UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Asma severo: quale farmaco per quale paziente

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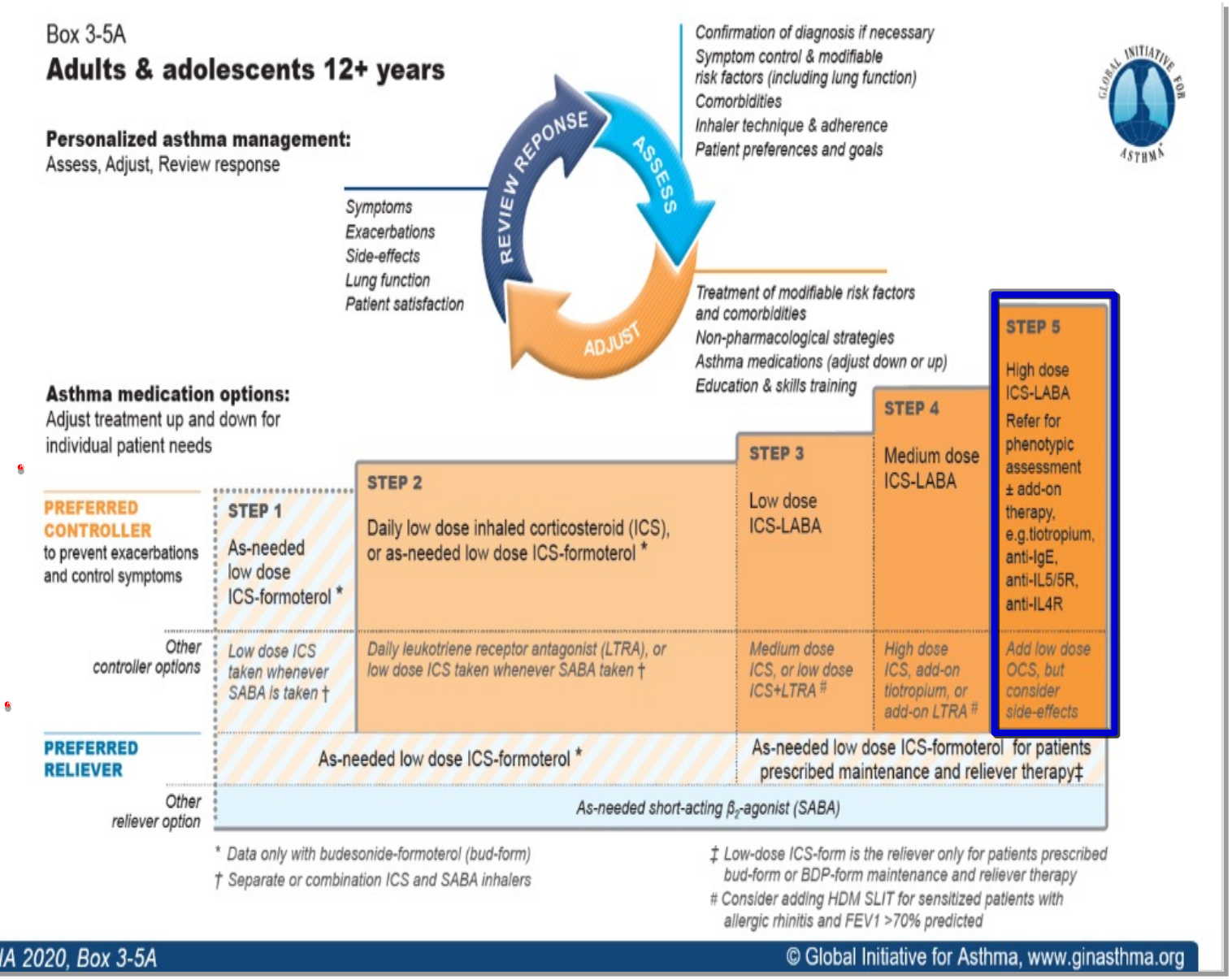
GINA 2020



2020 GINA Report, Global Strategy for Asthma Management and Prevention. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf5.

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

TABLE 3 Definition of severe asthma for patients aged ⩾6 years

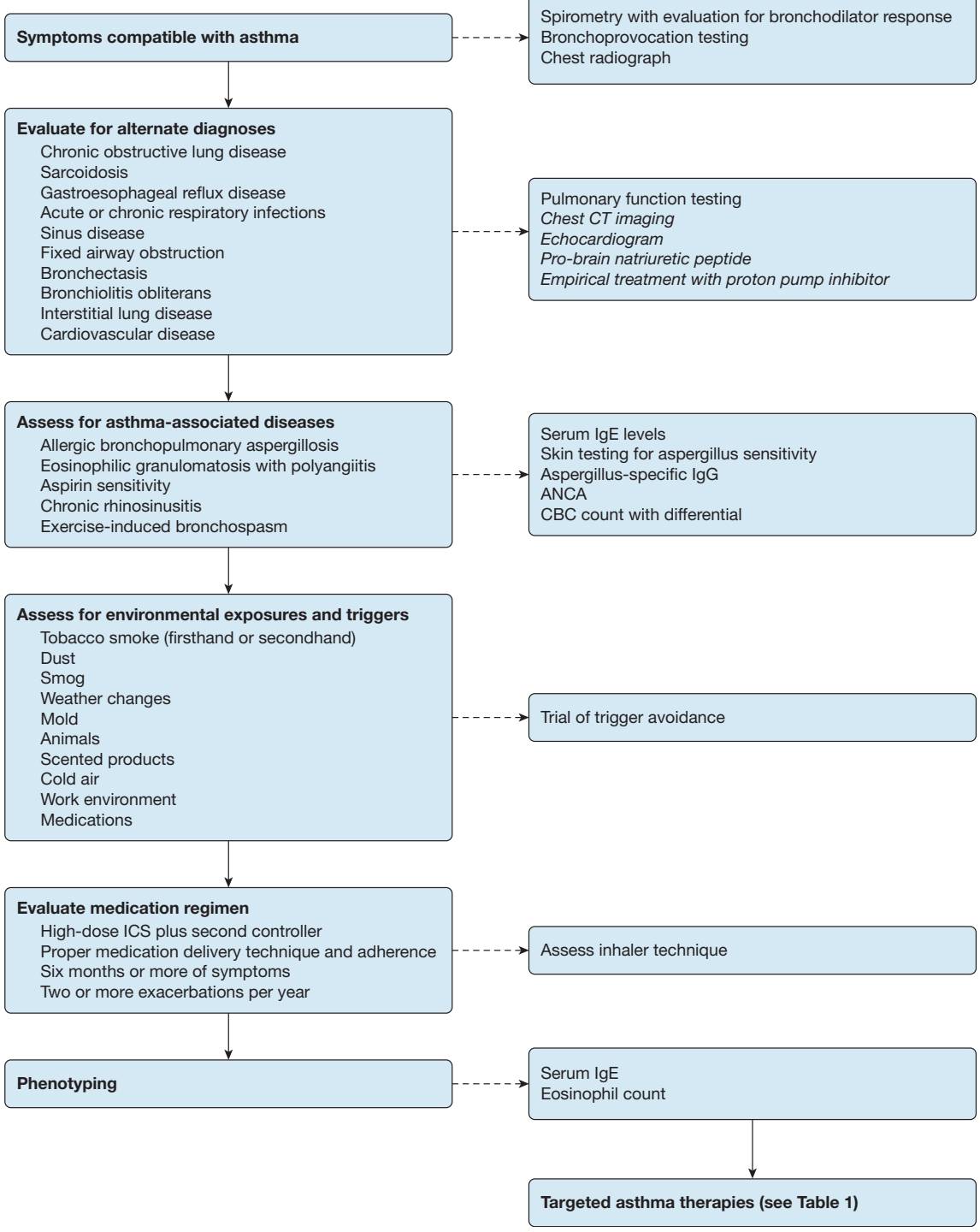
Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

