What's new in GINA 2025?

GINA Global Strategy for Asthma Management and Prevention

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Diagnosis of asthma in adults, adolescents and children 6–11 years

GINA 2025

Criteria for initial diagnosis in adults, adolescents and children 6–11 years

Key features

- Typical variable respiratory symptoms (wheeze, shortness of breath, chest tightness and/or cough)
  - Worsening of symptoms after exercise is very distinctive for asthma
- Variable expiratory airflow, with spirometry or peak expiratory flow (PEF) – multiple options
  - Airflow limitation does not have to be present at time of diagnosis
  - When possible, test during symptoms or in the morning
- (Limited) role of FeNO and blood eosinophils to support diagnosis of Type 2 asthma

1. HISTORY OF TYPICAL VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and/or cough (Descriptors may vary by region and by age)	• Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms worsen after end-exercise (very distinctive) • Symptoms often appear or worsen with viral infections
2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW	
Feature	*Considerations, definitions, criteria*
Excessive variability in expiratory lung function (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confidently the diagnosis of asthma can be made. If spirometry is not possible, PEF† may be used, but it is less reliable.
Positive bronchodilator (BD) responsiveness (reversibility) test with spirometry (or PEF†) When possible, test during symptoms or in the morning	Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, long-acting bronchodilators 24–48 hours (see below). *Adults*: increase from baseline in FEV_1 or FVC of ≥12% and ≥200 mL, with greater confidence if the increase is ≥15% and ≥400 mL; or increase in PEF† ≥20% if spirometry is not available *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%)
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%* *Children*: average daily diurnal PEF variability >13%*
Increase in lung function after 4 weeks of ICS-containing treatment	*Adults*: increase from baseline in FEV_1 by ≥12% and ≥200 mL (or PEF† by ≥20%) after 4 weeks of daily ICS-containing treatment *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%).
Positive bronchial provocation test	*Adults*: Fall from baseline in FEV_1 of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge, or >10% and >200 mL with standardized exercise challenge. *Children*: fall from baseline in FEV_1 of >12% predicted (or fall in PEF† >15%) with standardized exercise challenge. If FEV_1 decreases during a challenge test, check that FEV_1/FVC ratio has also decreased, since incomplete inhalation, e.g., due to inducible laryngeal obstruction or poor effort, can result in a false reduction in FEV_1.
Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of ≥12% and ≥200 mL (or in PEF† of ≥20%) between visits. *Children*: variation of ≥12% in FEV_1 (or ≥15% in PEF†) between visits
ROLE OF TYPE 2 BIOMARKERS IN DIAGNOSIS OF ASTHMA	
In patients with typical asthma symptoms, if spirometry or PEF is not available or testing is negative, elevated FeNO (adults/adolescents: >50 ppb; children: >35 ppb) or blood eosinophils above the local reference range can support the diagnosis of Type 2 asthma, but can also be due to non-asthma conditions. Lower levels of FeNO or blood eosinophils do **not** rule out asthma. FeNO and blood eosinophils vary substantially by sex, age and (for FeNO) device and site (p.216). Blood eosinophils are higher in the morning, and FeNO is lower in the morning. See Appendix A for more details (p.216).	

Criteria for initial diagnosis in adults, adolescents and children 6–11 years - variable respiratory symptoms

Box 1-2. Criteria for initial diagnosis of asthma in adults (≥18 years) and children (6–17 years)

1. HISTORY OF TYPICAL VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and/or cough (Descriptors may vary by region and by age)	• Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms worsen after end-exercise (very distinctive) • Symptoms often appear or worsen with viral infections

Criteria for initial diagnosis in adults, adolescents and children 6–11 years - variable expiratory airflow

2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW	
Feature	*Considerations, definitions, criteria*
Excessive variability in expiratory lung function (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confidently the diagnosis of asthma can be made. If spirometry is not possible, PEF† may be used, but it is less reliable.
Positive bronchodilator (BD) responsiveness (reversibility) test with spirometry (or PEF†) When possible, test during symptoms or in the morning	Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, long-acting bronchodilators 24–48 hours (see below). *Adults*: increase from baseline in FEV_1 or FVC of ≥12% and ≥200 mL, with greater confidence if the increase is ≥15% and ≥400 mL; or increase in PEF† ≥20% if spirometry is not available *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%)
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%* *Children*: average daily diurnal PEF variability >13%*

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist

Criteria for initial diagnosis in adults, adolescents and children 6–11 years – variable expiratory airflow *(continued)*

