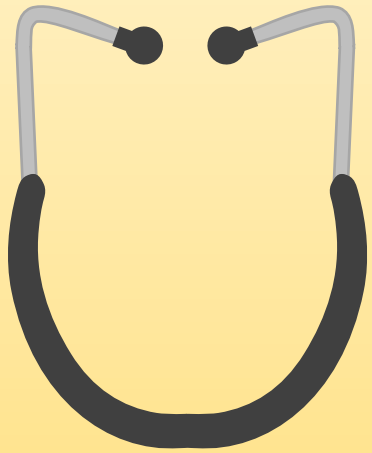

Is it Possible to Go from Control to Super Responder to Remission in Asthma?

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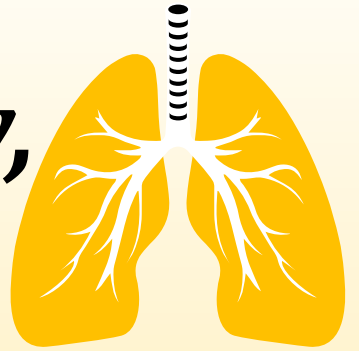
Clinical Professor of Pediatrics

Medical College of Georgia at Augusta University

Augusta, Georgia

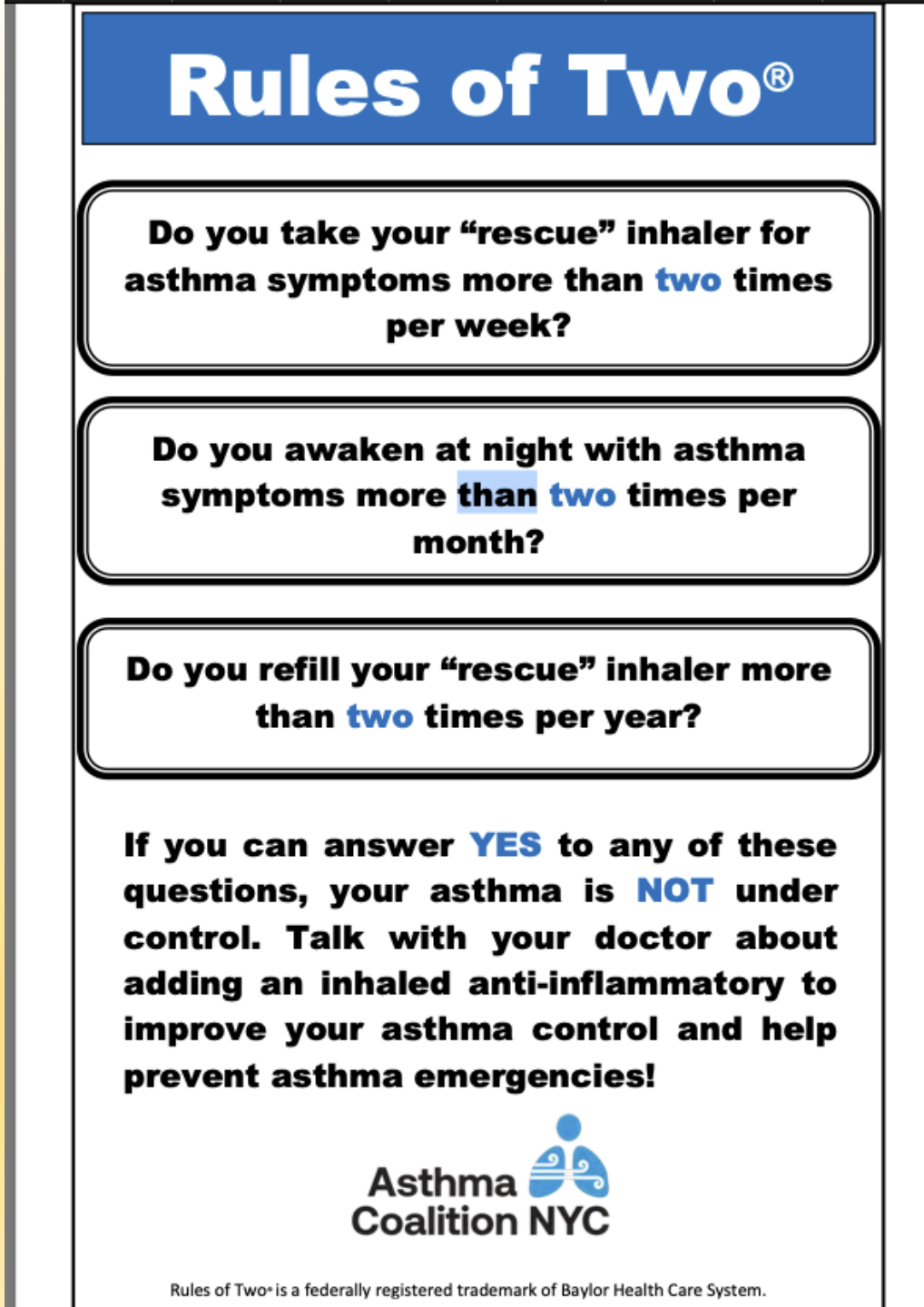
Upon completion of this learning activity, participants should be able to:



- Examine the differences between asthma control and remission
- Identify the different definitions of remission in asthma
- Explore data assessing if super responder and remission can be achieved in asthma
- Describe the basis for the Joint Consensus Statement of the ACAAI, AAAAI, and ATS on remission on treatment in asthma

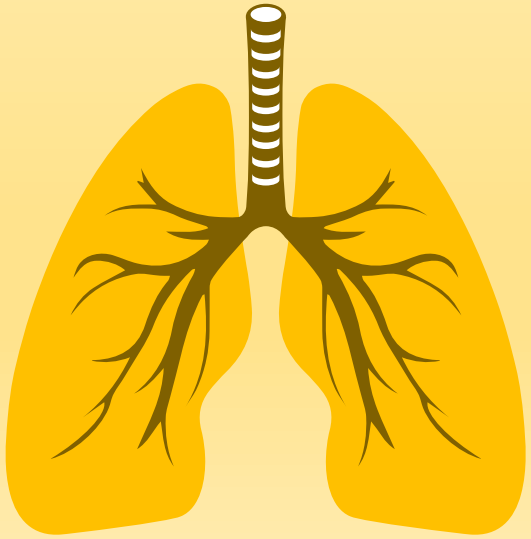
Asthma Control

- With the use of inhaled corticosteroids in the 1970's , the age of asthma control began.
- Addressing inflammation led to decrease symptoms, exacerbations, and improved lung function



GINA 2024 “What is meant by Asthma Control?”

