

Biomarkers in Asthma

Markers of Inflammatory Drivers of Asthma

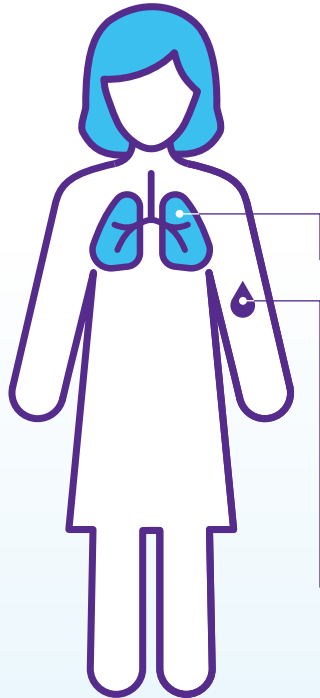
Asthma is a chronic, heterogeneous, and dynamic disease that encompasses distinct clinical phenotypes, likely arising from different pathological mechanisms.¹⁻³

A variety of cellular pathways are activated in patients with asthma (right), mediating airway inflammation, airway hyperresponsiveness, and potential remodeling.²⁻⁴

Biomarkers have been examined in individuals as a way to identify a patient's drivers of asthma inflammation and potentially allow tailored therapies for severe, uncontrolled asthma.^{2,3}

Biomarker Sampling Methods in Asthma: Advantages and Limitations

Asthma biomarkers can be sampled from different body compartments including the respiratory tract, peripheral blood, and exhaled breath. It is important to understand some of the advantages and limitations of each sampling method since they may not all provide comparable information.³



Local vs Systemic	Sampling Method ³	Key Biomarkers ³	Advantages ³	Limitations ^{1,3}
Lung-specific Measurements (local)	Bronchoscopy <ul style="list-style-type: none"> ▪ Biopsy ▪ BAL ▪ Brushings 	<ul style="list-style-type: none"> ▪ Eosinophils ▪ Cytokines and chemokines ▪ Neutrophils 	<ul style="list-style-type: none"> ▪ Tissue/disease specific method to assess airway inflammation 	<ul style="list-style-type: none"> ▪ Invasive ▪ Technically complex ▪ Often not feasible outside of trials or in very severe disease with compromised lung function and/or concomitant CVD
	Sputum induction ⁹	<ul style="list-style-type: none"> ▪ Eosinophils ▪ Cytokines and chemokines ▪ Neutrophils 	<ul style="list-style-type: none"> ▪ Reproducible cell differentials ▪ Suitable for disease phenotyping and monitoring in experienced centers 	<ul style="list-style-type: none"> ▪ Semi-invasive ▪ Technically complex and time consuming, restricted to specialized centers ▪ Adapted protocol needed for very severe disease with compromised lung function (contraindicated if FEV₁ <1L and/or with concomitant CVD)
	Exhaled breath	<ul style="list-style-type: none"> ▪ FeNO 	<ul style="list-style-type: none"> ▪ Noninvasive ▪ Simple method ▪ Suitable for disease phenotyping and monitoring 	<ul style="list-style-type: none"> ▪ Various confounding factors affecting FeNO levels ▪ Clinical utility to measure asthma control is debated
Systemic Measurements	Peripheral blood	<ul style="list-style-type: none"> ▪ Eosinophils ▪ IgE (total/specific) ▪ Cytokines and chemokines 	<ul style="list-style-type: none"> ▪ Easy to collect 	<ul style="list-style-type: none"> ▪ High intra-subject diurnal variability ▪ Does not always correlate with lung-specific measurements (ie, eosinophils during corticosteroid treatment)

Select Asthma Inflammatory Phenotypes³

Allergic	total IgE >30–76kU/L (serum)
Non-allergic eosinophilic	eosinophils: >2–3% (sputum) or >150–300 cells/μL (blood)
Mixed	eosinophils: >2–3% (sputum), >150–300 cells/μL (blood), and neutrophils: >61–76% (sputum)
Non-allergic non-eosinophilic	eosinophils: <2% (sputum), <150 cells/μL (blood), FeNO: >50 ppb, and total IgE <30–76 kU/L (serum)

⁹A diagnostic technique in which the patient inhales nebulized saline solution to expectorate sputum.¹

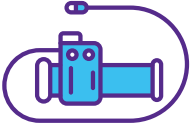



BAL, bronchoalveolar lavage; CVD, cardiovascular disorder; FeNO, fractional concentration of exhaled nitric oxide; Ig, immunoglobulin.