Increase in lung function after 4 weeks of ICS-containing treatment	*Adults*: increase from baseline in FEV_1 by ≥12% and ≥200 mL (or PEF† by ≥20%) after 4 weeks of daily ICS-containing treatment *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%).
Positive bronchial provocation test	*Adults*: Fall from baseline in FEV_1 of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge, or >10% and >200 mL with standardized exercise challenge. *Children*: fall from baseline in FEV_1 of >12% predicted (or fall in PEF† >15%) with standardized exercise challenge. If FEV_1 decreases during a challenge test, check that FEV_1/FVC ratio has also decreased, since incomplete inhalation, e.g., due to inducible laryngeal obstruction or poor effort, can result in a false reduction in FEV_1.
Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of ≥12% and ≥200 mL (or in PEF† of ≥20%) between visits. *Children*: variation of ≥12% in FEV_1 (or ≥15% in PEF†) between visits

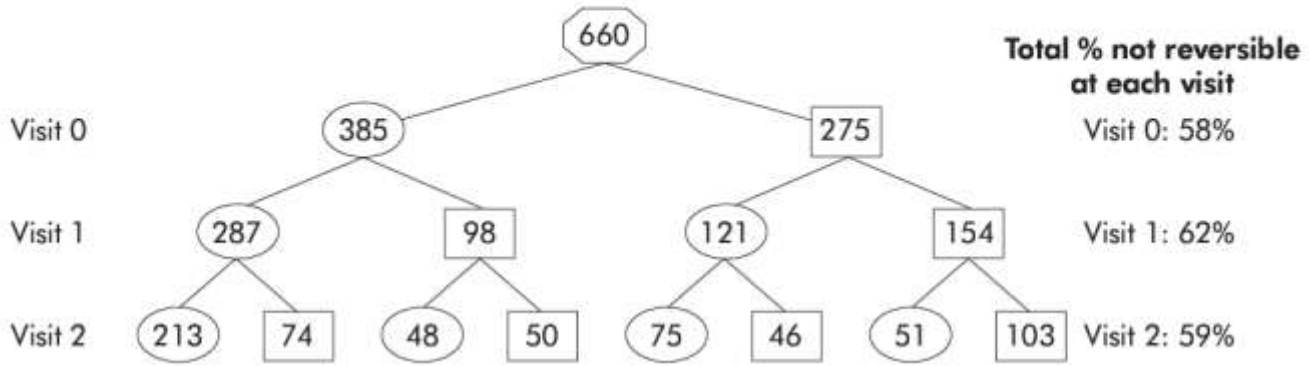
FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroid; PEF: peak expiratory flow; SABA: short-acting $beta_2$-agonist

Bronchodilator reversibility testing in chronic obstructive pulmonary disease

P M A Calverley, P S Burge, S Spencer, J A Anderson, P W Jones, for the ISOLDE Study Investigators

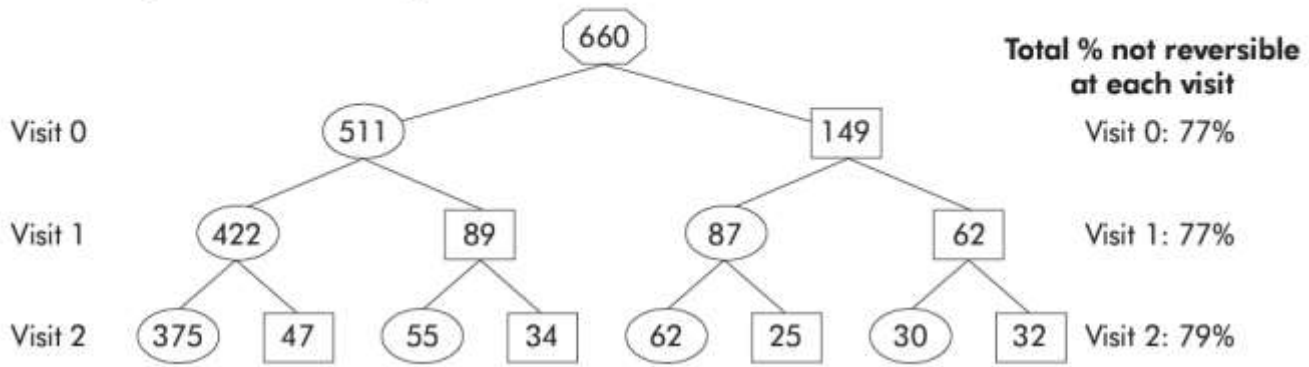
A

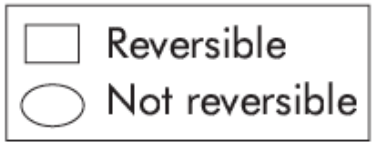
Reversibility defined according to ATS criteria