[#]: the definition of high dose inhaled corticosteroids (ICS) is age-specific (table 4). GINA: Global Initiative for Asthma; LABA: long-acting β_2-agonists; CS: corticosteroids; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; NAEPP National Asthma Education and Prevention Program.



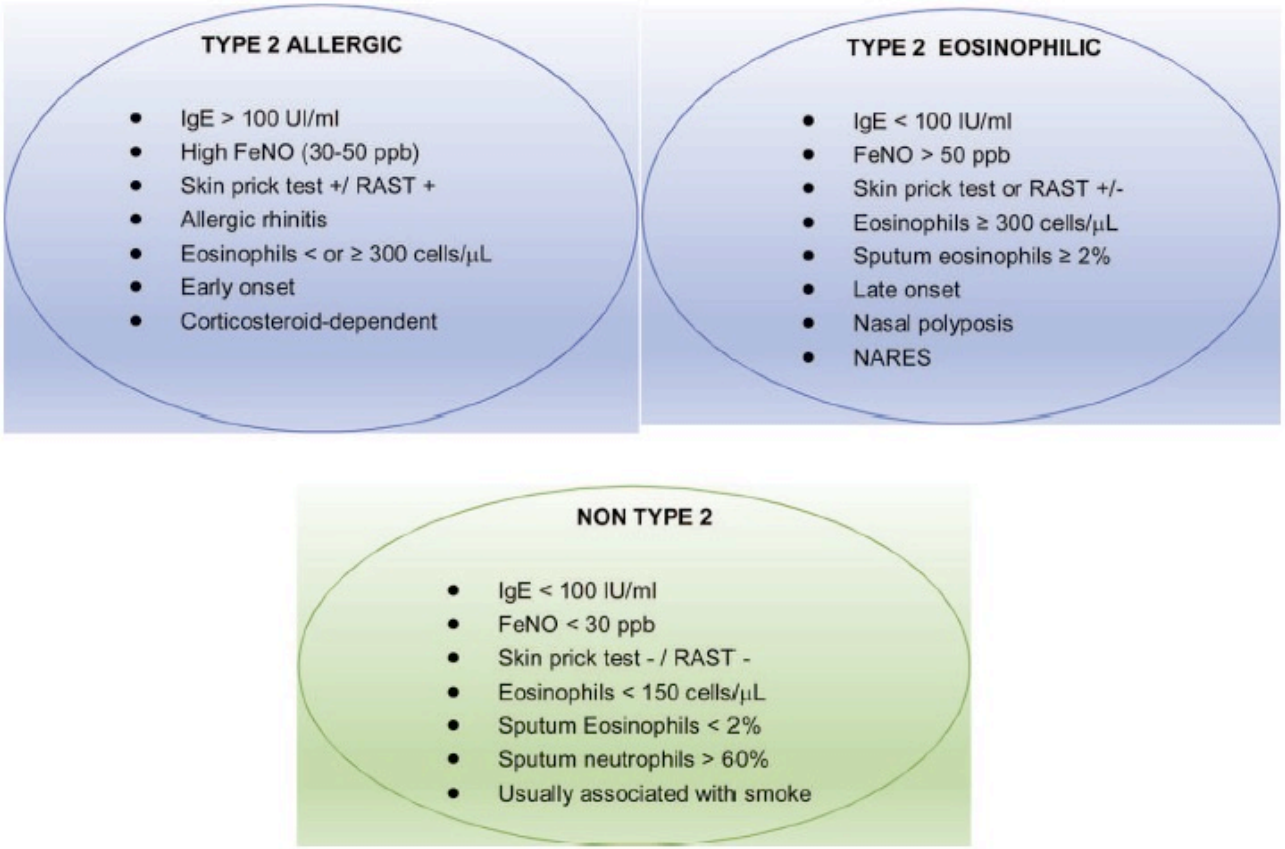
Nathan Schoettler, MD, PhD; and Mary E. Strek, MD