- The level of asthma control is the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment.
- Asthma control has two domains: symptom control and future risk of adverse outcomes



Box 2-2. GINA assessment of asthma control in adults, adolescents and children 6–11 years

A. Asthma symptom control

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA* reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

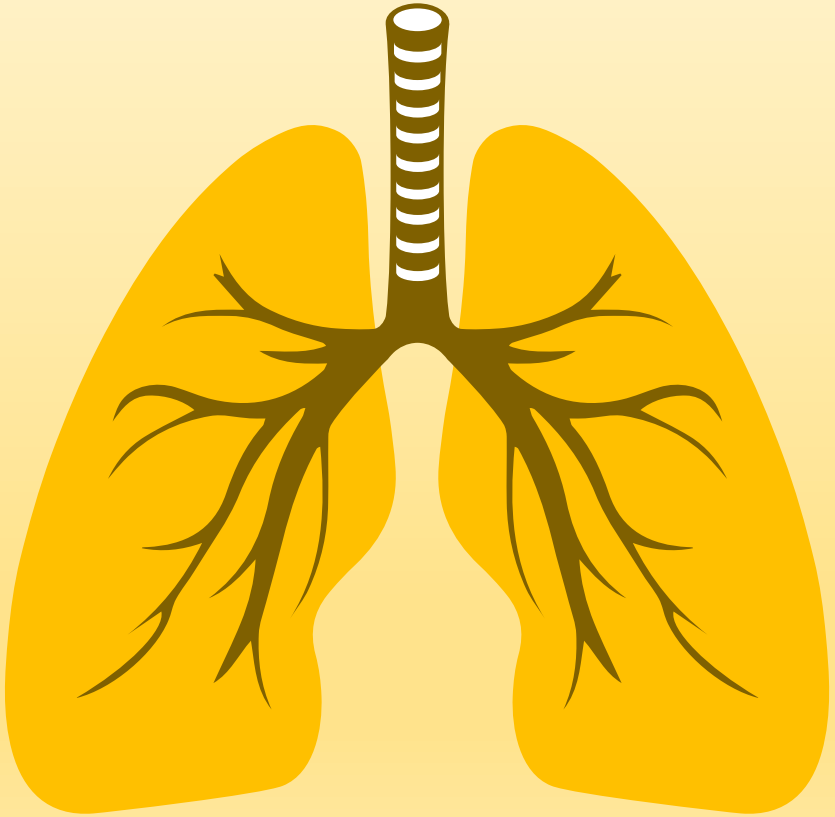
B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.

Measure FEV_1 at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

GINA 2024

Let’s talk about Remission



Remission in Different Disease States

- Cancer-National Cancer Institute
  - A decrease in or disappearance of signs and symptoms of cancer.
  - In partial remission, some, but not all, signs and symptoms of cancer have disappeared.
  - In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.
- Type 2 Diabetes-American Diabetes Association
  - Remission should be defined as a return of HbA1c to less than 6.5% that occurs spontaneously or following an intervention and that persists for at least three months in the absence of usual glucose-lowering pharmacotherapy.
- Rheumatoid Arthritis-American College of Rheumatology and the European League Against Rheumatism
  - One or fewer swollen joints
  - One or fewer tender joints
  - An assessment by the patient that on a 0–10 scale, arthritis activity is 1 or less
  - A blood test showing little or no inflammation in levels of C-reactive protein, a key marker of inflammation
  - Disease-modifying antirheumatic drugs (DMARDs) and biologics have greatly increased remission in this condition

RA as a Model for How to Achieve Remission in Asthma

Rheumatoid arthritis	Severe asthma
Incurable inflammatory condition[1]	✓ Incurable inflammatory condition[4]
Disease progression results in irreversible joint damage and visible disability[2]	✓ Disease progression results in irreversible lung function decline[5] and disability that is not visibly perceived; underestimated disease burden contributes to worse outcomes[6]
Multiple targeted treatments, including DMARDs available with a realistic goal of clinical remission[1,3]	? Multiple targeted treatments available[7]; whether remission can be achieved is currently being explored[8]

DMARD = disease modifying anti-rheumatic drug.

1. Girdler SJ, et al. *J Orthop.* 2019;17:17-21; 2. Brown PM, et al. *Clin Med (Lond).* 2014;14(Suppl 6):s50-55; 3. Felson DT, et al. *Arthritis Rheum.* 2011;63:573–586; 4. Busse WW, et al. *Eur Respir Rev*. 2022;31(163):210183; 5. Pascual, RM, Peters SP. *J Allergy Clin Immunol.* 2009;124(5):883-892; 6. Crespo-Lessmann A, et al. *BMJ Open Respir Res.* 2017;4:e000189; 7. Pelaia C, et al. *Front Immunol.* 2020;11:603312; 8. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765.

Different Types of Remission in Asthma

- Clinical Remission (on or off treatment)
  - No symptoms, no exacerbations, normal lung function
- Complete Remission (on or off treatment)
  - No symptoms, no exacerbations, normal lung function, normalization of asthma pathology
- Inflammatory Remission
  - Normalization of biomarkers in asthma

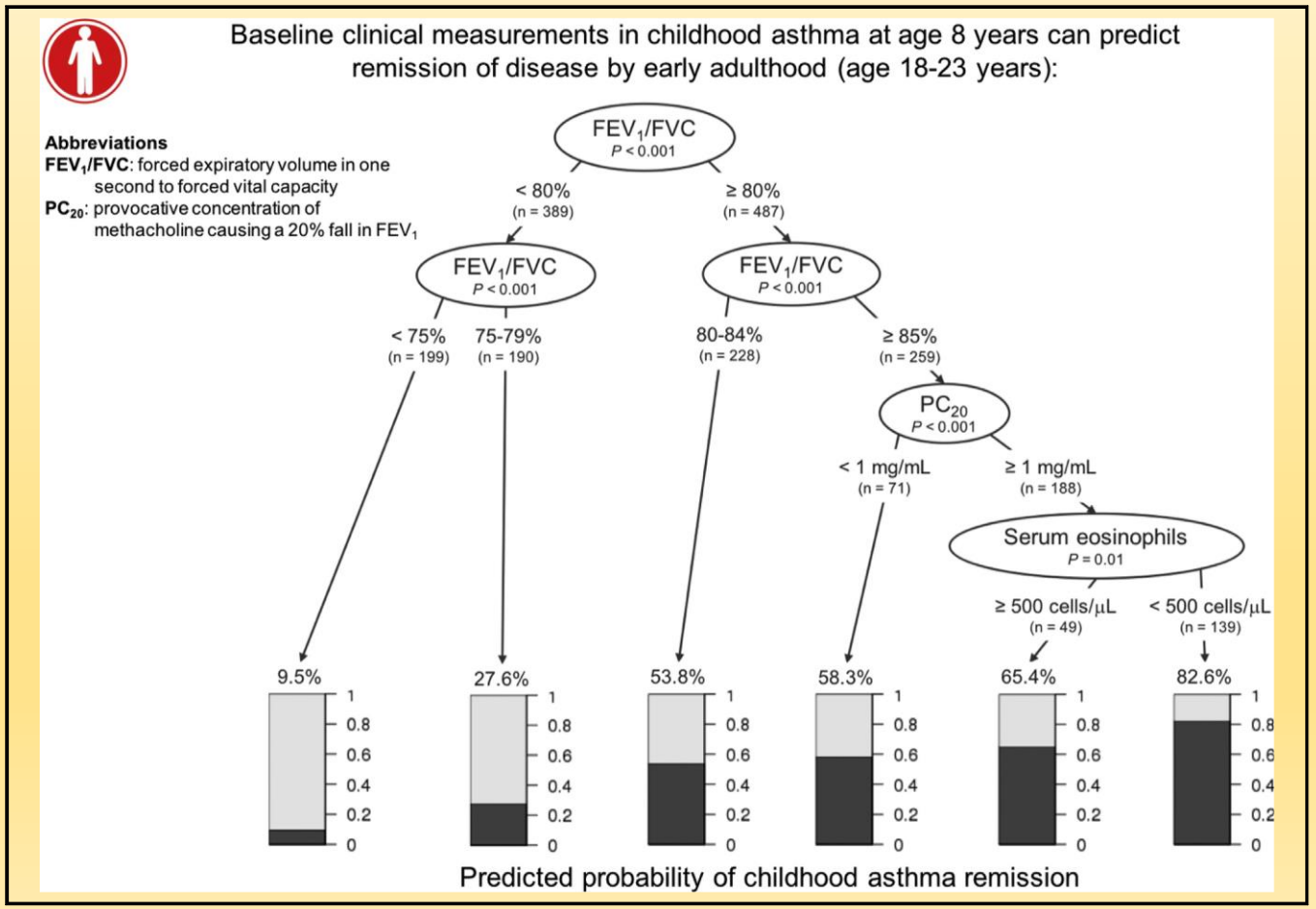
How do we Assess Remission in Asthma?

