Defining T2 high and T2 low asthma in daily clinical practice

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- Roche
- Sanofi
- Teva

The Problem: Asthma is a Heterogeneous Disease

Asthma is a complex diseases with patient to patient differences in:	
Triggers and drivers	Degree of inflammation
Severity of symptoms	Response to treatment

**Identifying the different patients groups (phenotypes)
is vital to improve therapeutic options**

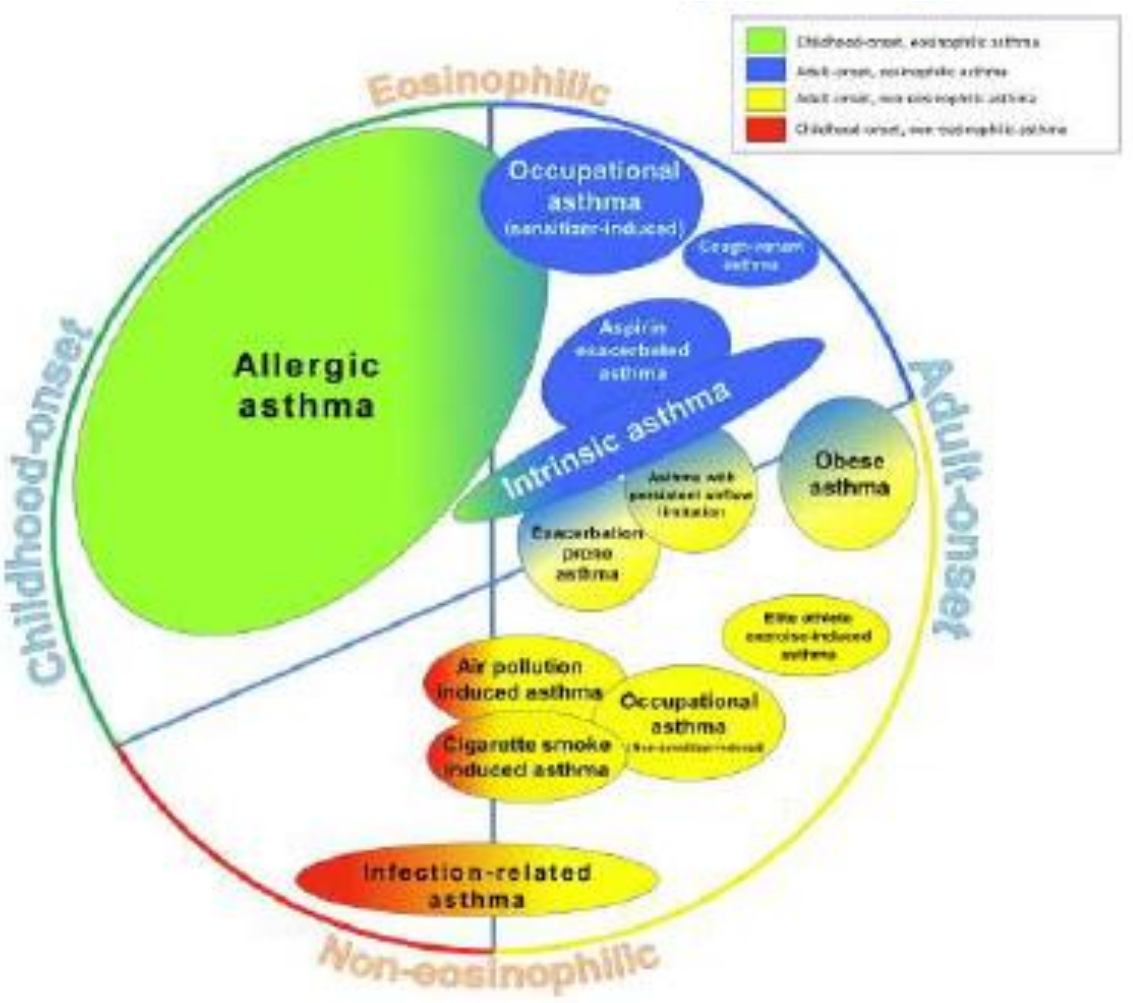
Approaches to Asthma Phenotyping

Age at onset
- Early onset likely to be atopic/allergic
- Later onset more heterogeneous

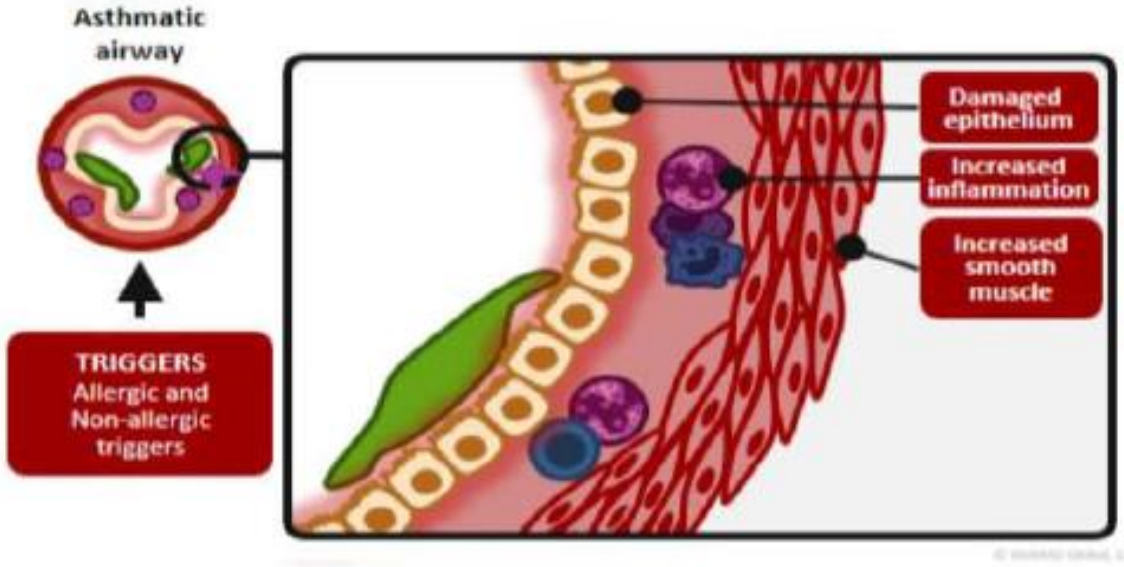
Patient exposures/triggers and host characteristics
- Age
- Smoking and other exposures
- BMI
- Infection triggers