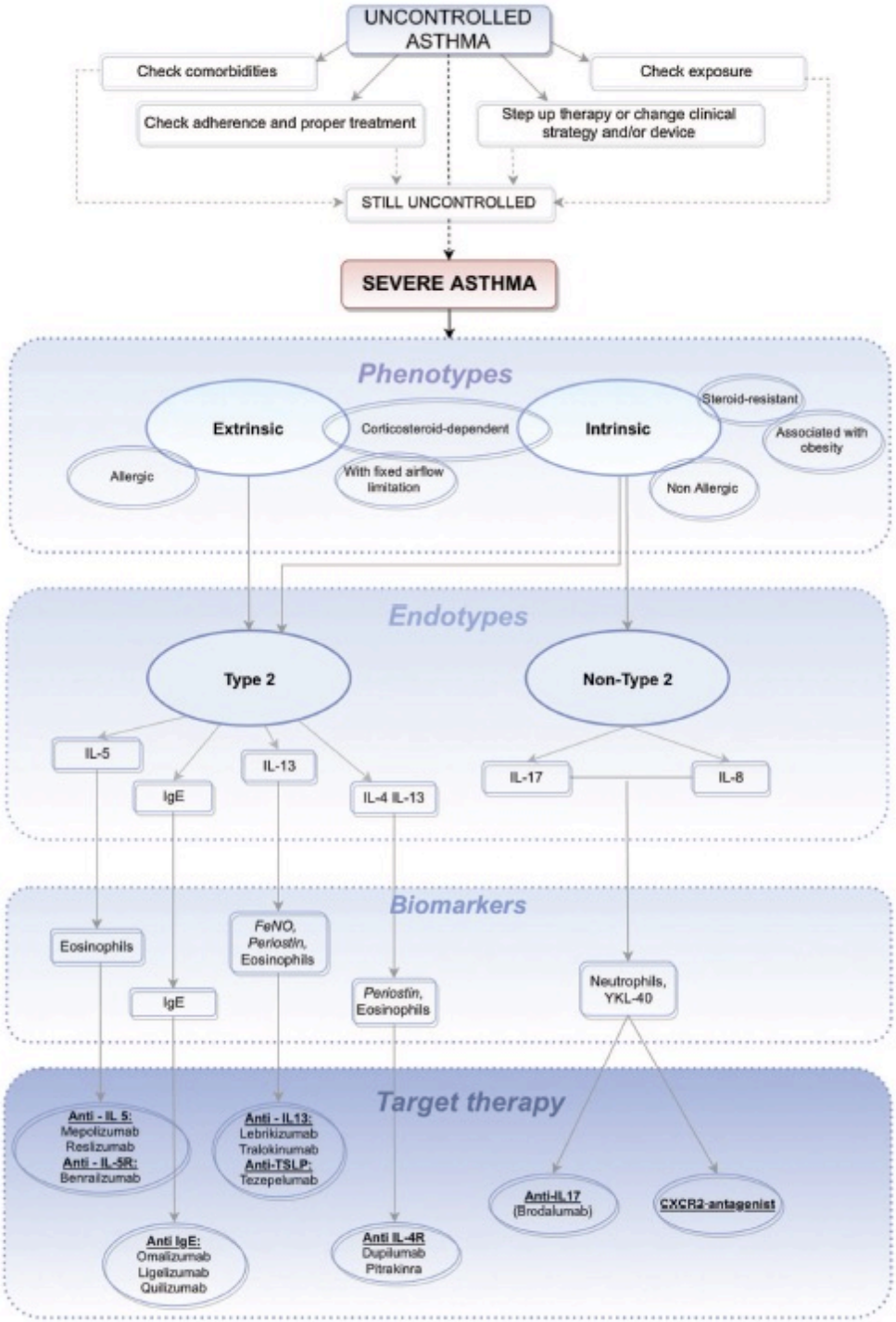
CHEST 2020; 157(3):516-528

Invited Review

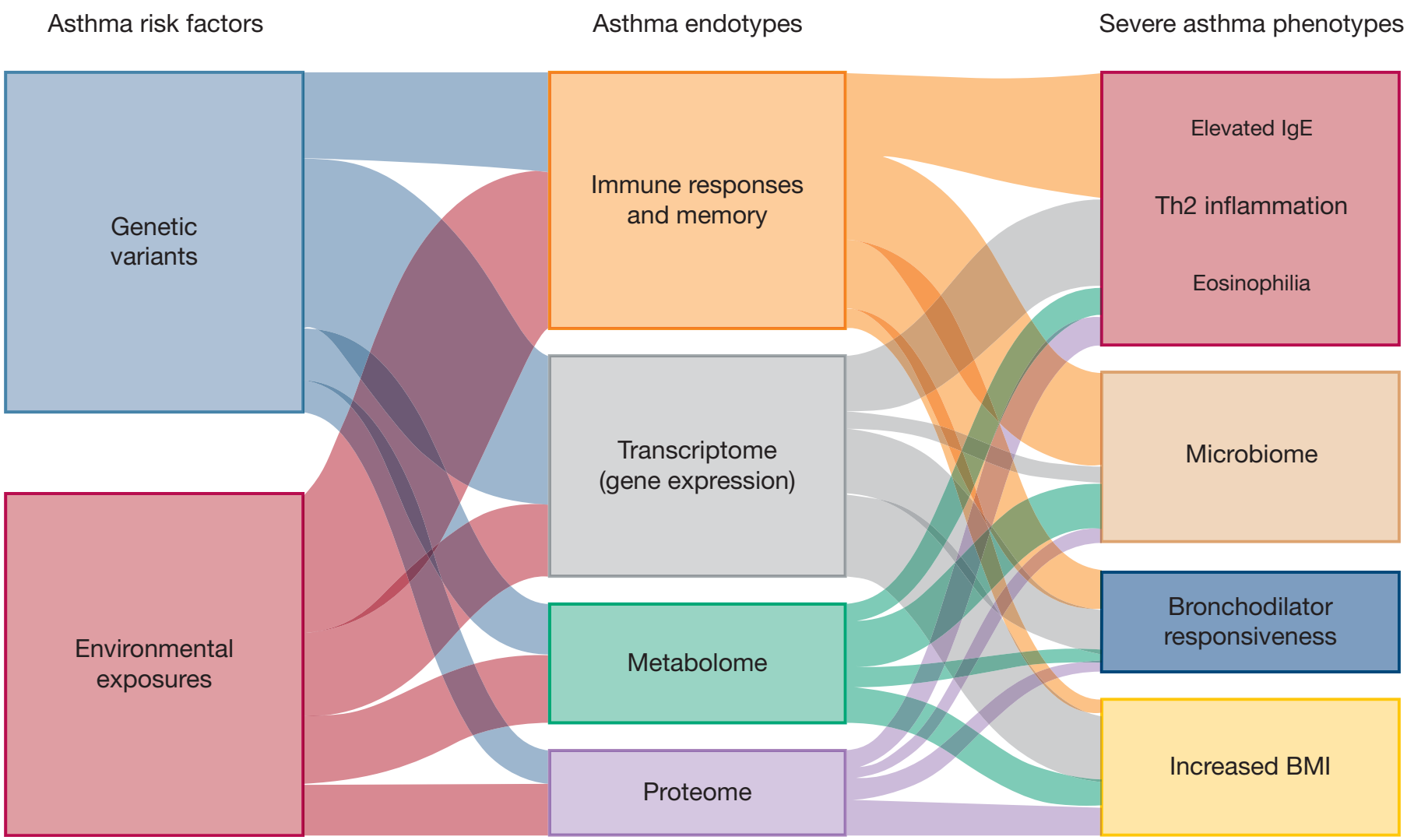
Current and future targeted therapies for severe asthma: Managing treatment with biologics based on phenotypes and biomarkers