- Clinical symptoms
  - Sustained absence of symptoms (6 months, 1 year, etc.)
  - Validated Instruments (ACQ score ⩽1.5 or ⩽ 0.75 or ACT score ⩾20 or AIRQ <2)
  - Use of bronchodilators
- No exacerbations
  - No bursts of corticosteroids
  - No ED visits or hospitalization
  - No unscheduled office visits due to asthma
  - No missed school or work due to asthma
- Lung function
  - Stable or normal lung function (FEV1 ⩾80% predicted; absolute improvement of FEV1 by ≥100 ml from baseline values; improvement of FEV1 of >10%)
- Medication requirements
  - Decrease in controller medications (ICS; LABA, LAMA, etc.)
  - Rescue inhaler use
- Normalization of asthma pathophysiology
  - Normal level of biomarkers of inflammation (Blood eosinophils, sputum eosinophils, FeNO, etc.)
  - Negative Bronchoprovocation Test
  - Normal histology (no basement member thickening, etc.)

Is Remission Possible?

- Remission in childhood asthma is a common phenomenon. It is part of the natural history of the disease.
- Based on normal lung function and the absence of symptoms, exacerbations, and medication use.

GRAPHICAL ABSTRACT



Wang AL, Datta S, Weiss ST, Tantisira KG. Remission of persistent childhood asthma: Early predictors of adult outcomes. J Allergy Clin Immunol. 2019 May;143(5):1752-1759

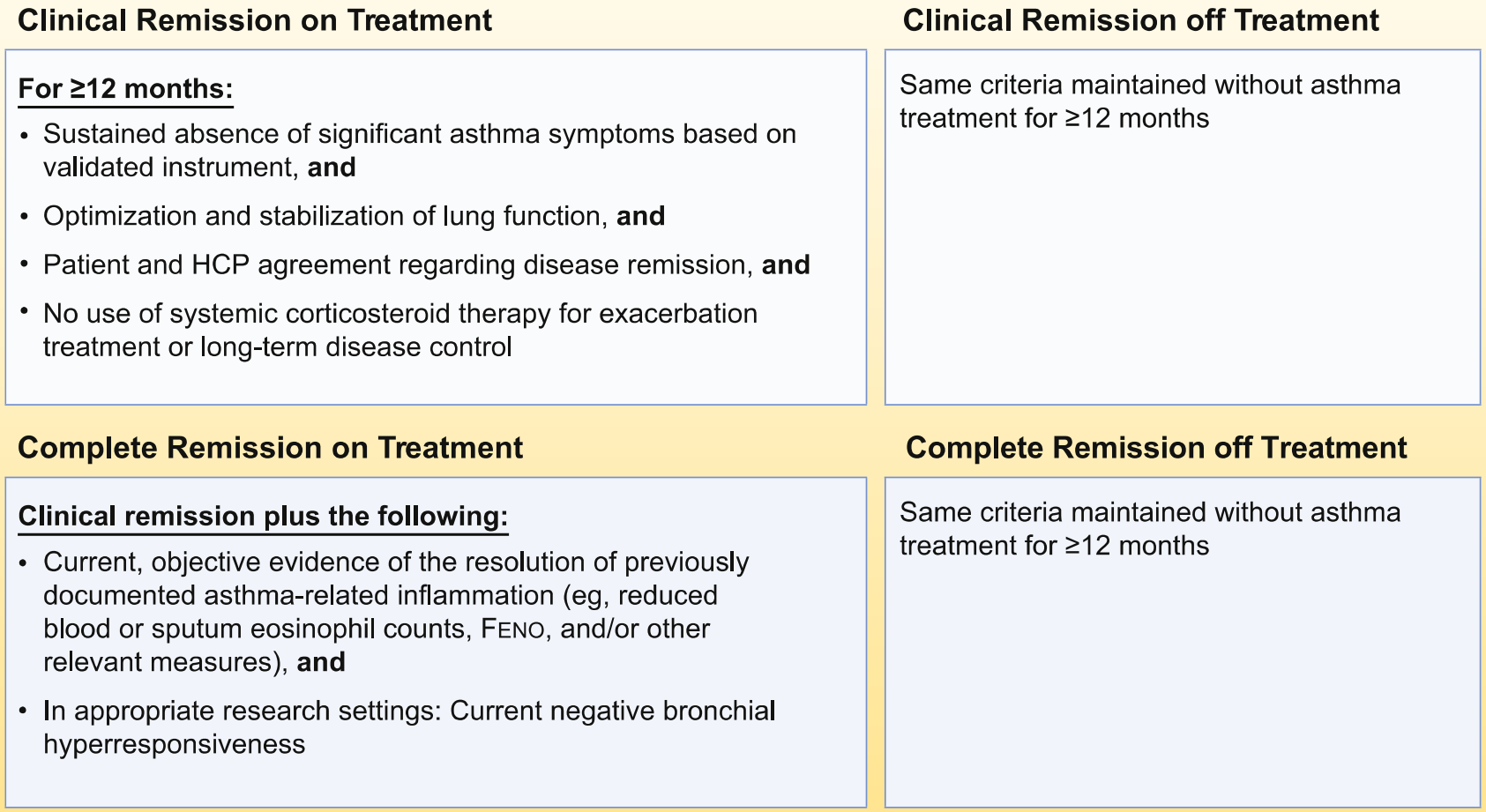


FIG 1. Generalized framework for remission in asthma. Criteria for clinical and complete remission, on and off treatment, were identified by consensus among clinical experts. *FENO*, Fractional exhaled nitric oxide. *Blood eosinophil counts and FENO are less relevant for T2-low asthma.

Menzies-Gow A, Bafadhel M, et. al. J Allergy Clin Immunol. 2020 Mar;145(3):757-765.