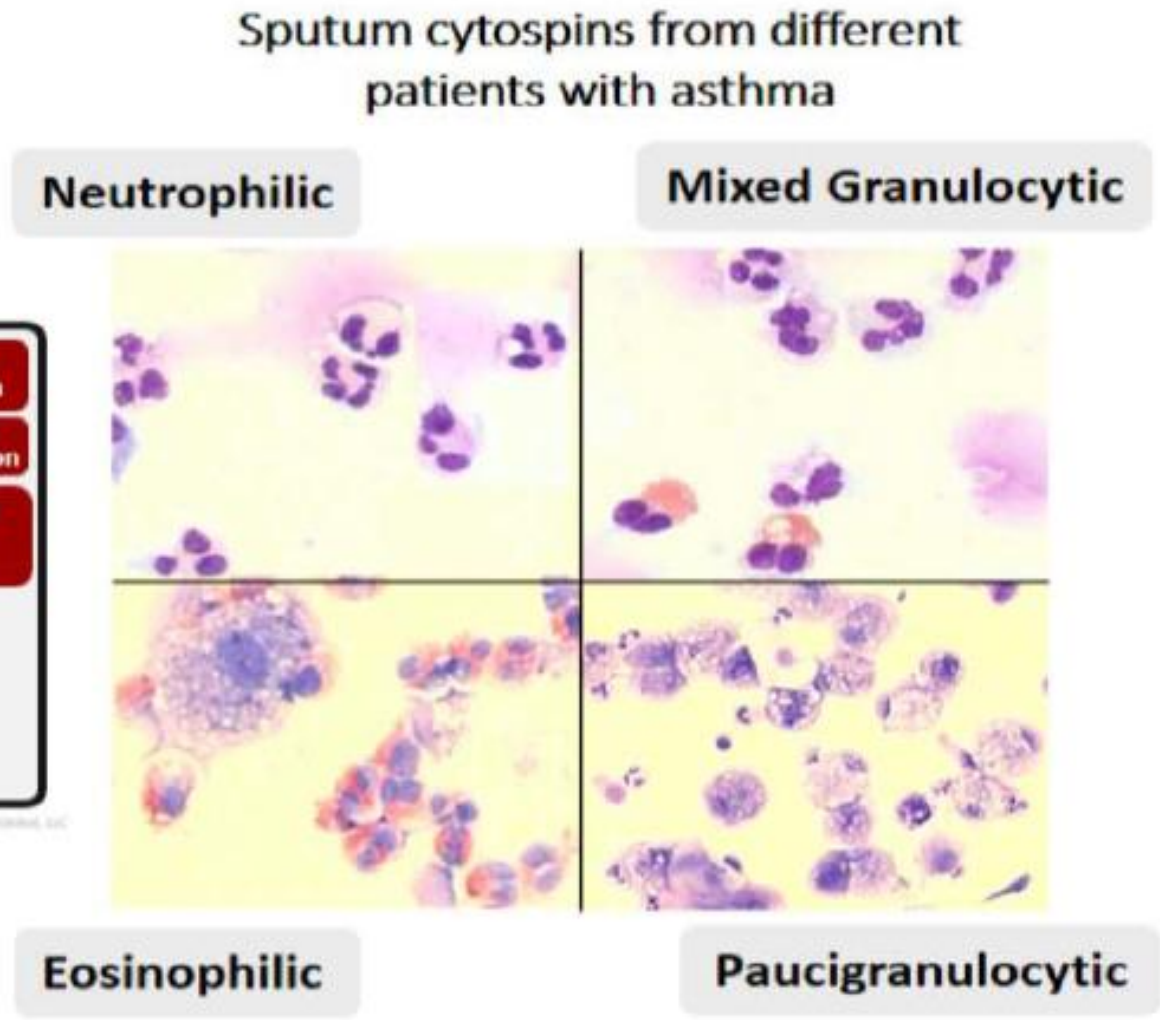
Asthma course
- Frequent exacerbation

Biomarkers
- T2- inflammation
  - Sputum and blood eosinophils
  - FeNO
  - IgE/atopy
- Absence of T2- inflammation
  - Sputum neutrophils
  - Paucigranulocytic



Using Sputum for Asthma Phenotypes





Brightling CE. *Chest* 2006; 129:1344-8

Biomarkers: Their Role in Asthma Phenotyping

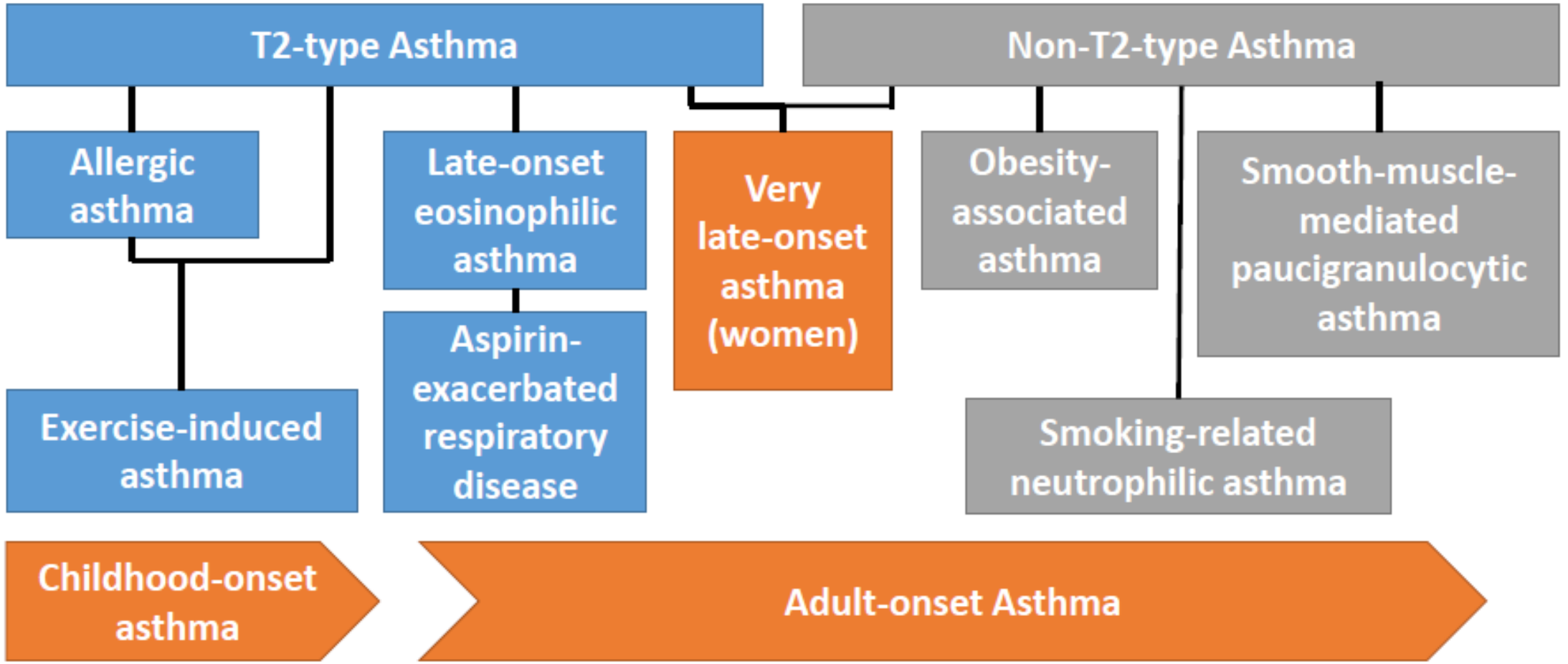
Blood eosinophils

FeNO

IgE/RAST

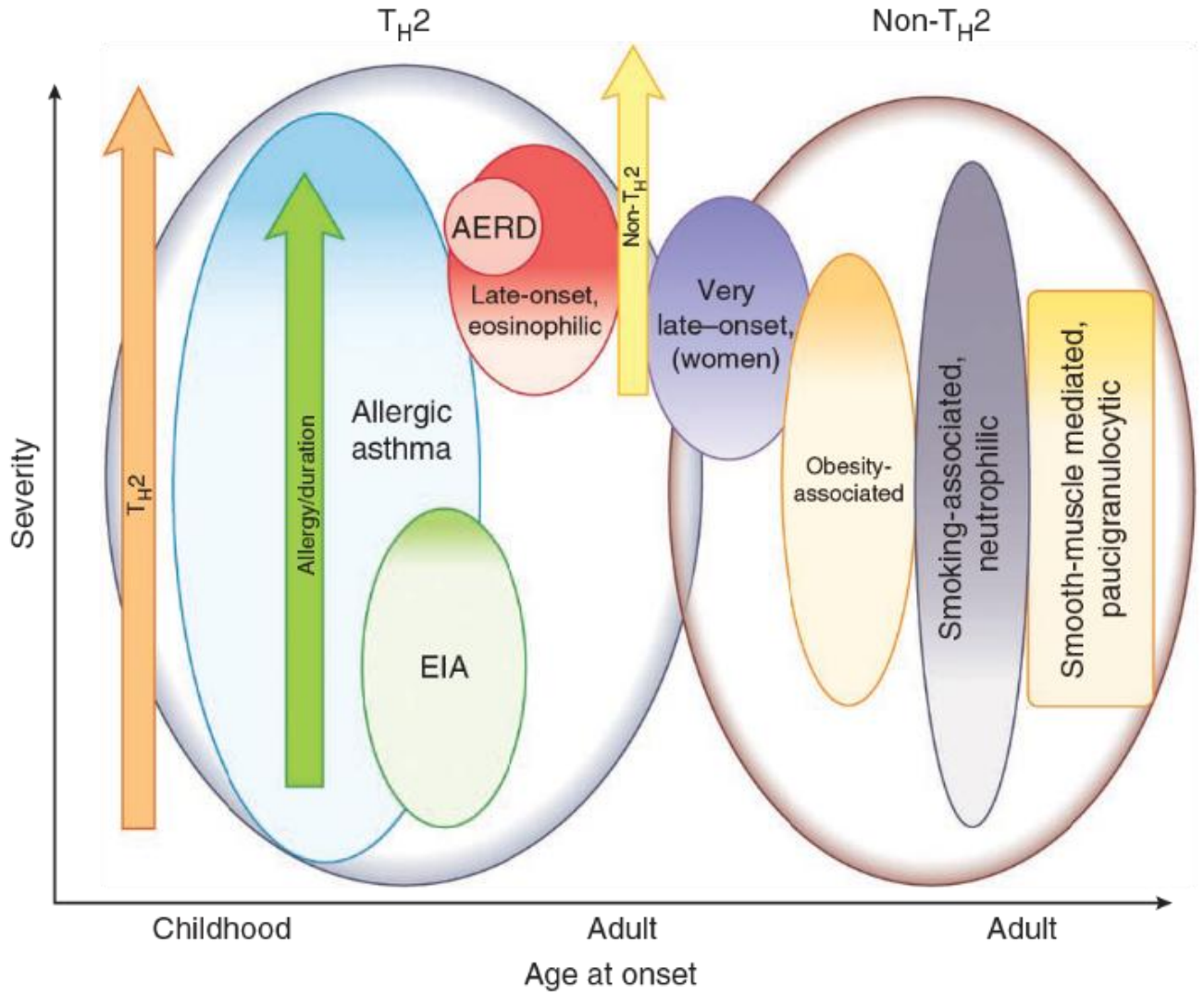
Adapted from: Kim MA, et al. Curr Opin Allergy Clin Immunol. 2014;14(1):49-54; Chung KF, et al. Eur Respir J. 2014;43(2):343-373; and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. www.ginasthma.org. Accessed November, 2019.