Pierachille Santus[a,*], Marina Saad[a], Giovanni Damiani[b], Vincenzo Patella[c], Dejan Radovanovic[a]





P. Santus, et al.
Pharmacological Research 146 (2019) 104296



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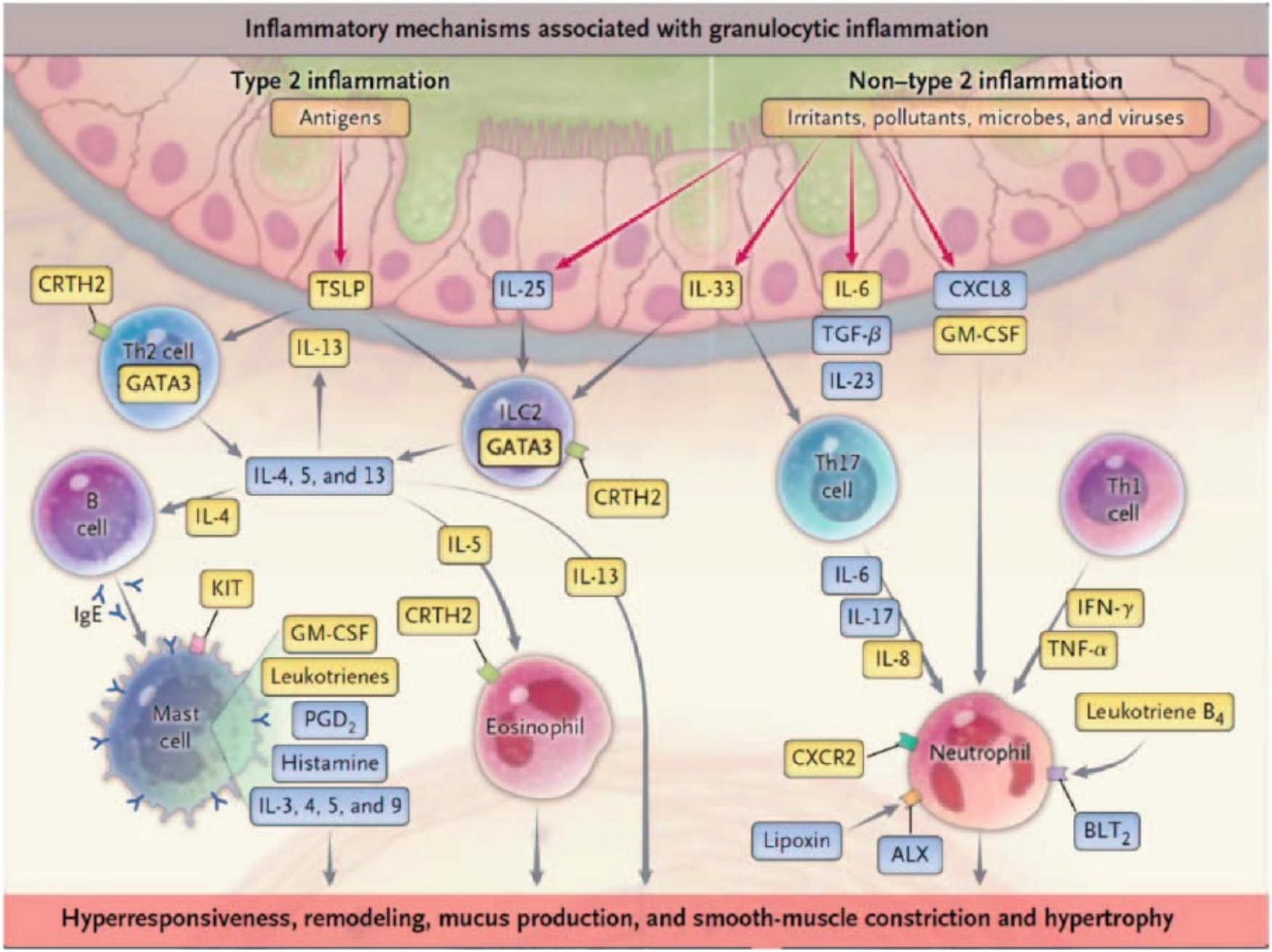


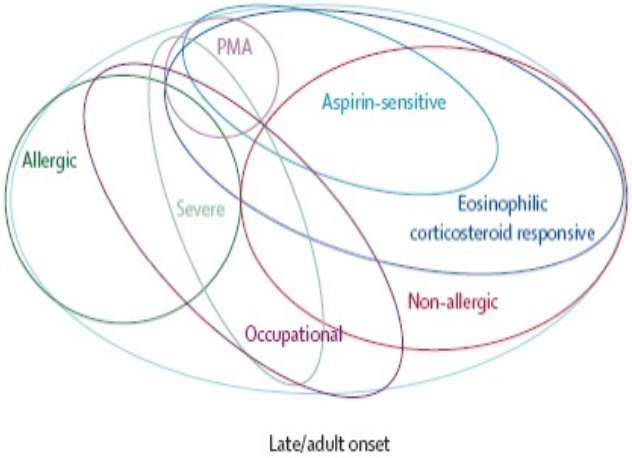
Curr Opin Allergy Clin Immunol 2018, 18:509–518