B

Reversibility defined according to ERS criteria



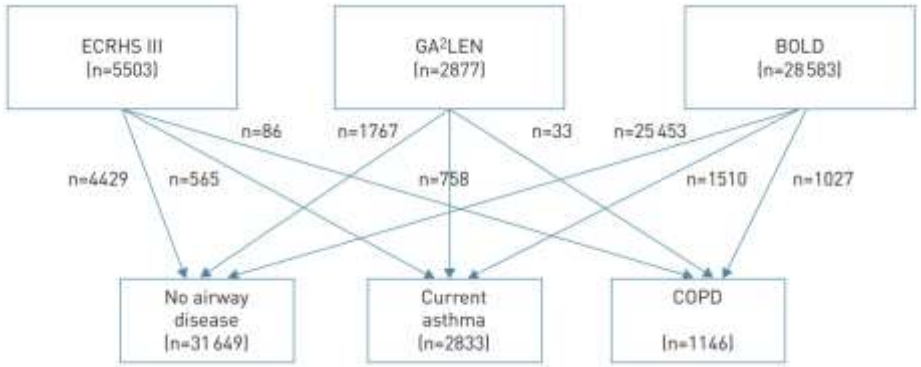


Thorax 2003;**58**:659–664

Bronchodilator reversibility in asthma and COPD: findings from three large population studies

TABLE 1 Characteristics and prevalence of bronchodilator reversibility

	No airway disease (controls)	Current asthma	p-value *versus* controls	COPD
Subjects n	31 649	2833		1146
Characteristics				
Female	53.0	63.1	<0.0001	26.4
Age years	54±11	53±12	<0.0001	60±11
Smoking history			<0.0001	
Never-smoker	61.2	54.6		0
Ex-smoker	21.8	30.4		40.9
Current smoker	17.0	15.1		59.1
BMI kg·m^{-2}			<0.0001	
<20	8.3	5.3		14.8
20–25	33.6	29.6		37.4
>25–30	35.3	32.2		32.8
>30	22.8	32.9		15.0
Pre-bronchodilator FEV_1 % pred	87±18	78±21	<0.0001	65±20
Pre-bronchodilator FVC % pred	90±18	88±18	<0.0001	87±20
Pre-bronchodilator FEV_1/FVC %	77±7	69±13	<0.0001	57±10
Post-bronchodilator FEV_1 % pred	89±18	82±21	<0.0001	69±20
Post-bronchodilator FVC % pred	90±18	90±18	>0.99	92±20
Post-bronchodilator FEV_1/FVC %	79±7	73±12	<0.0001	58±9
Flow response				
ΔFEV_1 ⩾12% from baseline	5.9	20.2	<0.0001	24.5
ΔFEV_1 ⩾10% pred	8.9	25.8	<0.0001	29.8
ΔFEV_1 ⩾12% and 200 mL from baseline	5.1	17.3	<0.0001	18.4



Eur Respir J 2019; 54: 1900561

Bronchodilator (BD) responsiveness

- **Untreated asthma:** patients obtain quick symptomatic relief with rapid-onset BD
  - Reflected in an increase in FEV_1 and PEF (and sometimes FVC) within 10-15 minutes
- **Random BD testing** has very limited utility, especially if long after disease onset
  - Asthma is variable: symptoms (and bronchoconstriction) not present all the time
  - ICS-containing treatment → increased pre-bronchodilator FEV_1 → decreased BD responsiveness
  - Longer asthma duration → some patients develop persistent airflow limitation → decreased BD responsiveness
  - Some patients with a diagnosis of COPD (with/without asthma) have significant BD responsiveness
- **Current ERS/ATS criterion for BD responsiveness in clinical practice** is an increase in FEV_1 or FVC from baseline by ≥12% and ≥200 mL of the **baseline** value
  - Used as one of gold standards in 2022 ERS Guidelines on Diagnosis of Asthma *(Louis et al, ERJ 2022)*
- **ERS/ATS Technical Standards Committee** *(Stanojevic et al, ERJ 2021)* proposed changing this criterion to an increase in FEV_1 or FVC from baseline by >10% of the **predicted** value
  - Based on data for mortality; not yet widely compared with other diagnostic tests for asthma
  - The Technical Committee did not advocate adoption of this change for clinical practice
- GINA will review this again when more data are available; no change recommended in the meantime