Several Countries Have Recommended Clinical Remission Definitions[1-5]

For ≥12 months:	Germany[1]	Spain[2*]	Italy[3]	Japan[4]	US[5]
1. Symptom assessment	Absence of symptoms	Absence of symptoms	ACT 20-25; ACQ <1.5	ACT ≥23	ACT >20; AirQ <2; ACQ <0.75
2. Lung function	Stabilized	Optimized and stabilized	Stabilized	Assessed if other criteria are achieved	Optimized and stabilized
3. No exacerbations	✓	✓	✓	✓	✓
4. No OCS use	✓	✓	✓	✓	✓
Other criteria	—	—	—	—	5. No missed work or school; 6. Low-medium ICS dose; 7. Reliever use ≤1 per month

*A broad consensus definition is being developed with over 120 experts and is expected in the GEMA 5.4 update.
ACQ, asthma control questionnaire; ACT, asthma control test; AirQ, asthma impairment and risk questionnaire; ICS, inhaled corticosteroids; OCS, oral corticosteroids.
1. Lommatzsch M, et al. S2k-Leitlinie zur fachärztlichen Diagnostik und Therapie von Asthma 2023 [S2k guidelines for specialist diagnostics and treatment of asthma 2023]. Published by the German Respiratory Society (DGP) 6 March 2023. Accessed 11 May 2023. https://register.awmf.org/assets/guidelines/020-009l_S2k_Fachaerztliche-Diagnostik-Therapie-von-Asthma_2023-03.pdf. 2. GEMA 5.3: Guía Española para el manejo del asma [GEMA 5.3: Spanish asthma management guidelines]. Accessed 11 May 2023. https://www.separ.es/node/1827 3. Canonica GW, et al. *J Allergy Clin Immunol Pract*. Published online 7 August 2023. doi:10.1016/j.jaip.2023.07.041. 4. Japan Asthma Society (JAS). Practical Guidelines for Asthma Management (PGAM). Updated July 2023. Accessed August 30, 2023. https://jasweb.or.jp/guideline.html 5. Blaiss M, et al. *Ann Allergy Asthma Immunol*. Published online September 7, 2023. doi: 10.1016/j.anai.2023.08.609.

Figure 1

Criteria for Remission	Dupilumab		Benralizumab			Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	**2022**[2] TRAVERSE OLE	**2022**[3] SIROCCO/ CALIMA Phase 3	**2022**[4] ANDHI Phase 3b	**2023**[5] XALOC-1	**2022**[6,7] NAVIGATOR Phase 3	**2022**[8] REDES	**2022**[9] CHRONICLE	**2022**[10] Danish Registry
Absence of symptoms[a,b] **and**	ACQ-5 < 1.5	ACQ-5 < 1.5	ACQ-6 < 1.5" or ≤ 0.75	ACQ-6 < 1.5" or ≤ 0.75	ACQ-5 < 1.5 or ACT ≥ 16	ACQ-6 ≤ 1.5[a,b]	ACT ≥ 20	Majority ≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function **and**	Post-BD FEV_1pp ≥ 80%	Post-BD FEV_1 ≥ 80% *OR* pre-BD FEV_1 ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Pre-BD FEV_1 increase ≥ 100 mL	Not included	Pre-BD FEV_1pp > 80% *OR* Pre-BD FEV_1 > 20% from baseline; FEV1 > 95% of baseline**	Not included	Not included	Post-BD FEV_1pp ≥ 80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	26.3%"	28.7%	43%	14%ˆ- 28.5%**	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted. ˆ Includes agreement between physicians and patient assessments of control (clinical global impression of change CGI-C; Patient Global Impression of Severity)

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Jackson DJ Poster presented at AAAAI 2023 San Antonio TX USA 6. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 7. Wechsler, M ERS 2023 Milan, Italy (Unpublished) 8. Ribas DC et al. Drugs 2021;81(15):1763-1774. 9. Chipps, B et al. JACI 2022;149:Suppl AB147 10. Hansen S et al ERJ 2022;60:3553

Lugogo NL, Mohan A, Akuthota P, Couillard S, Rhoads S, Wechsler ME. Are We Ready for Asthma Remission as a Clinical Outcome? Chest. 2023 Oct;164(4):831-834
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Phase 3 Studies Post-Hoc Analysis for Remission at 12 months

Criteria for Remission	Benralizumab[1]	Dupilumab[2]	Tezepelumab[3]
Asthma control	ACQ-6≤ 0.75	ACQ-5 <1.5	ACQ-6 ≤ 0.75
Lung function	Pre-BD FEV_1 increase ≥ 100 mL	Post-BD FEV1pp≥80%	pre-BD FEV of > 20% from baseline or pre-BD FEV1 percentage predicted value of > 80%
No OCS use and exacerbations	None of the patients at baseline were on mOCS	None of the patients at baseline were on mOCS	None of the patients at baseline were on mOCS
Clinical remission rate	14.5%	20%	12.7%*

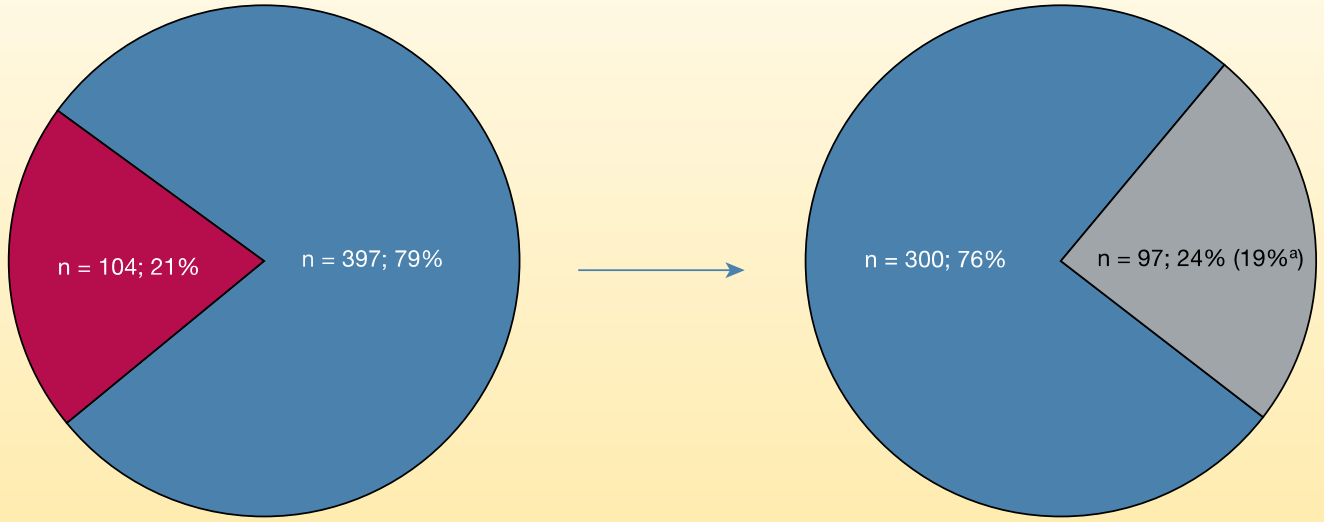
*Other measures used: HCP and Patient Assessments of Severity (Clinical Global Impression of Change and Patient Global Impression of Change)

1. Menzies-Gow A, Hoyte FL, et al. Adv Ther. 2022 May;39(5):2065-2084.
2. Pavord ID et al. Ann Allergy Asthma Immunol 127 (2021) S19eS56.
3. Castro M, Ambrose C, et al. European Respiratory Journal 2022 60: 2287

Clinical Response and Remission in Patients With Severe Asthma Treated With Biologic Therapies

- The Danish Severe Asthma Register is a nationwide cohort including all adult patients receiving biologic therapy for severe asthma in Denmark.
- This observational cohort study
  - “Clinical response” to treatment following 12 months
    - > 50% reduction in exacerbations and/or a > 50% reduction in maintenance oral corticosteroid dose, if required
  - “Clinical remission” following 12 months of treatment
    - Cessation of exacerbations and maintenance oral corticosteroids
    - Normalization of lung function (FEV1 > 80%)
    - ACQ-6 < 1.5

Hansen S, Baastrup Søndergaard M, et al. Chest. 2024 Feb;165(2):253-266.



