukin-5 signaling or its receptors to halt the maturation, recruitment, and survival of tissue-damaging eosinophils.
Upstream blockade	* **IL4-ra:** Blocks the shared alpha subunit of the Interleukin-4 receptor to simultaneously shut down both IL-4 and IL-13 tissue-remodeling pathways.
	* **T2 cytokines:** Interrupts broader Type 2 inflammatory signaling to mitigate mucus production and smooth muscle hyperreactivity.

Anti-IgE: Omalizumab

- Recombinant humanized monoclonal antibody that serves as the pioneering agent in the Anti-IgE biologic therapy class
- Mechanism and clinical profile
  - Selective Free IgE Binding
  - Interruption of the Allergic Cascade
  - Downstream Cytokine Suppression
- Indication
  - Moderate-to-Severe Persistent Allergic Asthma
  - Documented Atopic Reactivity
- Impact
  - Reduction in exasperation
  - Decrease hospital admissions

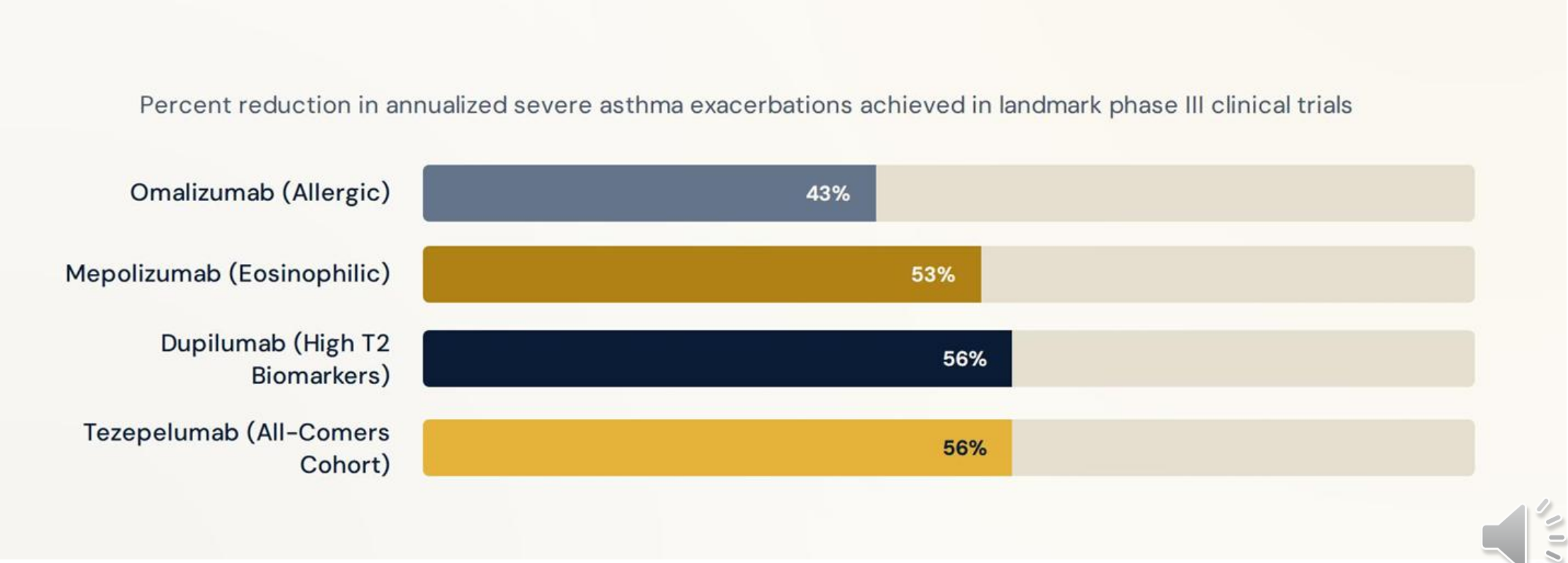
Anti-IL-4 & Anti-TSLP(Thymic Stromal Lymphopoietin)

- Used as add-on maintenance treatments for severe, persistent, or uncontrolled asthma.
- They are designed to prevent major asthma attacks (exacerbations) and improve daily lung function
- Not a rescue medication
- Dupilumab (Anti- IL-4Ra)
  - Specifically attacks Th2- high inflammatory asthma
  - Eosinophilic phenotype asthma
- Tezepelumab (Anti-TSLP and both Th2 high and low)
  - Attacks severe asthma across the board

Targeting IL-5 pathways

- Elevated levels of IL-5 have been strongly associated with various inflammatory and allergic diseases, most notably severe eosinophilic asthma and atopic dermatitis.
- Targeting the IL-5 pathway is highly effective in reducing eosinophil numbers in both the blood and tissue, thereby suppressing the chronic inflammation associated with these diseases.
- IL-5 Receptor Targeting (Benralizumab)
- IL-5 Ligand Blockade (Mepolizumab and Reslizumab)

Exasperation and rate reduction



Summary

- Clinical heterogeneity
- Phenotypes versus endotypes
- The inflammatory divide
- Actionable biomarkers
- Precision clinical pathway
- Targeted monoclonal biologics
- Proven clinical efficacy

References

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