Role of Type 2 biomarkers in initial diagnosis of asthma in adults, adolescents and children 6–11 years

- In a patient with typical asthma symptoms, if spirometry or PEF is not available, or testing is negative, the diagnosis of Type 2 asthma is supported by:
  - FeNO: >50 ppb (adults/adolescents); >35 ppb (children)
  - Blood eosinophil count: above the national/regional reference range
- However, blood eosinophils and FeNO can also be elevated because of other non-asthma conditions, including allergic conditions and parasitic infections
  - Many factors affect FeNO and blood eosinophil counts, including time of day
- Low blood eosinophils and low FeNO do not rule out asthma

FeNO: fractional exhaled nitric oxide; PEF: peak expiratory flow

Factors affecting blood eosinophils and FeNO in adults/adolescents

Blood eosinophils are higher:

- In males than females
- In the morning than the afternoon
- In current smokers
- With parasitic infections
- In allergic diseases, e.g., atopic dermatitis, allergic rhinitis, or after allergen exposure
- In other non-asthma conditions, e.g., eosinophilic bronchitis, EGPA

Blood eosinophils are lower:

- In some asthma phenotypes
- In patients taking oral corticosteroids (also with inhaled or nasal corticosteroids)

FeNO is higher:

- In males than females
- In the afternoon than the morning
- In allergic diseases, e.g., atopic dermatitis, allergic rhinitis
- About 24 hours after allergen exposure (if sensitized)

FeNO is lower:

- In current smokers
- During bronchoconstriction and with lower lung function
- During the early allergic response
- In patients taking inhaled corticosteroids (also with oral or nasal corticosteroids)

EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide

Clinical utility of Type 2 biomarkers in adults/adolescents with asthma

- Phenotyping in patients with confirmed diagnosis of asthma
  - Blood eosinophil count ≥ upper limit of normal (regional/national) is consistent with eosinophilic asthma
  - FeNO >50ppb in ICS-naïve (or ≥25 ppb on medium-dose ICS, or ≥20 ppb on high-dose ICS) is consistent with eosinophilic asthma
- Prognosis: association with severe exacerbations
  - In ICS-treated patients with a history of ≥1 exacerbations in previous year, high eosinophils or high FeNO are associated with higher risk of exacerbations
  - Greatest risk if both blood eosinophils and FeNO are high
  - Other factors are also associated with risk of severe exacerbations, independent of Type 2 biomarkers, including exacerbation history, poor symptom control, low lung function, smoking history, allergic rhinitis *(e.g., Meulmeester et al, Lancet Respir Med 2025)*

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids

Clinical utility of Type 2 biomarkers in adults/adolescents with asthma (continued)

- Selecting treatment or predicting response
  - **AIR-only and MART** reduce severe exacerbations compared with regimens with a SABA reliever in patients with low or high blood eosinophils or FeNO *(Beasley et al, NEJMed 2019; Hardy et al, Lancet 2019; Brusselle et al, ERJ 2021)*, i.e. independent of Type 2 biomarkers
    - For MART, even greater benefit when blood eosinophils are high *(Brusselle et al, ERJ 2021)*
  - **If FeNO is high and asthma is uncontrolled** despite medium or high-dose ICS-LABA: first check and correct adherence and inhaler technique before considering increase of ICS dose or adding biologic therapy *(e.g. Heaney et al, AJRCCM 2019)*
  - **If both blood eosinophils and FeNO are low**, consider other treatment options before increasing ICS dose (see GINA severe asthma decision tree)