	No response	Clinical response[b]	*P*
mOCS	n = 65 (63%)	n = 146 (37%)	< .001
Exacerbations	3 (1, 4)	3 (2, 5)	< .001
Blood eosinophils ≥ 0.3 (cells × 10^9L)	n = 42 (44%)	n = 222 (59%)	.01
Eosinophilic pneumonia	n = 8 (9%)	n = 10 (3%)	.01

	Clinical response[c]	Clinical remission	*P*
Female	n = 162 (54%)	n = 37 (38%)	.01
BMI, kg/m^2	28 ± (6)	26 ± (4)	.01
Disease duration, y	23 ± (19)	18 ± (17)	.02
Age at asthma onset, y	33 ± (21)	38 ± (21)	.04
Blood eosinophils (cells × 10^9L)	0.32 (0.13, 0.58)	0.50 (0.25, 0.75)	.01
COPD	n = 70 (24%)	n = 9 (9%)	.003
Dysfunctional breathing	n = 30 (10%)	n = 2 (2%)	.01
Nasal polyposis	n = 114 (38%)	n = 52 (54%)	.01

[a]Proportion in the entire population
[b]Clinical response, including remission
[c]Clinical response, excluding remission

Figure 2 – *Response pattern and predictors of response following 12 months of treatment with biologic therapy in biologic-naive patients in the Danish Severe Asthma Register (N = 501).* [a]*Proportion in the entire population.* [b]*Clinical response, including remission.* [c]*Clinical response, excluding remission. mOCS = maintenance oral corticosteroid.*

Hansen S, Baastrup Søndergaard M, et al. Chest. 2024 Feb;165(2):253-266.

The Danish Respiratory Society's criteria for commencing biologic therapies for severe asthma

mOCS: maintenance oral corticosteroid, OCS: oral corticosteroid, ICS: inhaled corticosteroid, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, LTRA: leukotriene receptor antagonist, FeNO: fractional exhaled nitric oxide

ALL BIOLOGIC THERAPIES		
In the past 12 months: High dose inhaled corticosteroid corresponding to at least 1600 µg budesonide equivalent dose AND a second controller (LABA, LRTA or LAMA) OR maintenance oral corticosteroid (mOCS) at least 50% of the time		
Systematic assessment with the purpose of excluding reasons for uncontrolled disease (adherence, inhalation technique, comorbidities, exposures)		
AND		
At least 2 exacerbations in the past 12 months or mOCS at least 50% of the time		
DRUG SPECIFIC REQUIREMENTS		
Anti-IgE Omalizumab	Anti-IL-5 /IL-5R Mepolizumab Reslizumab Benralizumab	Anti-IL-4Rα Dupilumab
Perennial allergy and symptoms after exposure to allergen	Blood eosinophils >= 0.30 cells x 10^9L the past 12 months or Blood eosinophils >= 0.15 cells x 10^9L currently or Sputum eosinophils >= 3%	Blood eosinophils >= 0.30 cells x 10^9L the past 12 months or Blood eosinophils >= 0.15 cells x 10^9L currently or Sputum eosinophils >= 3% and/or FeNO >= 25 ppb
		If maintenance OCS, no requirement for increased blood eosinophils

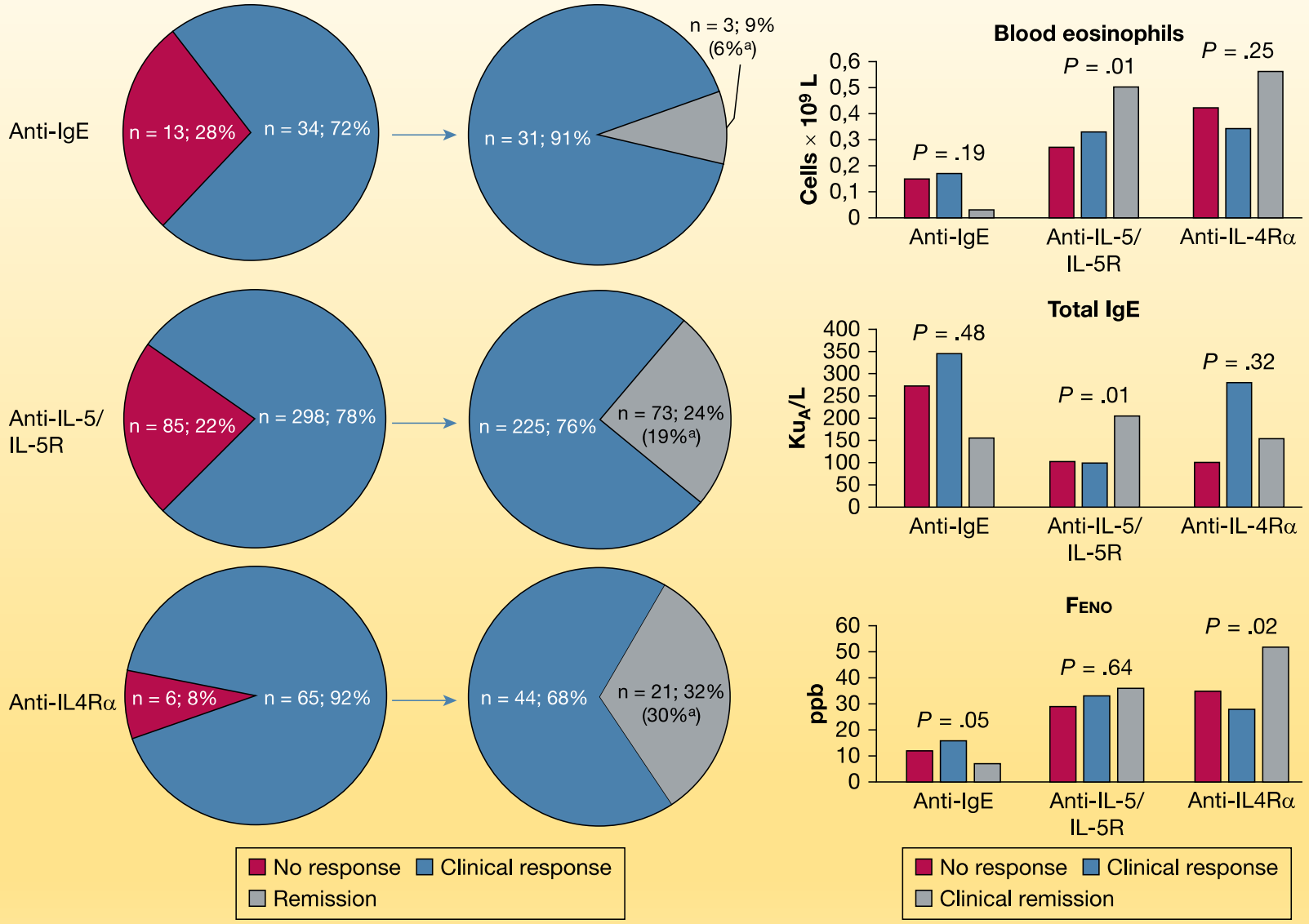


Figure 3 – *Response pattern following 12 months of treatment with biologic therapy and baseline biomarkers predicting remission in each drug class compared with patients with a clinical response.* [a]*Proportion in the entire population.* FENO *= fractional exhaled nitric oxide.*

Hansen S, Baastrup Søndergaard M, et al. Chest. 2024 Feb;165(2):253-266.