Asthma Phenotypes



Holgate ST, et al. *Nat Rev Dis Primers.* 2015;1:15025

Theoretical Grouping of Emerging Asthma Phenotypes Based on the Distinction Between Th2-high and Non-Th2 Asthma



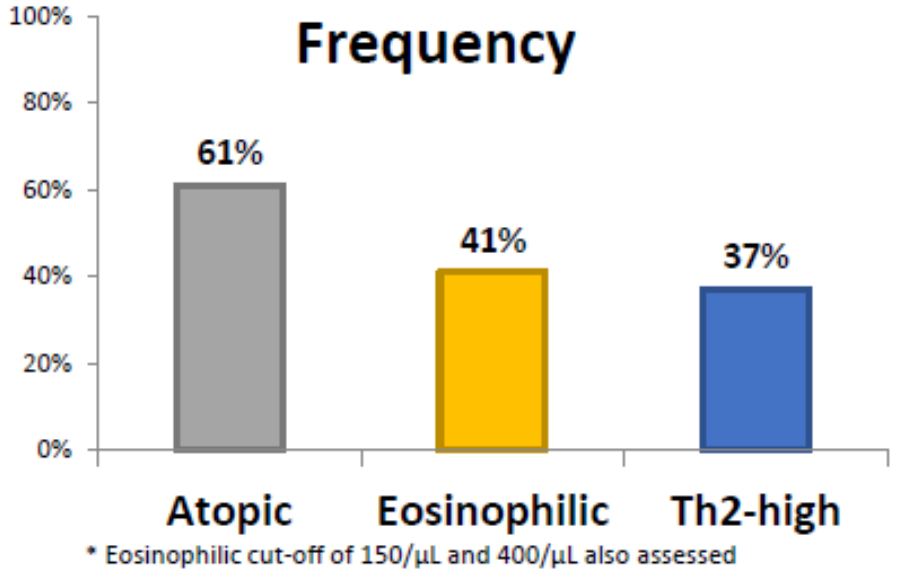
AERD, Aspirin-exacerbated respiratory disease; EIA, Exercised-induced asthma; Adapted from Wenzel SE. Nat Med 2012; 18:716-25

Frequency and Overlap of Asthma Phenotypes in the General Asthma Population

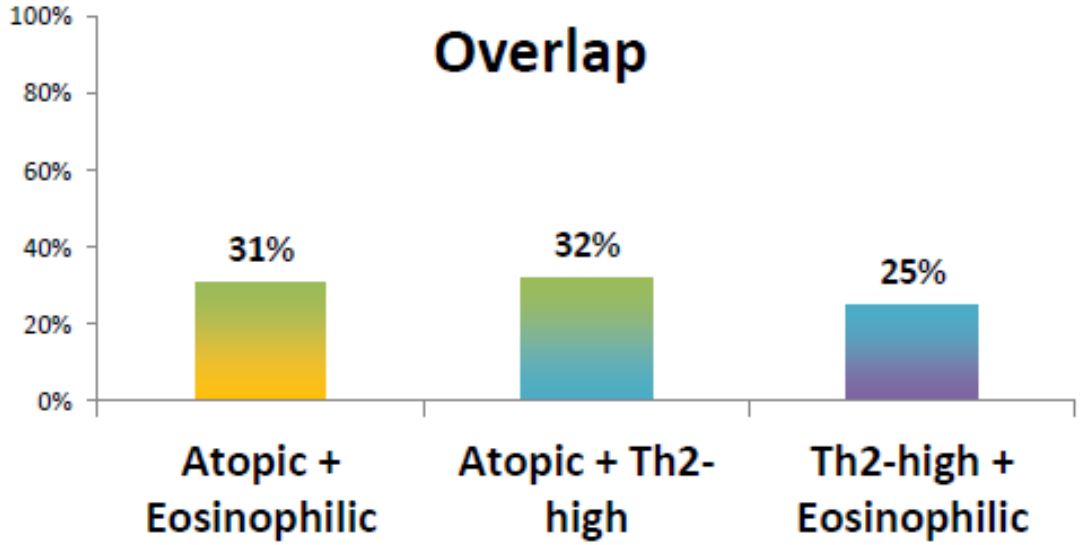
Data from NHANES (2005–2006) of 310 adults with self-reported asthma

Asthma Phenotypes

- **Atopic:** allergen specific IgE ≥0.35 IU/mL
- **Th2-high:** algorithm requiring total IgE ≥100 IU/mL and eosinophils ≥140/µL
- **Eosinophilic:** blood eosinophils ≥300/µL*



* Eosinophilic cut-off of 150/µL and 400/µL also assessed



Adapted from Tran TN, et al. *Ann Allergy Asthma Immunol* 2016; 116:37–42

Overlap between atopic/allergic and eosinophilic phenotype in a general asthma population?

Frequency table of eosinophilic, atopic, and overlap of atopic and eosinophilic asthma phenotypes

Asthma phenotype	Children % (6-17 years)	Adults % (18-64 years)	p-value
Eosinophilic asthma			
Cutoff of 150/µL	78	69	0.13
Cutoff of 300/µL	57	41	0.02
Atopic* asthma	63	61	0.63

What is the overlap?

Asthma phenotype	Children % (6-17 years)	Adults % (18-64 years)
Frequency of atopics among Eosinophilic asthmatics		
Cutoff of 150/µL	72	81
Cutoff of 300/µL	68	74
Frequency of eosinophilic among Atopic asthmatics		
Cutoff of 150/µL	89	75
Cutoff of 300/µL	78	51

Atopic asthma was defined as current asthmatic patients with an allergen-specific IgE level of 0.35 IU/mL to any of the 9 tested perennial allergens, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat epithelium and dander, dog dander, German cockroach, *Alternaria alternata*, *Aspergillus fumigatus*, and rat and mouse urine proteins.