Un punto di vista che è cambiato

Asthma: defining of the persistent adult phenotypes

Sally E Wenzel

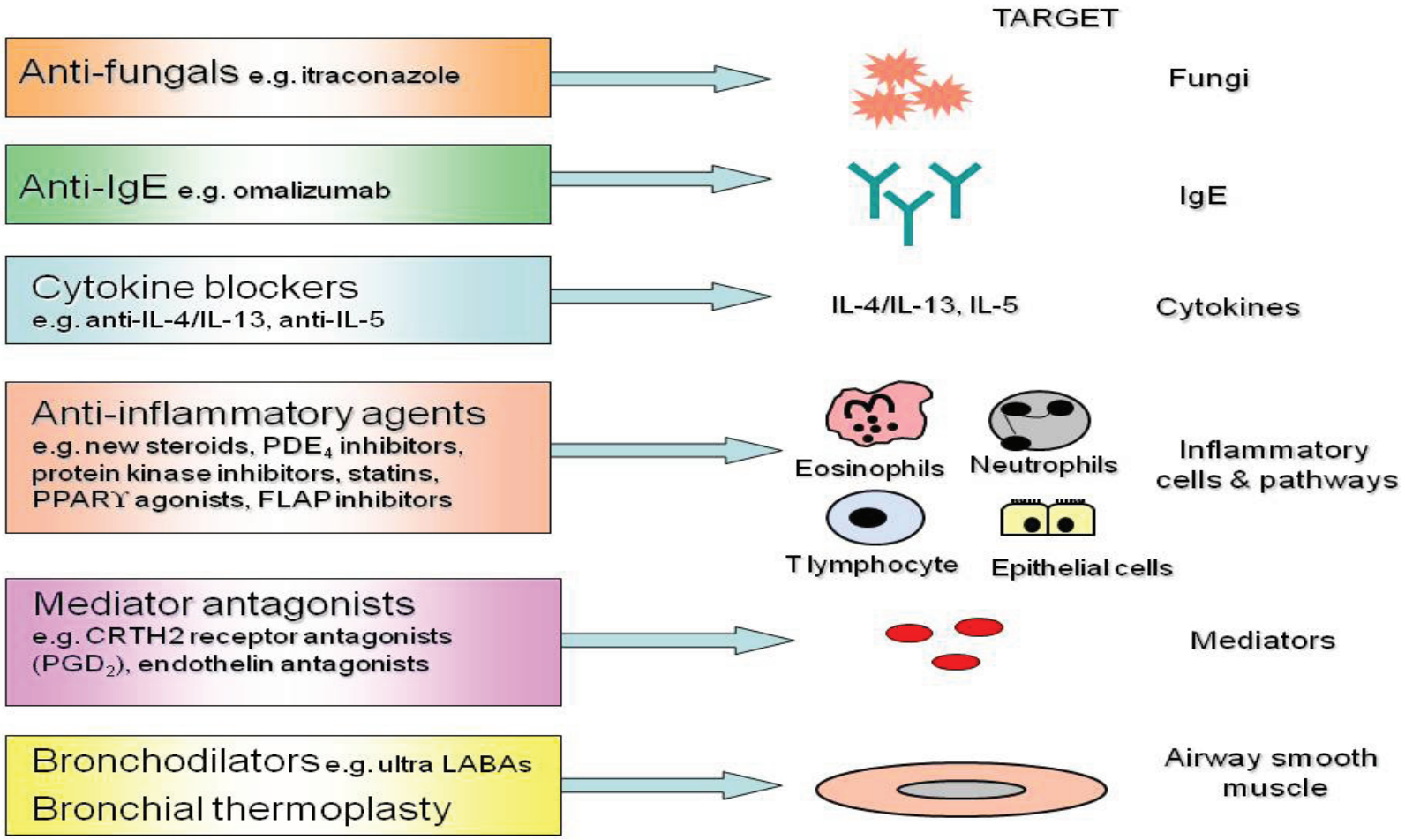
The common disease asthma is probably not a single disease, but rather a complex of multiple, separate syndromes that overlap. Although clinicians have recognised these different phenotypes for many years, they have remained poorly characterised, with little known about the underlying pathobiology contributing to them. Development of targeted therapies for asthma, and phenotype-specific clinical trials have raised interest in these phenotypes. Improved understanding of these phenotypes in complex diseases such as asthma will also improve our ability to link specific genotypes to their associated disease, which should help development of biomarkers. However, there is no standardised method to define asthma phenotypes. This Review analyses some of the methods that have been used to define asthma phenotypes and proposes an integrated method of classification to improve our understanding of these phenotypes.



