

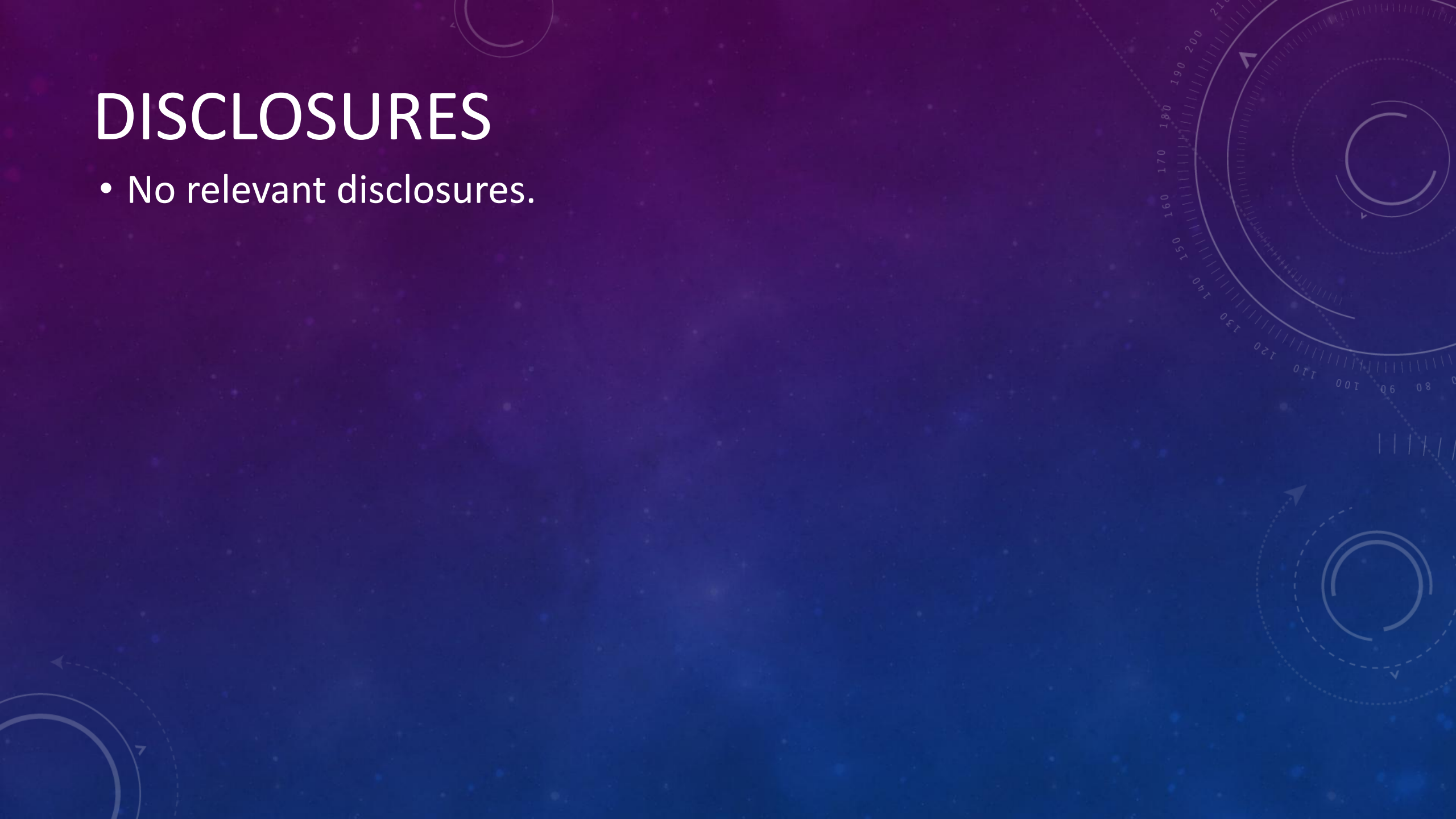
The background is a gradient of dark blue and purple. On the left side, there are several concentric circles and a large circular scale with degree markings from 140 to 260. Some of the circles have arrows indicating a clockwise direction. The overall aesthetic is technical and scientific.