Defining a Severe Asthma Super-Responder: Findings from a Delphi Process

- 81 participants (94% specialist pulmonologists or allergists) from 24 countries using a modified Delphi process, to develop an international consensus-based definition of a severe asthma SR.
- Why this definition?
  - Clinicians who treat severe asthma patients with novel add-on therapies are increasingly recognizing a subgroup of patients who experience remarkable clinical benefits.
  - The extent of improvement may be dramatic, much larger than the typical improvements reported in large RCTs.
  - Sometimes referred to as super-responders (SRs), such patients may report that their lives have been transformed.

Upham JW, Le Lievre C, et al. . J Allergy Clin Immunol Pract. 2021 Nov;9(11):3997-4004.

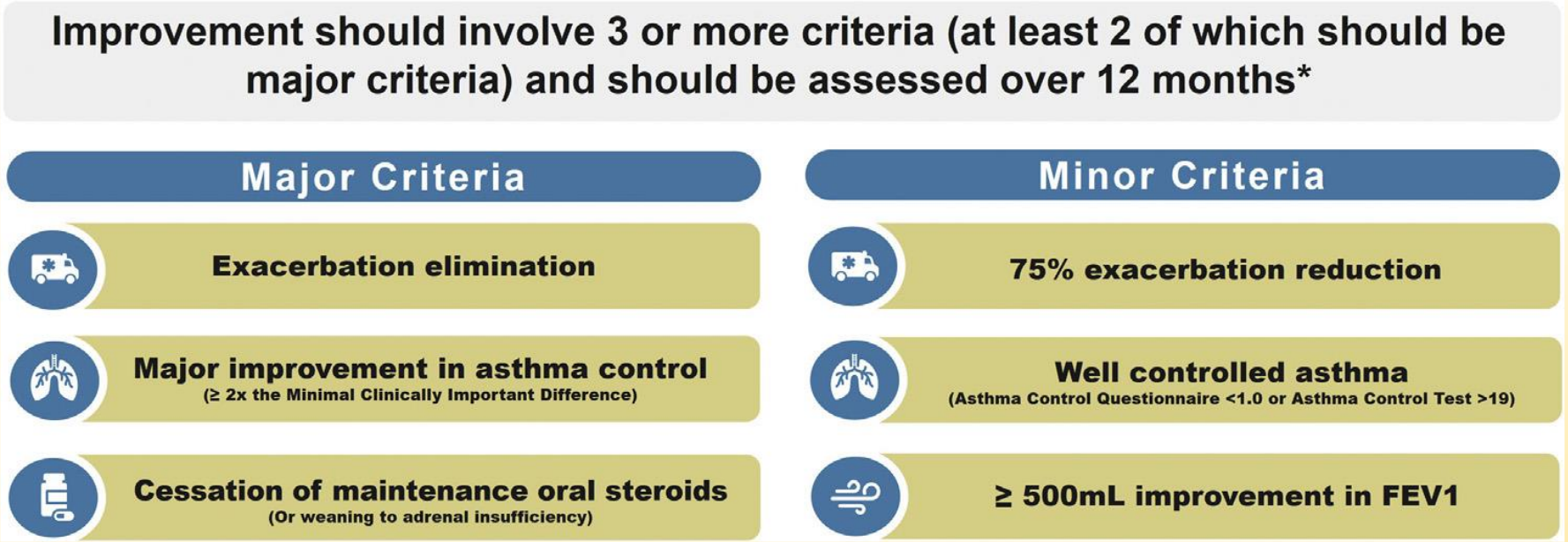


FIGURE 2. Major and minor criteria for defining a super-responder. *If exacerbation elimination has been achieved, it is inappropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to double-counting, because exacerbation elimination always includes a 75% exacerbation reduction.

The magnitude of a major improvement in asthma control should be at least twice the MCID for the ACQ and ACT. Thus, an improvement of 1.0 or greater in ACQ score or an improvement in ACT score of 6.0 or greater would be necessary to qualify as an SR.

Upham JW, Le Lievre C, et al. .J Allergy Clin Immunol Pract. 2021 Nov;9(11):3997-4004.