Biomarker Sampling Methods in Asthma: Interpreting Results

Persistent airway inflammation in patients with asthma may be driven by type 2 mechanisms, mediated by increased release of type 2 cytokines from T helper 2 and group 2 innate lymphoid cells, increased production of total and allergen-specific IgE (allergic inflammation), mast cells, and infiltration of eosinophils (eosinophilic inflammation).^{3,4}

Single or composite biomarkers may help identify inflammatory phenotype in patients with asthma.³



	Key Biomarkers ³	Description ^{1,3-5}	Cutoff Level and Interpretation ^{3,6,7}
	Bronchoscopy <ul style="list-style-type: none"> Eosinophils Neutrophils Cytokines and chemokines 	<ul style="list-style-type: none"> Airway inflammation is manifested as infiltration of the submucosa by inflammatory effector cells, such as eosinophils, neutrophils, and mast cells (tryptase+ or chymase+) 	<ul style="list-style-type: none"> Clear cutoff values lacking Increased level of eosinophils indicates airway eosinophilia Increased level of neutrophils indicates airway neutrophilia
	Sputum <ul style="list-style-type: none"> Eosinophils Neutrophils 	<ul style="list-style-type: none"> Asthma inflammatory phenotype may be diagnosed by the presence of different types of granulocytes in airway fluid obtained by sputum induction 	In general: <ul style="list-style-type: none"> Eosinophils: $\geq 3\%$ indicates sputum eosinophilia Neutrophils: $\geq 61\%$ indicates sputum neutrophilia
	Exhaled breath <ul style="list-style-type: none"> FeNO 	<ul style="list-style-type: none"> Inflamed airway epithelial cells and eosinophils may produce increased levels of NO, a process activated by type 2 cytokines such as IL-13 High FeNO in exhaled breath is considered a surrogate marker of ongoing eosinophilic airway inflammation 	<ul style="list-style-type: none"> High FeNO: >50 ppb (>35 ppb in children) may suggest airway eosinophilia likely Low FeNO: <25 ppb (<20 ppb in children) may suggest airway eosinophilia unlikely
	Peripheral blood <ul style="list-style-type: none"> Eosinophils IgE (total/specific) Cytokines (IL-4, IL-5, IL-13) 	<ul style="list-style-type: none"> Peripheral blood eosinophilia is predictive of asthma exacerbation, poor control, and greater airway obstruction¹ IgE triggers hypersensitivity to aeroallergens; increased level of serum IgE is associated with allergic asthma inflammation and/or other allergic responses Type 2 asthma is characterized by increased release of type 2 cytokines IL-4, IL-5, and/or IL-13, which induce IgE production or recruit eosinophils to the lung 	<ul style="list-style-type: none"> Eosinophils: >150 cells/μL indicates blood eosinophilia Total IgE: $>30-76$ kU/L Increased levels of serum IL-5 or IL-13 may indicate type 2 asthma inflammation

FeNO, fractional concentration of exhaled nitric oxide; Ig, immunoglobulin; IL, interleukin; NO, nitric oxide; ppb, parts per billion.

1. Tiotiu A. *Asthma Res Pract.* 2018;4:10. 2. Denton E, et al. *J Allergy Clin Immunol Pract.* 2021;9:2680-2688. 3. Diamant Z, et al. *Allergy.* 2019;74:1835-1851. 4. Fahy JV. *Nat Rev Immunol.* 2015;15:57-65. 5. Méndez-Enríquez E, Hallgren *J Front Immunol.* 2019;10:821. 6. Bradding P, et al. *Allergy Asthma Clin Immunol.* 2008;4:84-90. 7. Ray A, Kolls JK. *Trends Immunol.* 2017;38:942-954.