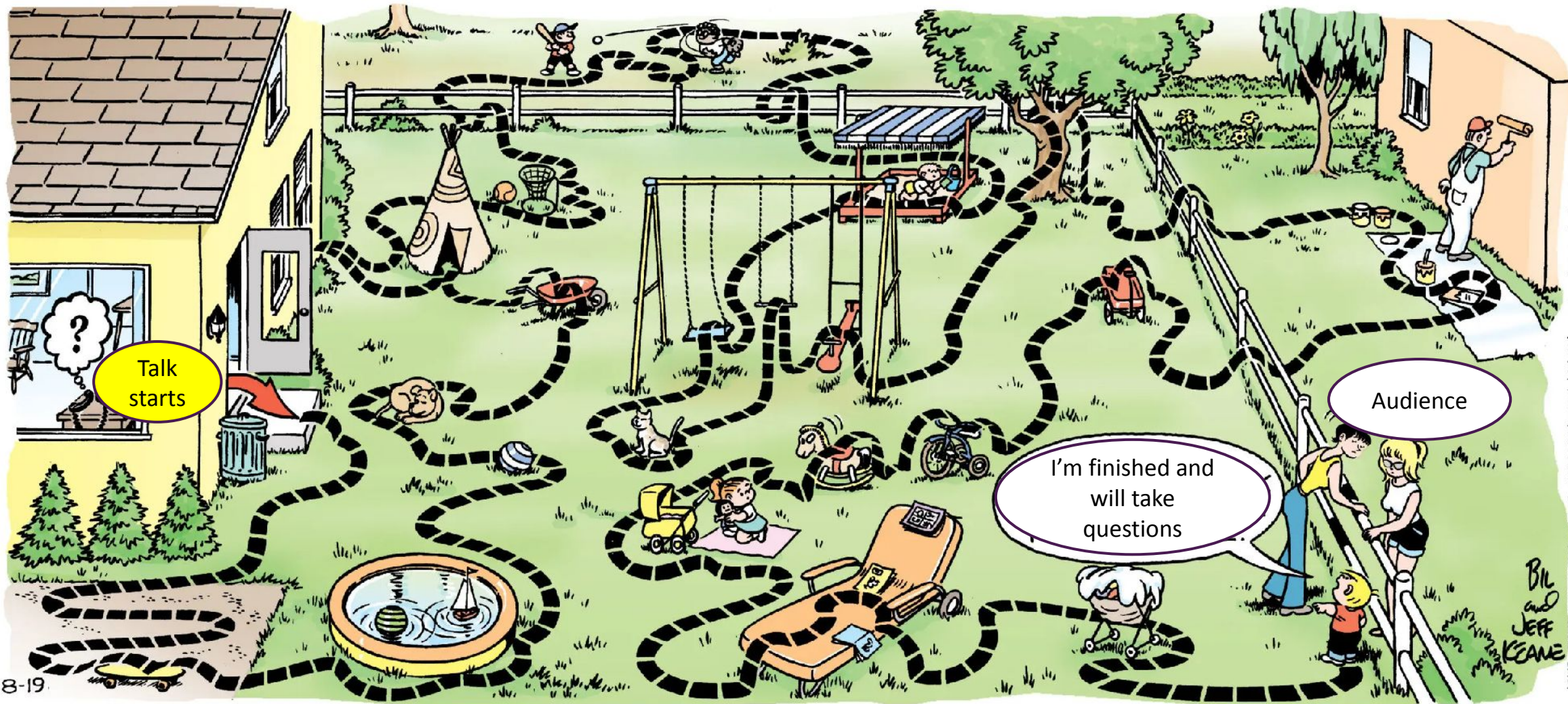
ALLERGIC RHINITIS: DETERMINING WHEN AND HOW TO STOP ALLERGEN IMMUNOTHERAPY

KIRK H. WAIBEL, MD FAAAAI, FAAAAI

DISCLOSURES

- No relevant disclosures.





OBJECTIVES

- Develop an on-going strategy when discussing the "how, when, and why" regarding AIT cessation vs continuation
- Recognize variables (clinical, immunologic) which can stratify candidates for cessation of AIT
- Understand the natural course of allergic rhinitis

WHY....