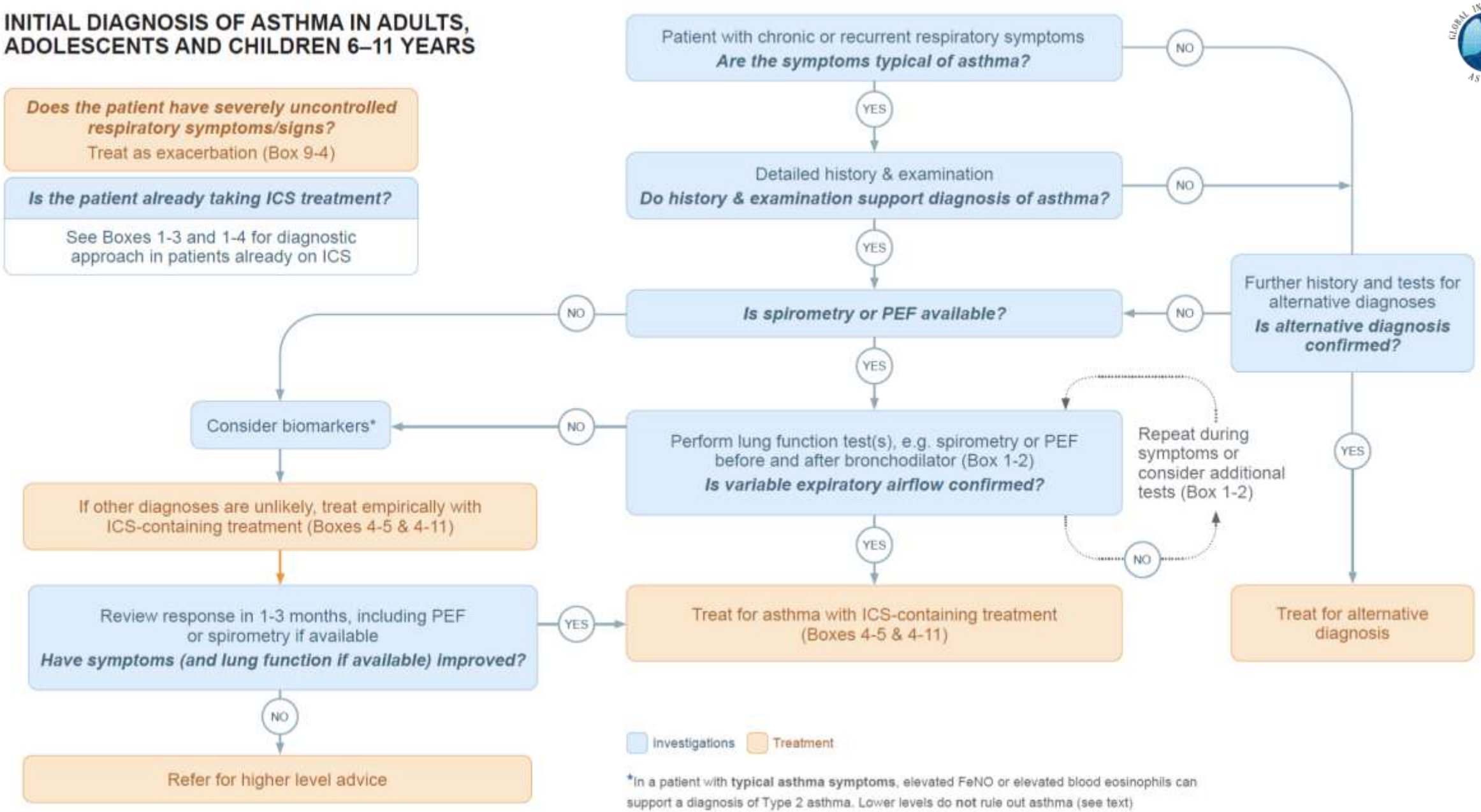
AIR:anti-inflammatory reliever; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; MART: maintenance-and-reliever therapy with ICS-formoterol; SABA: short-acting beta$_2$-agonist

Clinical utility of Type 2 biomarkers in adults/adolescents with asthma *(continued)*

- Selecting treatment in severe asthma
  - May need to repeat blood eosinophils and FeNO up to 3 times, if not initially elevated
  - Measure ≥1–2 weeks after OCS burst, or on lowest OCS dose, or after pausing OCS for 1–2 days
- Predicting response in severe asthma
  - High blood eosinophil count in patients taking medium- to high-dose ICS-LABA predicts better asthma response to all current biologics, compared with lower eosinophil count
  - High FeNO predicts better asthma response to add-on dupilumab, omalizumab and tezepelumab than a lower FeNO
  - Efficacy of anti-IL5/5R (mepolizumab, reslizumab, benralizumab) is independent of FeNO levels
  - Patients with severe asthma treated with dupilumab or tezepelumab have the greatest clinical response if both blood eosinophils and FeNO (pre-biologic) are high, compared with lower levels

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; IL: interleukin; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

INITIAL DIAGNOSIS OF ASTHMA IN ADULTS, ADOLESCENTS AND CHILDREN 6–11 YEARS



FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; PEF: peak expiratory flow