ONE SIZE FITS ALL

Wenzel, Lancet 2006

Specifiche terapie per specifici target immunoflogistici dell'asma



Thomson, BMC Medicine 2011

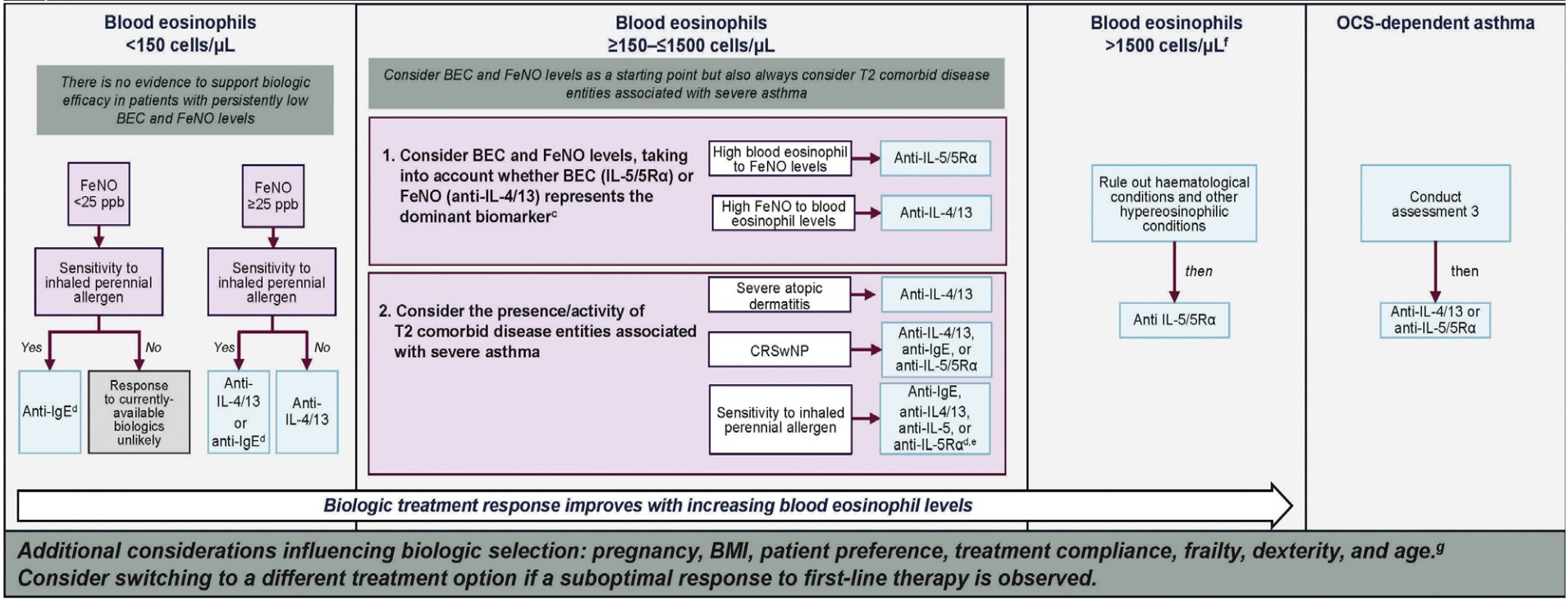
Pathway	IgE	IL-4 and IL-13	IL-5		
Mechanism	Blocks IgE-mediated immune stimulation	Binds to IL-4R alpha subunit and blocks IL-4 and IL-13 cytokine-induced inflammatory responses	Block IL-5 binding to the receptor and reduces survival of eosinophils		
Medication	Omalizumab	Dupilumab	Mepolizumab	Benralizumab	Reslizumab
Target	Anti-IgE monoclonal antibody	Anti-IL-4R alpha monoclonal antibody	Anti-IL-5 monoclonal antibody	Anti-IL-5 alpha monoclonal antibody	Anti-IL-5 receptor monoclonal antibody
Considerations	Elevated IgE	Atopic dermatitis and/or eosinophilia	Eosinophilia	Eosinophilia	Eosinophilia
Indications	Add-on therapy for patients ≥ 6 y old with moderate-to-severe persistent asthma inadequately controlled on ICS and a total serum IgE level between 30 and 700 units/mL and a positive allergen test	Moderate to severe asthma in patients ≥ 12 y old; oral corticosteroid-dependent asthma or asthma with severe atopic dermatitis or chronic rhinosinusitis with nasal polyps	Severe asthma in patients ≥ 12 y old with eosinophilia	Severe asthma in patients ≥ 12 y old with eosinophilia	Severe asthma in patients ≥ 18 y old with eosinophilia
Dosing route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	IV
Dosing interval	Every 2-4 wk depending on pretreatment serum IgE level	Every 2 wk	Every 4 wk	Every 4 wk for the first three doses, then once every 4 or 8 wk	Every 4 wk
Outcomes observed in clinical trials	Reduced exacerbations by approximately 25%-50% in subjects with an FEV_1 between 40% and 80% predicted	Reduced exacerbations by approximately 30% in patients with severe asthma compared with placebo and improvement in FEV_1 Among patients on oral glucocorticoids, 70% had a reduction in the dose, compared with 42% in placebo	Fewer exacerbations compared with placebo and reduced corticosteroid dose in patients requiring maintenance corticosteroids	Reduced exacerbation rate in moderate or severe asthma. In patients with eosinophil counts ≥ 300 cells/μL, rate ratio of < 0.55 for both dosing regimens and improved prebronchodilator FEV_1. Reduced glucocorticoid use with an odds of reduction of 4.09 compared with placebo	Decreased asthma exacerbations by as much as 59%. Improvement in lung function. Improvement in asthma symptoms and asthma-related quality of life

Pathway	IgE	IL-4 and IL-13	IL-5		
Common (> 3%) or severe side effects	Headache (6%-12%) Arthralgias (3%-8%) **Anaphylaxis (0.3%) – black box warning** **Serum sickness-like reaction** **Cardiovascular events, including transient ischemic attack and ischemic stroke** **Eosinophilic granulomatosis and polyangiitis**	Injection site reaction (10%-18%) Oral herpes simplex infection (4%) Antibody response with neutralizing activity (2%-4%) Conjunctivitis (10%) **Eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia** **Hypersensitivity reactions**	Headache (19%) Injection site reaction (8%-15%)	Antibody response with neutralizing activity (12%) Headache (8%) Pharyngitis (5%)	Antibody to medication (5%) Transient increased creatine phosphokinase (20%) Oropharyngeal pain (3%) **Increased malignancies observed at 6 mo (diverse types)** **Anaphylaxis (0.3%) – black box warning**