Tran et al., Ann Allergy Asthma Immunol 2016; 116:37-42

Overlap between atopic/allergic and eosinophilic phenotype in severe asthma

Blood eosinophil count in the 12 months before omalizumab initiation

		Minors n=149	Adults n=723
Eosinophil granulocytes (cells/µl)	Analysed	149	723
	Mean (± SD)	684.6 (± 507.6)	450.6 (± 600.4)
	Median	**619**	**308**
	Q1–Q3	280–930	166–560
	Min–Max	0–2640	0–8885

Humbert M, et al. *Eur Respir J* 2018

Overlap between atopic/allergic and eosinophilic phenotype in severe asthma

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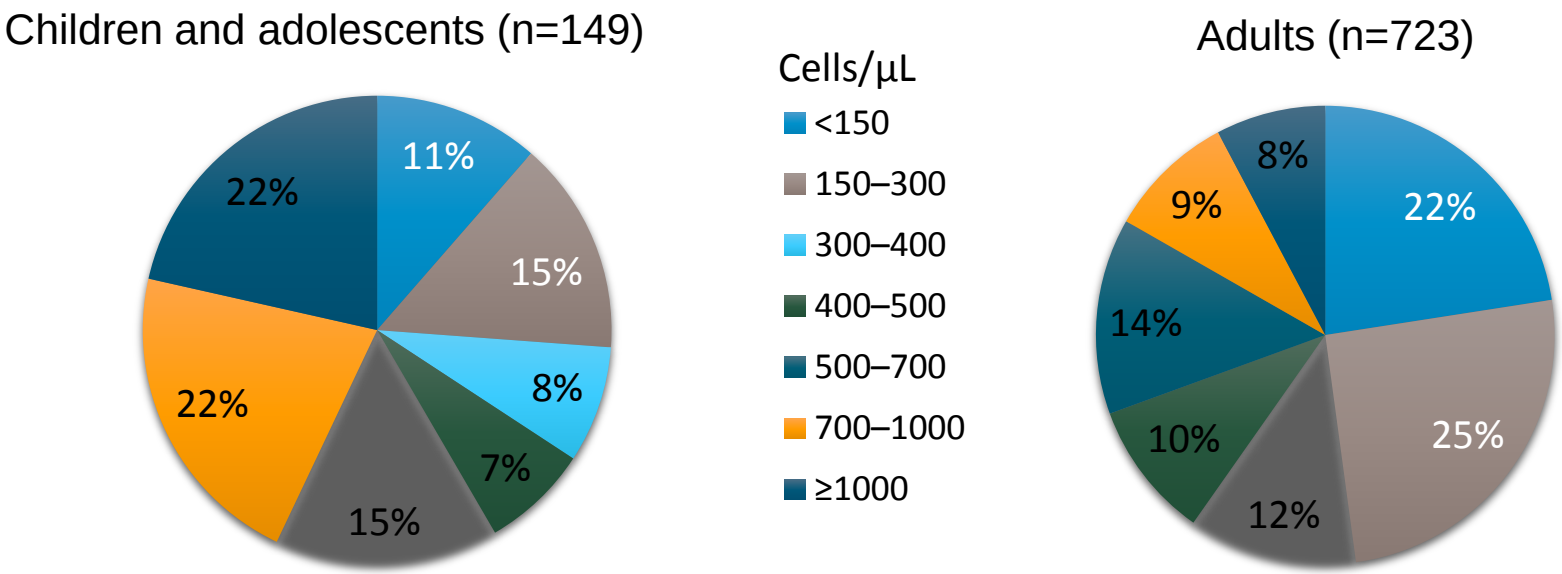


Cells/µL	Minors (n=149)	Adults (n=723)
<150	17 (11.4%)	163 (22.5%)
≥150	**132 (88.5%)**	**560 (77.5%)**
≥300	**110 (73.8%)**	**377 (52.1%)**
≥400	98 (65.8%)	291 (40.2%)
≥500	87 (58.4%)	221 (30.6%)
≥1000	32 (21.5%)	56 (7.7%)

Humbert M, et al. *Eur Respir J* 2018

Comparison of Type-2 Inflammation Biomarkers in Asthma

Biomarker	Type 2 Levels			Limitations
	Low	Medium	High	
Total IgE (IU)	<30	31–149	>150	Affected by age; poor predictor of response rate to biologic therapy. Does not correlate well with asthma severity. Elevations are not specific to asthma (also elevated in atopic dermatitis, allergic bronchopulmonary aspergillosis, etc.)
Blood eosinophils (cells/µL)	<150	151– 399	>400	Affected by weight, allergen exposure, steroids, and infection; optimal cut off value varies per therapy. Elevations are not specific to asthma (also elevated in allergic rhinitis, drug reactions, etc.)
Sputum eosinophils	-	-	≥3%	Semi-invasive; confined to research settings
FeNO (ppb)	<25	26–49	>50	Affected by age, weight, sex, smoking, and respiratory infections
Investigational				
Serum periostin (ng/mL)	-	-	≥50	Unknown competing causes of systemic increases; unclear differences between asthma and healthy subjects; studied only in context of anti-IL-13 and anti-IgE therapy
DPP-4	-	-	>Median	One of the newer biomarkers, lacks data from confirmatory studies in asthma

Adapted from Parulekar AD, et al. Curr Opin Pulm Med 2016; 22:59–68 & Peters MC, et al. Curr Allergy Asthma Rep 2016

Clinical Features and Biomarkers in Allergic and Eosinophilic-predominant Asthma

An algorithmic approach for the treatment of severe uncontrolled asthma

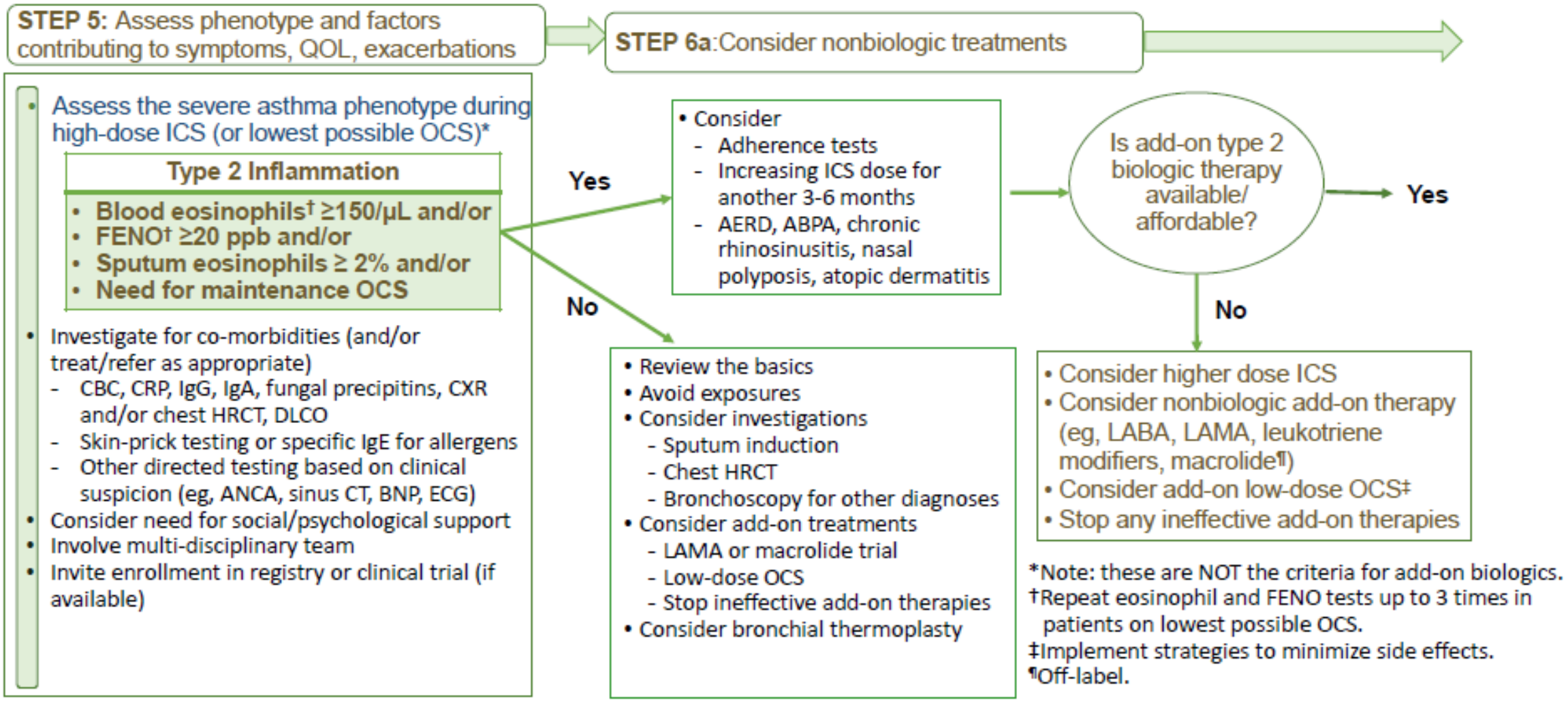
Eleftherios Zervas[1], Konstantinos Samitas[1], Andriana I. Papaioannou[2], Petros Bakakos[3], Stelios Loukides[2] and Mina Gaga[1]