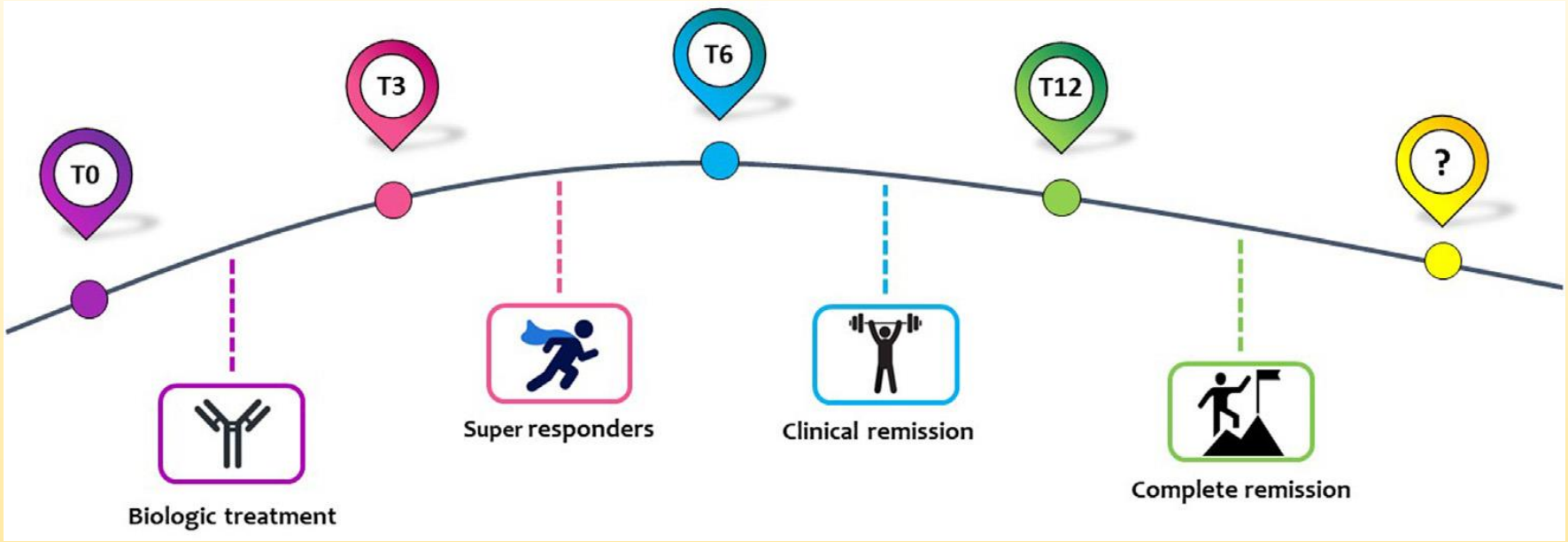
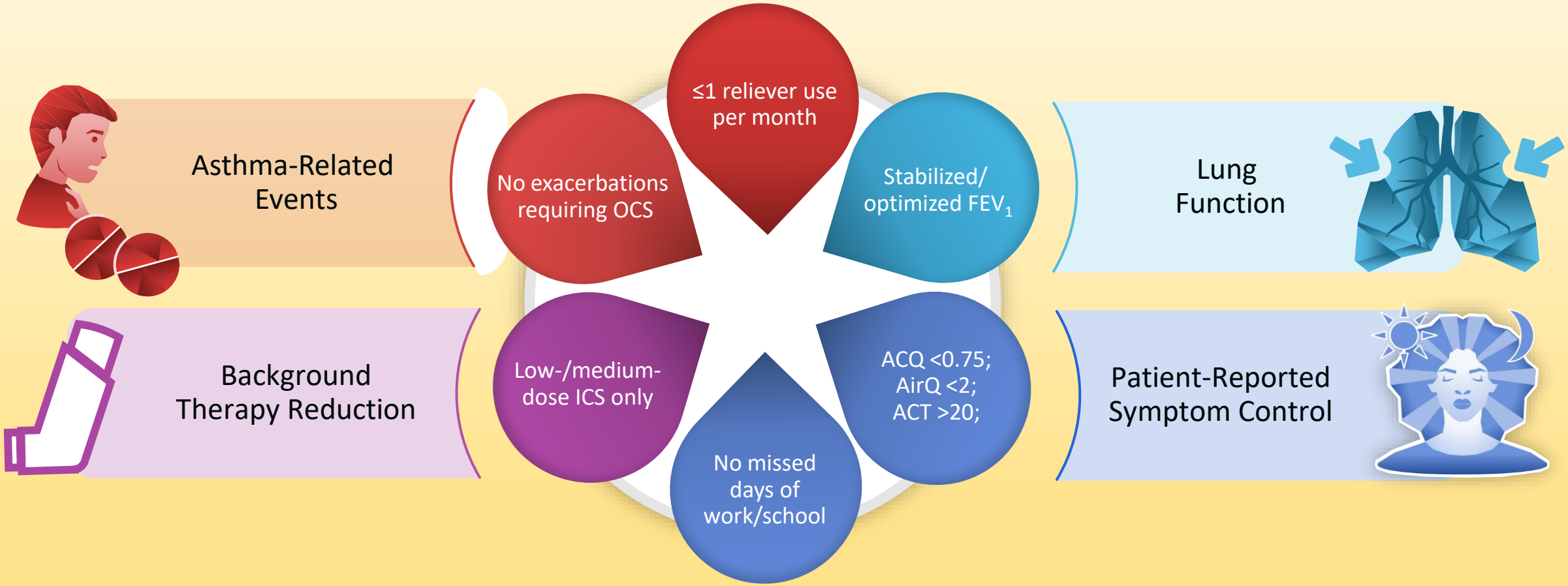


FIGURE 2. Pathway of super-response according to different follow-up times (T). After biologic treatment starts, super-responders should be identified between 3 (T3) and 6 (T6) months of follow-up. Clinical remission should be assessed up to 12 months of continuous therapy with monoclonal antibodies. A complete remission, defined as the sum of clinical remission, lack of airway hyper-responsiveness, and inflammation, should be stated only after a 1-year course of treatment.

Portacci A, Dragonieri S, Carpagnano GE. Super-Responders to Biologic Treatment in Type 2-High Severe Asthma: Passing Fad or a Meaningful Phenotype? J Allergy Clin Immunol Pract. 2023 May;11(5):1417-1420.

ACAAI, AAAAI, ATS Framework for On-Treatment Clinical Remission[1]



AAAAI, American Academy of Allergy, Asthma & Immunology; ACAAI, American College of Allergy, Asthma and Immunology; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AirQ, Asthma Impairment and Risk Questionnaire; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

1. Blaiss M, et al. *Ann Allergy Asthma Immunol*. Published online 7 September 2023. doi:10.1016/j.anai.2023.08.609 2. Thomas D, et al. *Eur Respir J.* 2022;60(5):2102583.

Why a Joint Consensus Statement for ACAAI, AAAAI, and ATS?

- It should be the professional medical societies developing a definition since FDA had no plans to develop one
- Confusion with all the different definitions in remission in asthma
- Setting the definition higher than “control”
- Need to develop a framework as a first step in an unified definition
- Along with the above organizations, the American Academy of Pediatrics had members on the consensus report
- The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) endorsed this statement

How did the Workgroup come up with the 6 criteria for On-Treatment Clinical Remission?

- Using a modified Delphi approach
- The workgroup unanimously agreed
  - 1. No exacerbations requiring physician visit, emergency care, hospitalization, and/or systemic steroid for asthma (oral, injectable)
  - 2. No missed work or school over a 12-month period due to asthma-related symptoms

How did the Workgroup come up with the 6 criteria for On-Treatment Clinical Remission? (cont.)

- 3. Stable and optimized pulmonary function results on all occasions measured over a 12-month period with a minimum of 2 measurements during the year.
    - Realizing that some with asthma may have pulmonary function that is below the accepted normal as their baseline owing to previous remodeling, we did not require any absolute numbers to comply
- 4. The criteria will allow continued use of controller (ICS, ICS/LABA, leukotriene receptor antagonist) only at low-to-medium dose of ICS (or less) as defined by most recent GINA guidelines.
    - Workgroup felt the need for a higher standard for remission and not just better “control”
    - Need to taper inhaled corticosteroids with realization that there are no studies long term studies

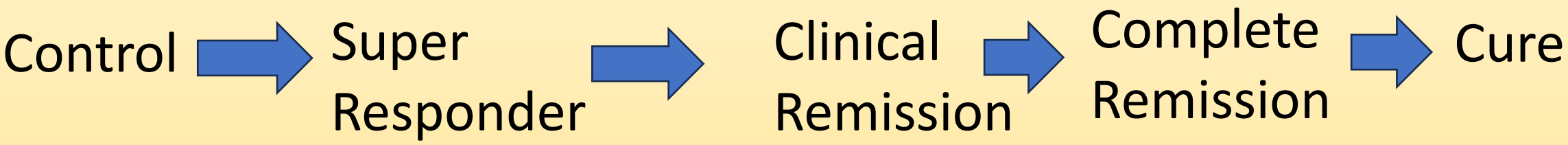
How did the Workgroup come up with the 6 criteria for On-Treatment Clinical Remission? (cont.)