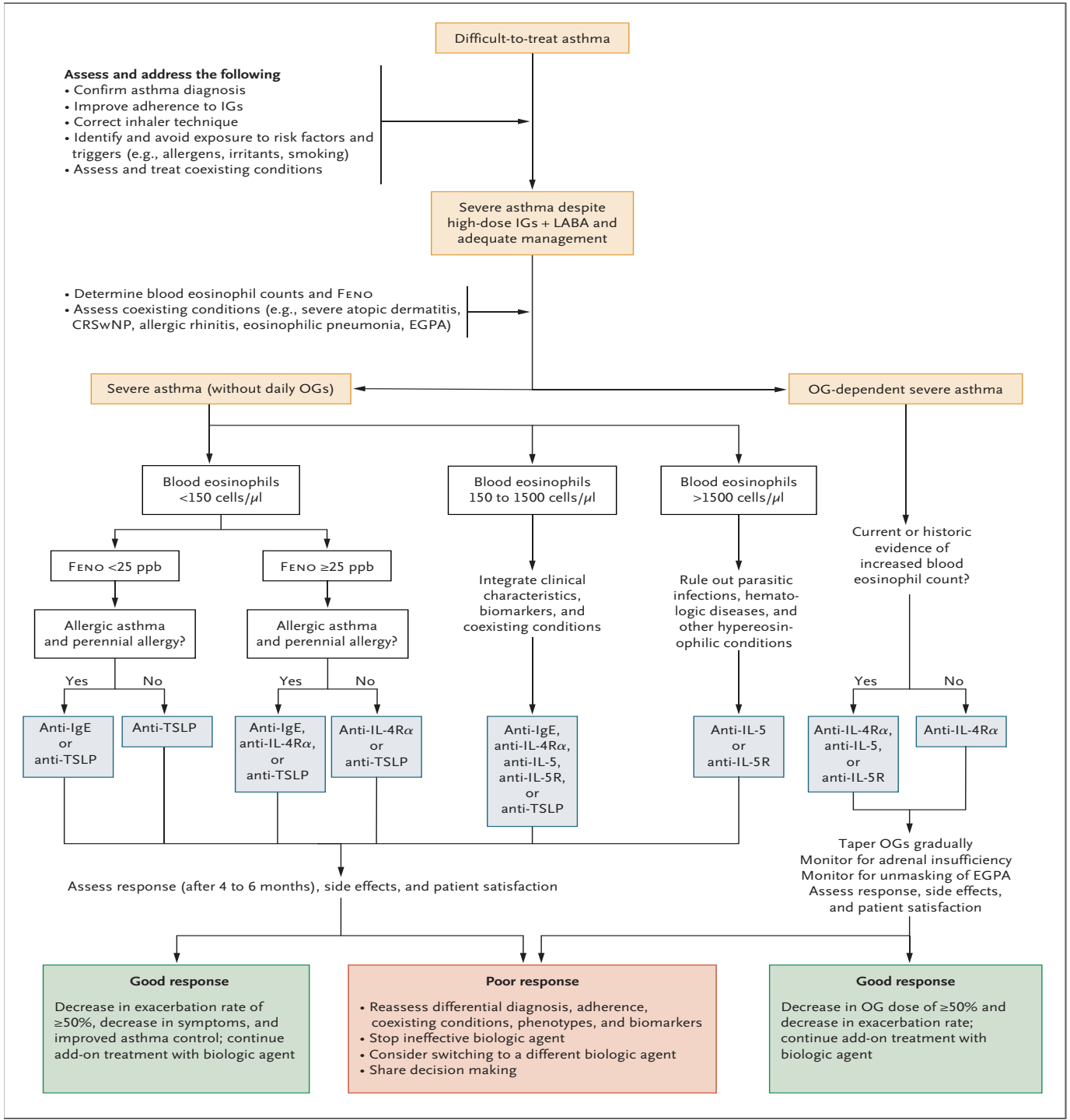
Biologic treatment algorithm for severe asthma

Baseline assessment

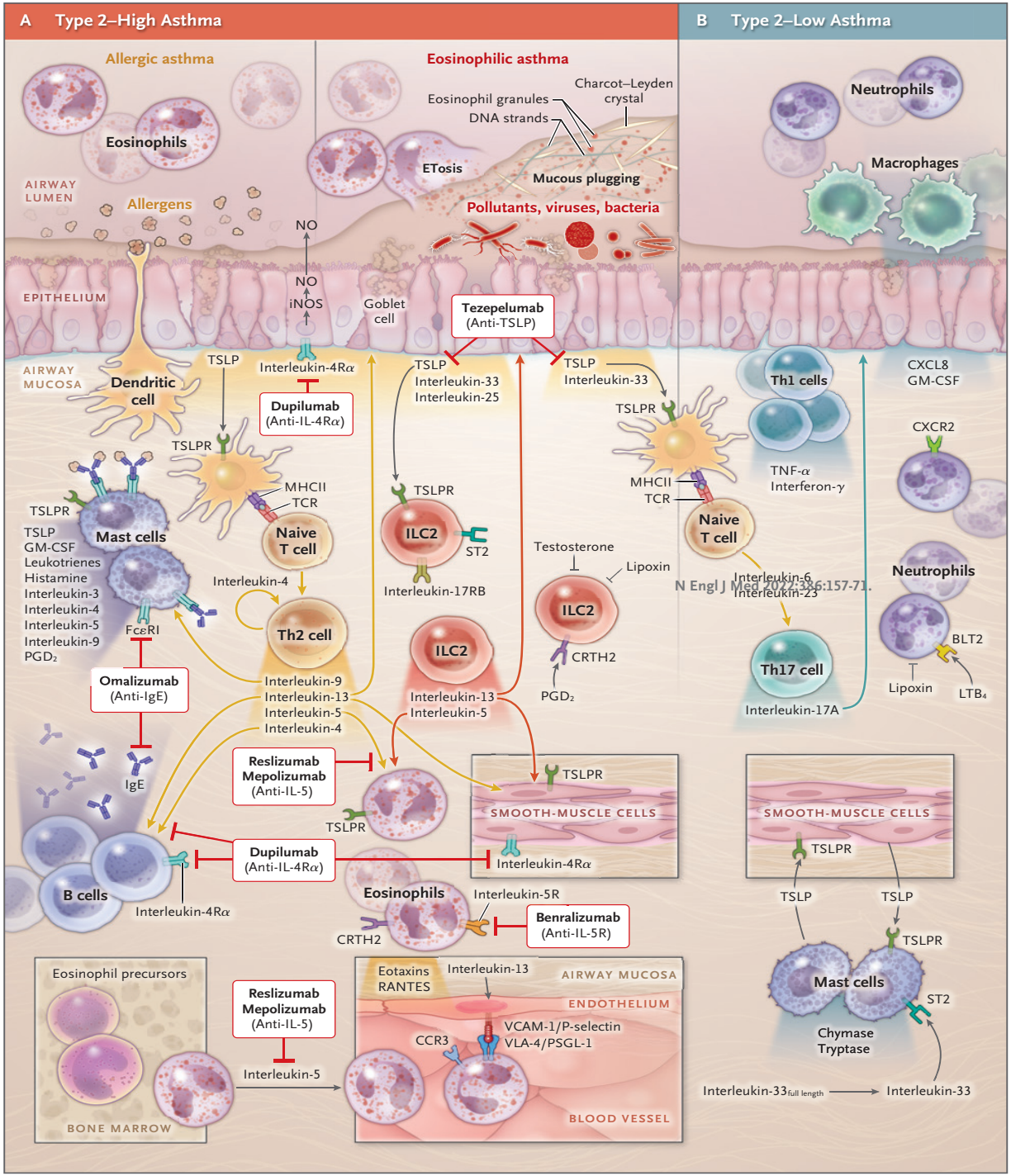
1	Confirm presence of severe asthma, according to the GINA report [12], and T2 inflammation (OCS dependency or exacerbations ≥2 per year). Identify and address adherence to ICS and other controller medication treatment, comorbidities, and potential exposure to risk factors and complicating factors[a]
2	Establish blood eosinophil levels and FeNO levels[b]
3	Validate eosinophil levels by reviewing historic blood eosinophil counts, performing repeat measures, and confirming the presence/activity of T2 asthma and comorbid disease entities associated with severe asthma. If historic eosinophil counts are not available, consider an OCS-tapering approach in asymptomatic patients receiving daily or frequent OCS treatment to assess for elevated eosinophil levels
4	Biomarkers and comorbid disease entities associated with severe asthma should be considered in combination and in context. Consider T2 comorbid disease entities associated with severe asthma (e.g., severe atopic dermatitis, CRSwNP, perennial allergy, EGPA, eosinophilic pneumonia, and hypereosinophilic syndrome), their severity relative to asthma, and whether they are a predictor of response to biologics or a treatment target — address the greatest clinical need for the patient