	A: allergic-predominant asthma	B: eosinophilic-predominant asthma
1	Early onset	Late onset
2	SPT/RAST+ with clinically significant allergies#	SPT/RAST– or + with no clinically significant allergies
3	IgE >100 IU·mL^{-1}	IgE <100 IU·mL^{-1}
4	Allergic rhinitis	Nasal polyps
5	High *F*ENO (30–50 ppb)	Very high *F*ENO (>50 ppb)
6	Blood eosinophils <300 cells·µL^{-1}	Blood eosinophils >300 cells·µL^{-1}#

SPT: skin prick test; RAST: radioallergosorbent test; *F*ENO: exhaled nitric oxide fraction. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic- or eosinophilic-predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma. #: obligatory characteristics for allergic and/or eosinophilic asthma.

Zervas E. et al. ERJ Open Res 2018; 4: 00125-2017

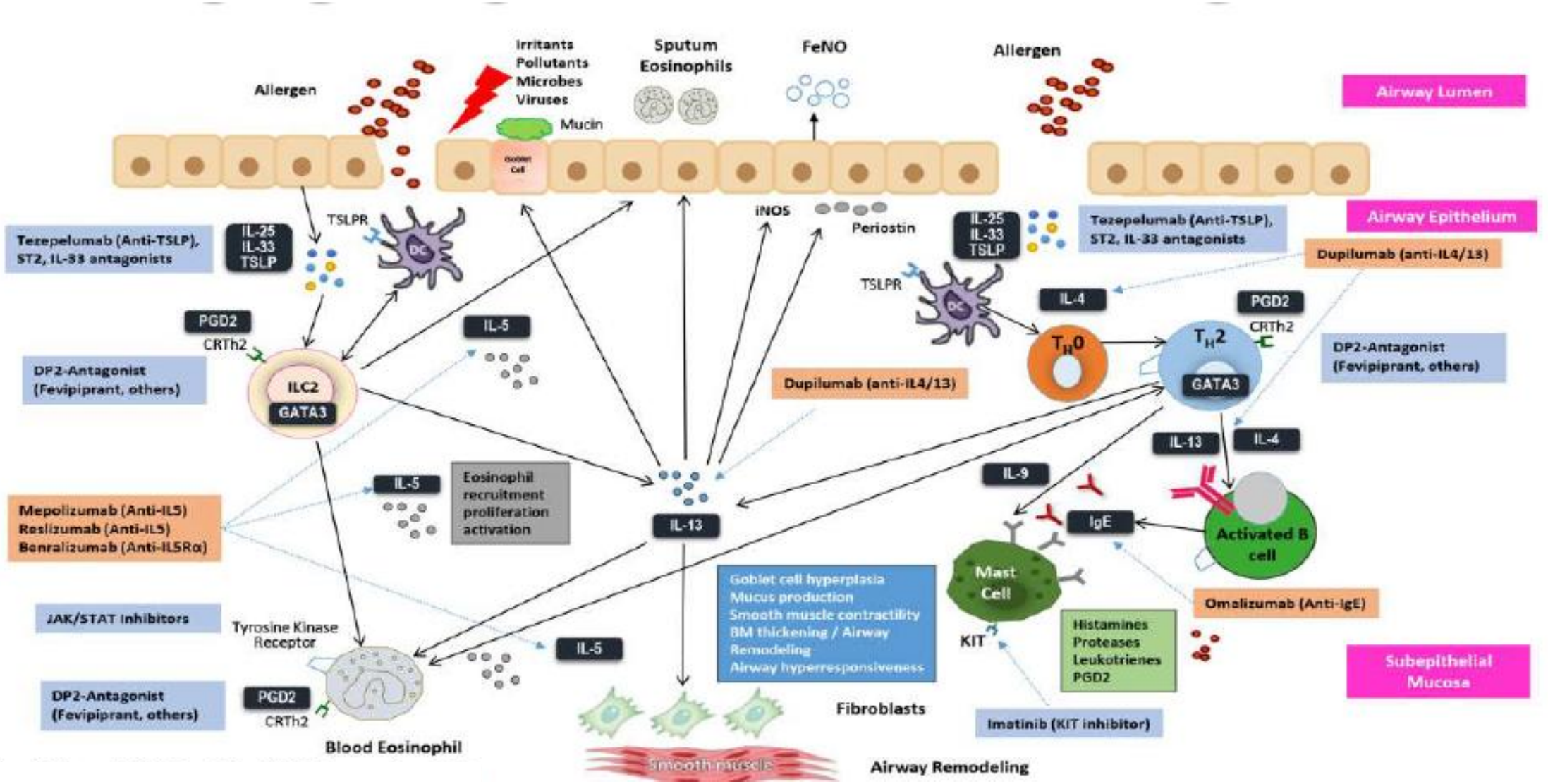
Assessing Severe Asthma Phenotype



ABPA = allergic bronchopulmonary aspergillosis; AERD = aspirin-exacerbated respiratory disease; ANCA = antineutrophil cytoplasmic antibodies; BNP = brain natriuretic peptide; DLCO = diffusing capacity of the lungs for CO.

GINA. Global Strategy for Asthma Management and Prevention: 2019 Update. ww.ginasthma.org.

Emerging Targets for Severe T2 High Asthma



Adapted from Assaf S, Hanania NA. Curr Opin All Clin Immunology 2019

Treatment of Type 2 Low Asthma

40 - 50% of asthma patients do not have Type 2 inflammation

- Severe, uncontrolled asthma without evidence for Type 2 inflammation referred to as “Type 2 low asthma”

Potential treatments for Type 2 low asthma:

- IL-17 indirectly recruits neutrophils
- IL-8 chemoattractant for neutrophils
- Macrolide antibiotics
- Bronchial thermoplasty
- Weight loss / bariatric surgery in case of obesity

Fajt ML, et al. Allergy Asthma Immunol Res 2017; 9:3-14
Zervas E. et al. ERJ Open Res 2018; 4: 00125-2017

Goals of Asthma Management: Reduce Current Impairment and Future Risk

Improve

- Symptom control (daytime symptoms, night-time awakening)
- Management of comorbidities
- Lung function