- 5. ACT > 20, AIRQ < 2, ACQ < 0.75 on all occasions measured in the previous 12-month period with minimum of 2 measurements during the year.
- 6. Symptoms requiring 1-time reliever therapy (short-acting bronchodilator, ICS-short-acting bronchodilator, ICS-LABA) no more than once a month.
  - Lots of debate between the workgroup members here
  - Most felt that the most rigid standard of the GINA guidelines of less than twice a week was too much albuterol use.
  - There was a lack of consensus based on the lack of data/research, but the group recommended no more than 2 puffs per month on average as a starting point

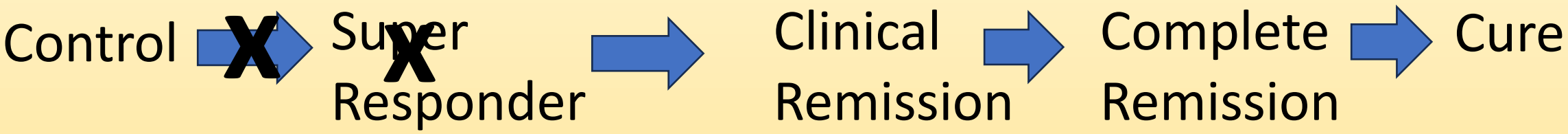
Need for Ways to Evaluate Daily Symptoms

- Exacerbations and oral corticosteroid bursts are not regular events
- Using rescue use and missing school and work, give us more information on whether daily asthma symptoms are occurring
- This is needed to show clinical remission is a step above control

Possible Progression in Asthma

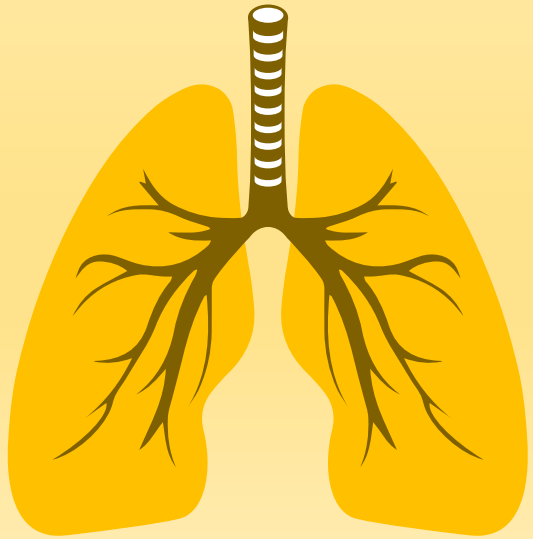


Possible Progression in Asthma

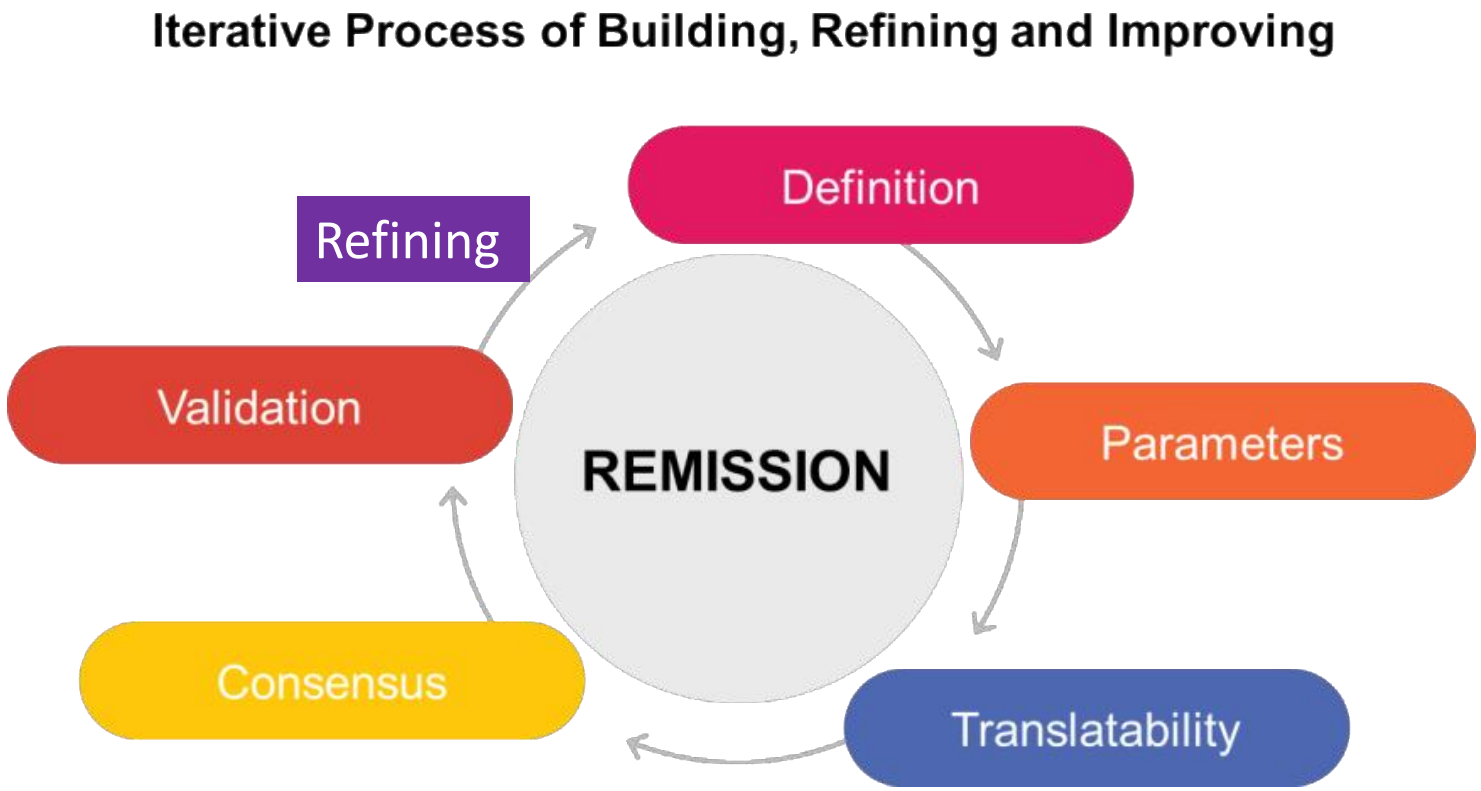


Possible Progression in Asthma

Control → Clinical Remission → Complete Remission → Cure



Remission in Asthma will Likely be an Evolving Process



HCP = health care practitioner; QOL = quality of life.

1. Singh JA, et al. *Arthritis Care Res (Hoboken);* 2016;68:1-25; 2. Menzies-Gow A, et al. *J Allergy Clin Immunol*. 2020;145:757-765

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- Validating proposed criteria for remission on treatment will depend on their intended purposes

1. Assessment tool for clinical practice
2. Prognosis for continued long-term stability
3. Identifying new targets of therapy

Conclusions

- Our ultimate goal in asthma is cure
- Presently, with innovative new treatments we may reach a higher level than control for some of our asthma patients---remission
- There are disagreements on exactly what is remission in asthma
- Is there a need to have a separate “super responder” definition?
- Consensus statement is a start in defining clinical remission in asthma