Additional considerations influencing biologic selection: pregnancy, BMI, patient preference, treatment compliance, frailty, dexterity, and age.[g]
Consider switching to a different treatment option if a suboptimal response to first-line therapy is observed.



N Engl J Med 2022;386:157-71.



Biologic Therapies for Severe Asthma

Guy G. Brusselle, M.D., Ph.D., and Gerard H. Koppelman, M.D., Ph.D.

N Engl J Med 2022;386:157-71.

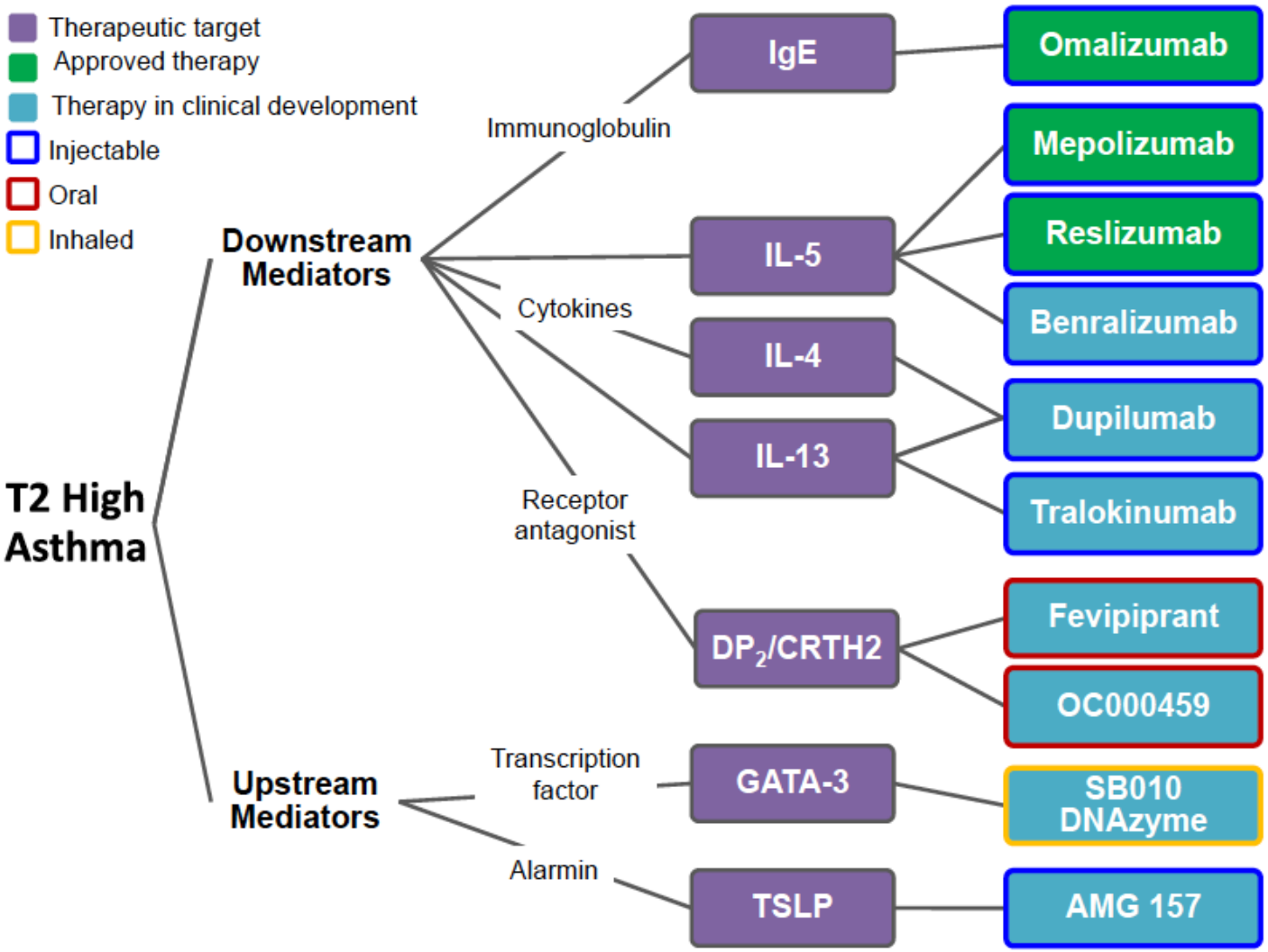


FIGURE 1. Biologic and novel therapies for the treatment of severe asthma. This figure includes only approved and emerging therapies with published human data. *CRTH2*, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *DP2*, prostaglandin D2 receptor 2; *IgE*, immunoglobulin E; *IL*, interleukin; *TSLP*, thymic stromal lymphopoeitin.

PEPPER ET AL Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:909-16)

Current Biomarkers in T2-High Inflammation

Currently available biomarkers may assist clinicians in the selection of targeted asthma treatments, most of which are specific for T2-high disease. Biomarkers in medicine are divided into 3 categories[17]:

- Type 0, a marker that relates to the natural history of disease;
- Type 1, a marker that reflects drug activity or drug responsiveness;
- Type 2, a marker that acts as a surrogate and defines potential disease process.[17]

GRAZIE