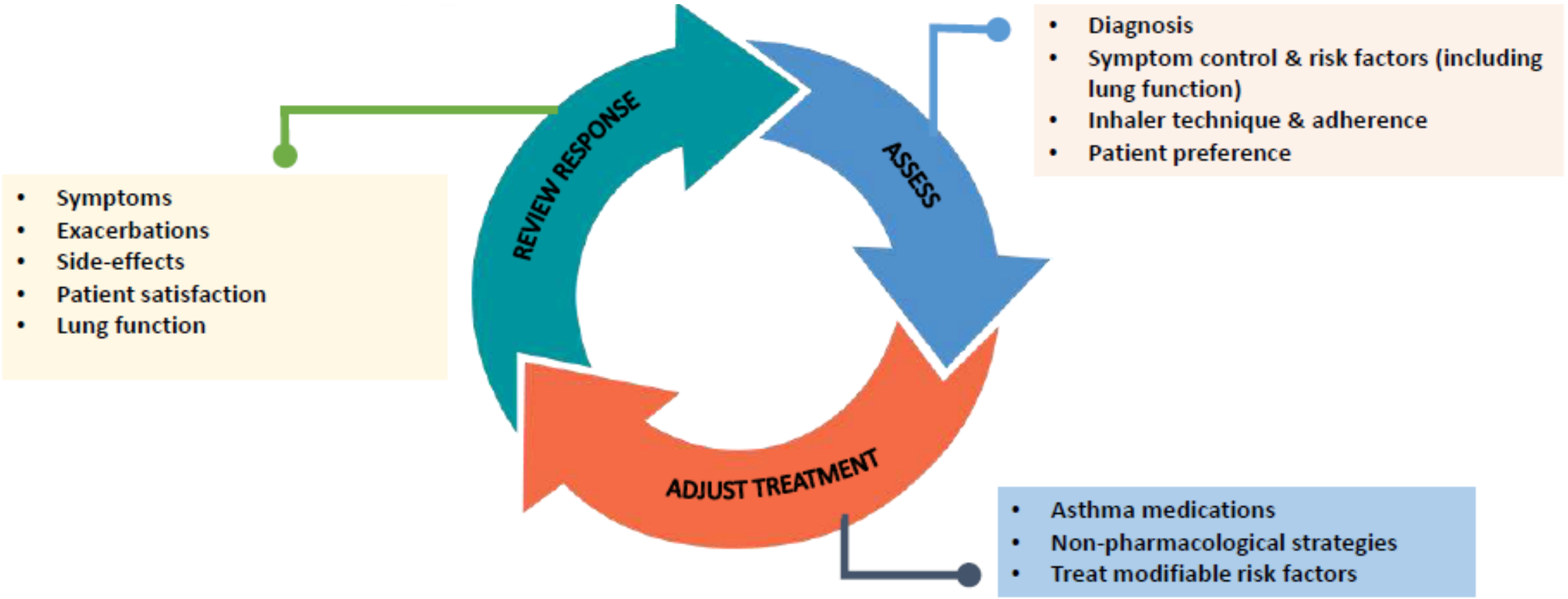
Reduce

- Exacerbations
- Rescue medication
- Treatment related AEs
- Emergency visits

Effective asthma management requires a partnership between patient and healthcare provider to define and achieve treatment goals

2019 GINA report, global strategy for asthma management and prevention. http://ginasthma.org/2019-gina-report-global-strategy-for-asthma-management-andprevention;
NHLBI. NAEPP EPR-3: guidelines for the diagnosis and management of asthma. Full report 2007. http://www.nhlbi.nih.gov/healthpro/guidelines/current/asthma-guidelines/full-report.

GINA Recommends a Control-Based Asthma Management Strategy: A Continuous Process



2019 GINA report, Global strategy for asthma management and prevention. http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention

Manage Allergic and Non-allergic Triggers of Asthma

Common Allergic Triggers

- House dust mite
- Pollen
- Mold
- Ragweed
- Cockroach
- Pet dander

Common Non-allergic Triggers

- Ozone
- Cigarette smoke
- Exercise
- Diesel particles
- Respiratory infection
- Cold air

Diagnostic Testing: Allergy skin tests, Blood tests (RAST)- allergen specific IgE

National Heart, Lung, and Blood Institute. NAEPP Expert Panel Report 3. Bethesda, MD: National Institutes of Health; 2007.

Factors Impacting Biologic Therapy Selection

Patient Characteristics
(*e.g.*, BMI, age)

Asthma phenotype and endotype

Concurrent comorbidities

Safety and efficacy profiles

Route of Administration
(IV vs SC)

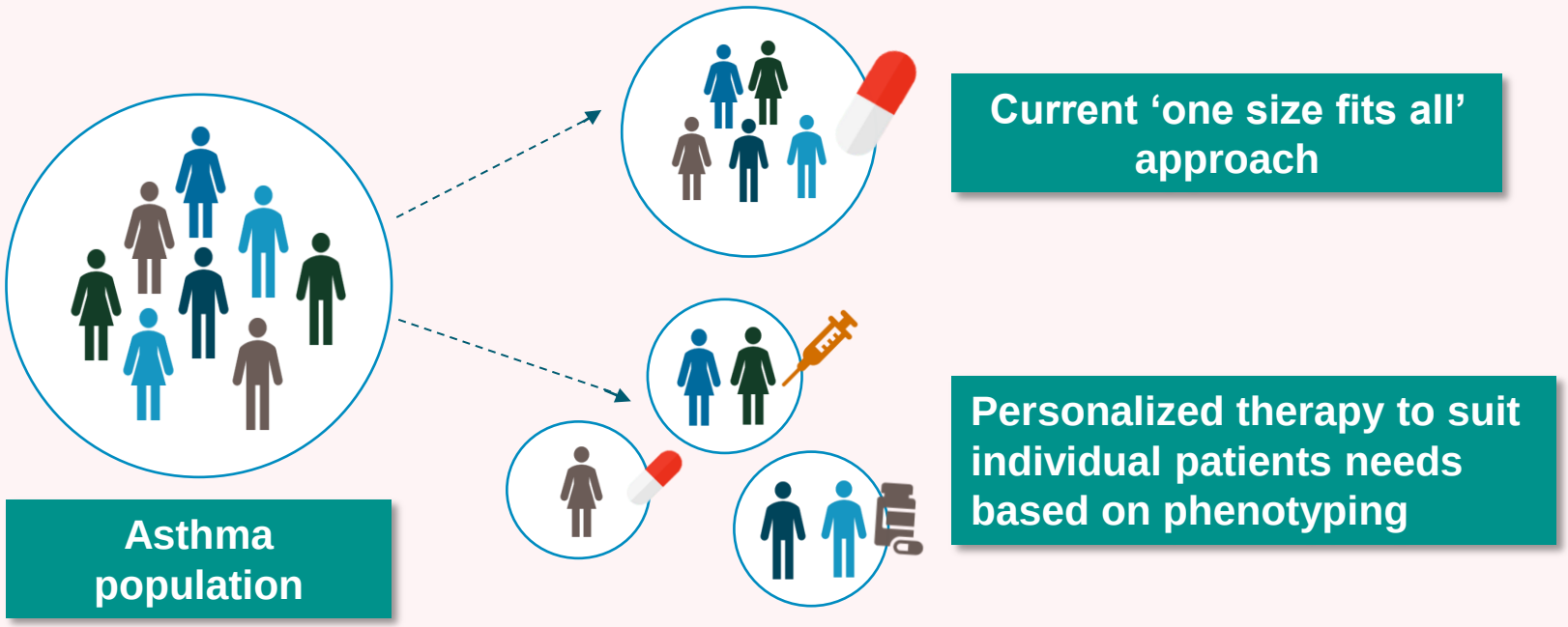
Frequency of Dosing

Adherence Considerations
(self-administration vs office visits)

Cost
(insurance coverage, prior authorization)

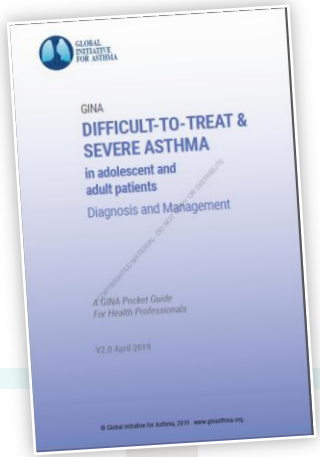
Personalized Therapy with Biologics

- Personalized therapy enables choosing a treatment which will be more likely to produce a beneficial response in the individual patient rather than a 'one size fits all' approach[1]
- Phenotyping or endotyping of asthma will help to determine new treatment strategies[2]
- Biomarkers will help to identify the group of patients who will respond to a specific targeted therapy[3]



1. Papaioannou A *et al. Respir Med* 2018;142:15–22
2. FitzGerald JM, *et al. Can J Resp Critical Care and Sleep Med* 2017; 1:199–221.
3. Chung KF. *J Intern Med* 2016; 279:192–204.

2019 diagnosis and management of difficult-to-treat and severe asthma in adolescent and adult patients (GINA pocket guide)



A Pocket Guide for Health Professionals to help **identify, assess** and **manage difficult-to-treat and severe asthma in adolescents and adults**

Health professionals involved in the management of people with asthma (GPs, PCPs, pulmonary specialists, others)

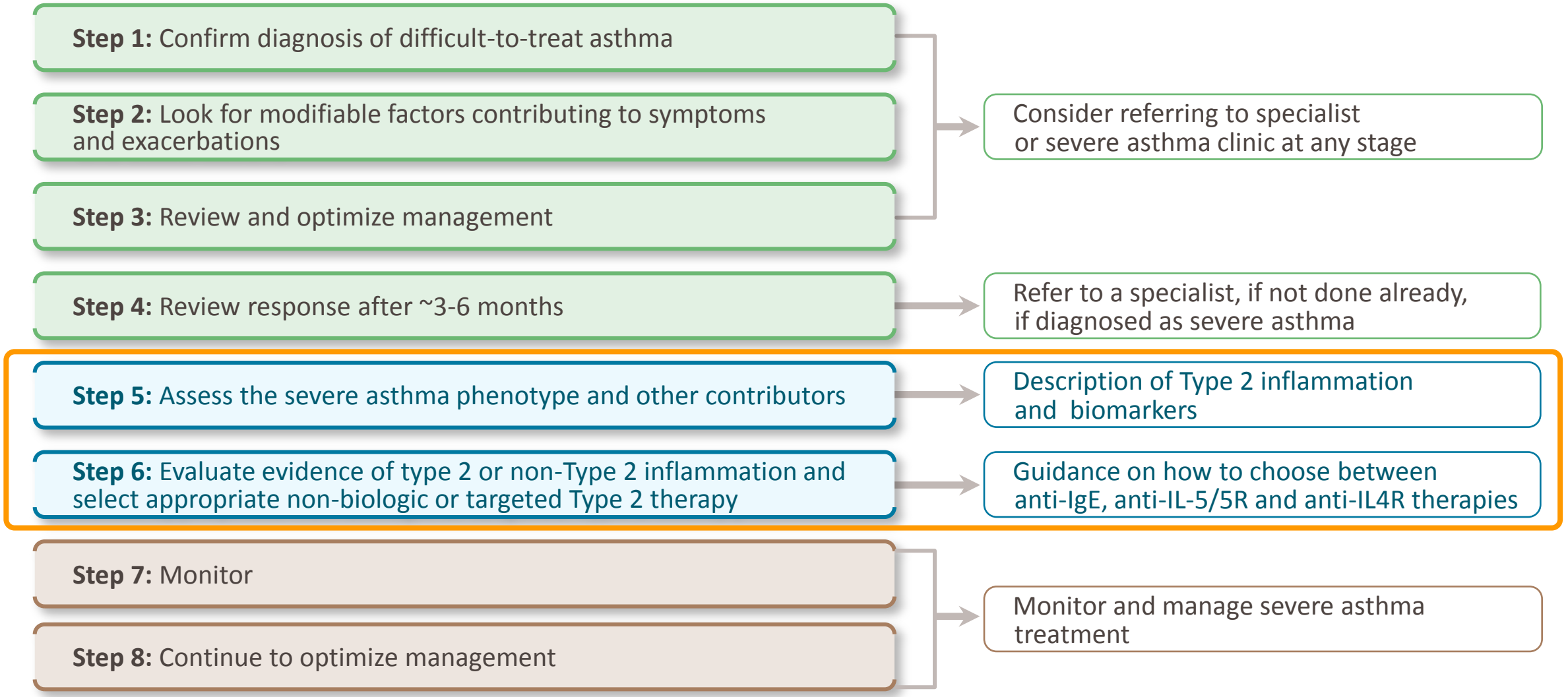
Based on evidence from good quality **systematic reviews** or **randomized controlled trials,** robust **observational data, consensus** by expert clinicians and researchers

Includes a **decision tree** about assessment and management of adults and adolescents with difficult-to-treat and severe asthma

GP, general practitioner; PCP, primary care physician.

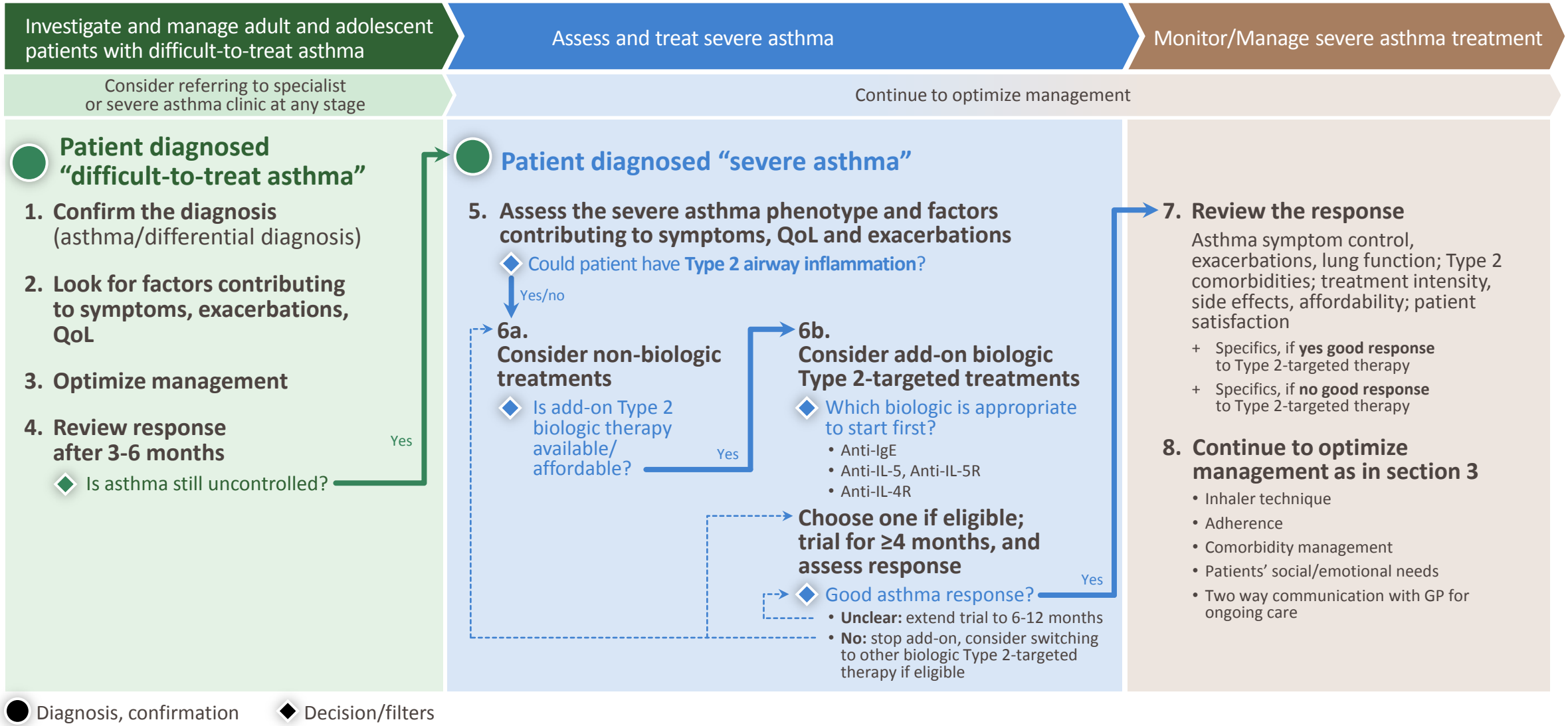
Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma. Available at: https://ginasthma.org/severeasthma/. [Accessed April 29, 2019].

Severe asthma clinical decision tree



Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma. Available at: https://ginasthma.org/severeasthma/. [Accessed April 29, 2019].

Summary



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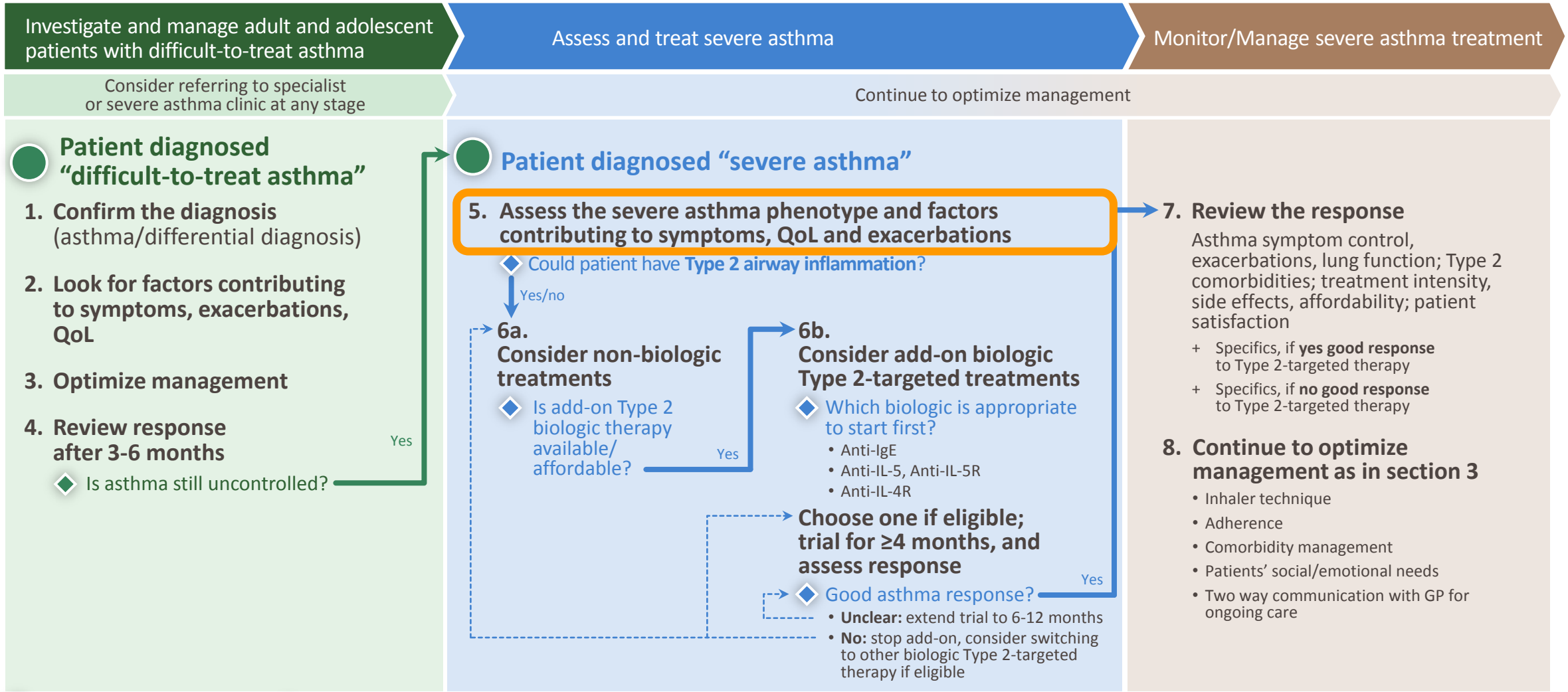
Step 5: Assess the severe asthma phenotype and factors contributing to symptoms, QoL and exacerbations



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Step 5: Assess the severe asthma phenotype and factors contributing to symptoms, QoL and exacerbations

Patient diagnosed "severe asthma"

Assessment of:

- **Patient's inflammatory phenotype: Type 2 or non-Type 2**
- More detailed assessment of comorbidities and differential diagnoses
- Need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

Type 2 inflammation

- Found in ~50% of people with severe asthma
- Characterized by IL-4, IL-5 and IL-13, produced by the adaptive immune system on recognition of allergen
- Characterized by eosinophils and may be accompanied by atopy
- In mild or moderate asthma, type 2 inflammation rapidly improves with proper ICS use
- In severe asthma, type 2 inflammation is relatively refractory* to high dose ICS. It may respond to OCS but their serious adverse effects mean that alternative treatments should be sought†

*The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS: blood eosinophils ≥150/µl, and/or FeNO ≥20ppb, and/or sputum eosinophils ≥2%, and/or asthma is clinically allergen-driven. †Since OCS rapidly reduce markers of Type 2 inflammation (blood eosinophilia, FeNO) in most patients, these tests should be performed before starting OCS (a short course, or maintenance treatment), or on the lowest possible OCS dose.

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IL, interleukin; OCS, oral corticosteroid.

Global Initiative for Asthma. Adolescents and adults with difficult-to-treat and severe asthma.
Available at: https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf. [Accessed March 22, 2019].

Step 5: Assess the severe asthma phenotype and factors contributing to symptoms, QoL and exacerbations

Patient diagnosed "severe asthma"

Assessment of:

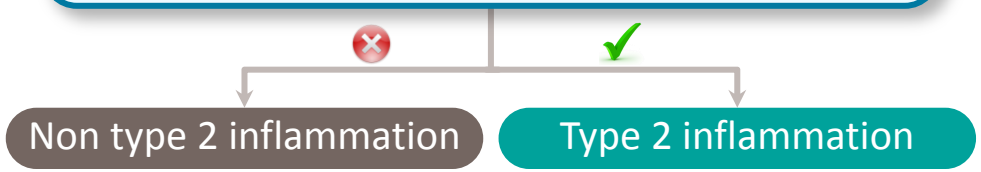
- **Patient's inflammatory phenotype: Type 2 or non-Type 2**
- More detailed assessment of comorbidities and differential diagnoses
- Need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in a registry (if available) or clinical trial (if appropriate

Assess the inflammatory phenotype during high dose ICS treatment* (or lowest possible dose of OCS)

Markers of Type 2 inflammation

- Blood eosinophils ≥150/µl, and/or
- FeNO ≥20ppb, and/or
- Sputum eosinophils ≥2%, and/or
- Clinically allergen-driven asthma

Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose



*Assessment of inflammatory phenotype on high ICS dose is recommended because most RCT evidence about Type 2 targeted biologics is in such patients. Currently, the high cost of biologic therapies generally precludes their widespread clinical use in patients whose symptoms or exacerbations and Type 2 biomarkers are found to respond to ICS when it is taken correctly.

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroid; ppb, parts per billion.

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Available at: https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf. [Accessed March 22, 2019].

Step 6: Treatment considerations based on inflammatory phenotype, Non-Type 2 or Type 2 inflammation

Patient diagnosed "severe asthma"

Non-Type 2 inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoidance of relevant exposure
- Consider additional diagnostic investigations
- Consider a trial of non-biologic add-on treatment
- Consider bronchial thermoplasty

No biologic options are currently available for non-Type 2 asthma

Type 2 inflammation

Consider non-biologic options before biologic Type 2 targeted treatments

- **Consider add-on Type 2 targeted biologic for patients with exacerbations or poor symptom control despite taking high dose ICS-LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS**

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroid.

Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma. Available at: https://ginasthma.org/severeasthma/. [Accessed April 29, 2019].

Step 6: Treatment considerations based on inflammatory phenotype, Non-Type 2 or Type 2 inflammation

Type 2 inflammation

Non-biologic options

- Assess adherence
- Consider clinical Type 2 phenotypes for which specific add-on treatment is available
- Consider increasing ICS dose

Add-on biologic options
Suggested duration: ≥4 months

	Anti-IgE for severe allergic asthma	Anti-IL-5/5R for severe eosinophilic asthma	Anti-IL-4R for severe eosinophilic asthma or OCS-dependent severe asthma
Eligibility criteria	• Sensitization to inhaled allergen(s) on skin prick testing or specific IgE • Total serum IgE and body weight within dosing range • More than a specified number of exacerbations within the last year	• More than a specified number of severe exacerbations in the last year • Blood EOS above specified level. EOS cutpoint may be different for patients taking OCS	• More than a specified number of severe exacerbations in the last year • Type 2 biomarkers above specified level (EOS FeNO) ***OR*** requirement for maintenance OCS
Predictors of good response	• High blood EOS • High FeNO • Childhood asthma • Allergy driven symptoms	• High blood EOS • Higher number of severe exacerbations in previous year • Adult-onset asthma • Nasal polyposis • Maintenance OCS at baseline	• High blood EOS • High FeNO
Additional benefit	-	-	• Indicated for moderate-severe AD • Improves nasal polyposis

AD, atopic dermatitis; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; IL, interleukin; OCS, oral corticosteroid.

Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma. Available at: https://ginasthma.org/severeasthma/. [Accessed April 29, 2019].

Key take-home points