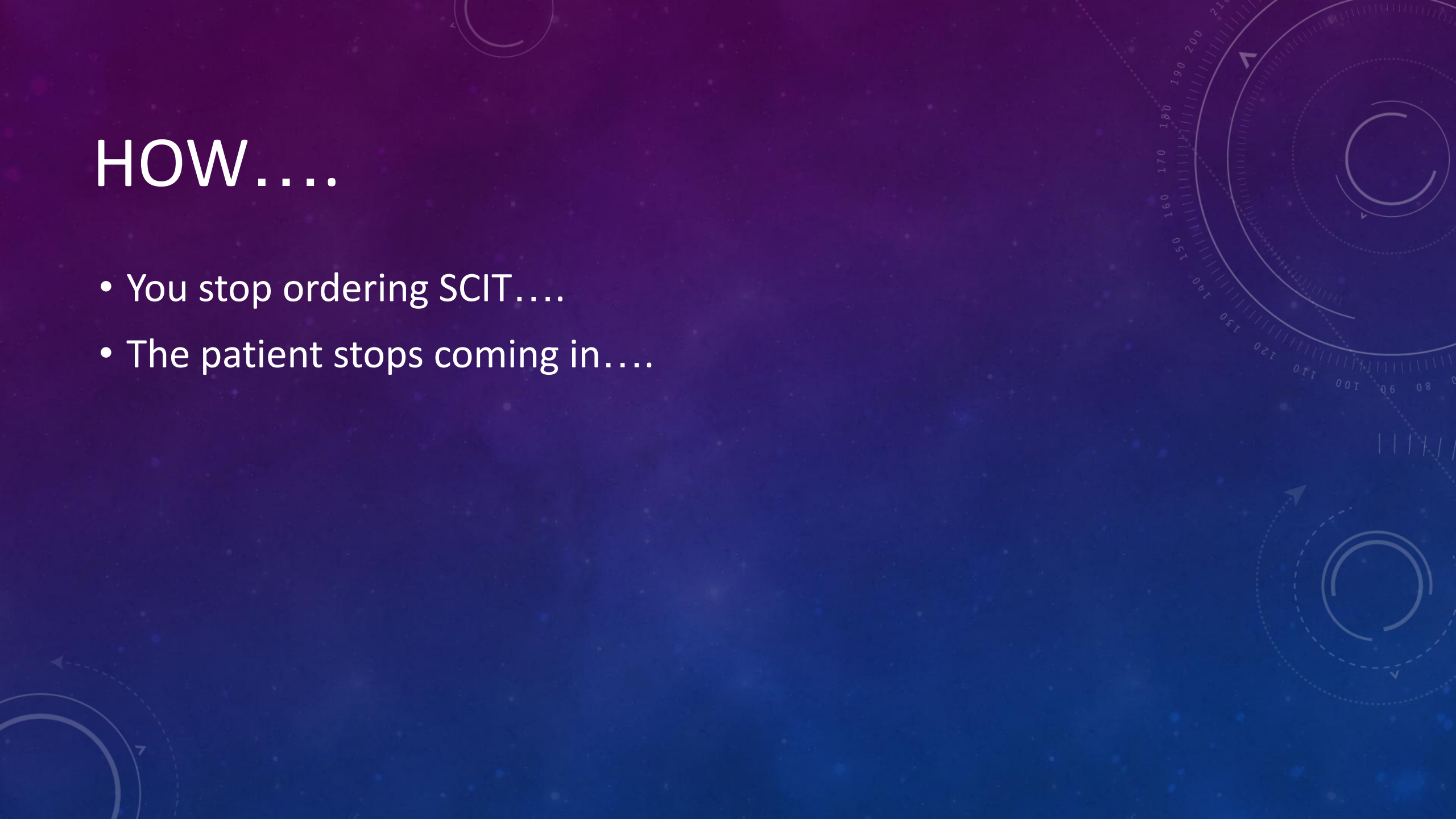
- Allergen immunotherapy (SCIT and FDA-approved SLIT) alters the natural course of allergic rhinitis resulting in long-term “resolution” of SAR/PAR

WHEN....

- When you want to stop.....
- When the patient wants to stop.....
- When external factors decide for you.....
 - Factors leading to premature discontinuation
 - Co-pay requirements (40%), Travel inconvenience (15%), Moved (8%), Other health issues (5%), perceived ineffectiveness (4%), patient perceived lack of need to continue (2%), adverse side effect (1% local, 0.5% systemic), 24.5% no reason provided

HOW....

- You stop ordering SCIT....
- The patient stops coming in....



MAIN FOCUS AREAS

- Assumptions
- Guidelines
- Relative and absolute contraindications
- Clinical or immunologic biomarkers
- Natural course of SAR/PAR

ASSUMPTIONS

- Appropriate workup (+hx, +relevant SPT, ID, or slgE results)
- Appropriate allergen dosing
- Patient reached the desired “maintenance dose”
- Patient demonstrated clinical improvement
- Completed at least 3 years of continuous SCIT (23%)¹



¹Vaswani R, Garg A, Parikh L et al. Ann Allergy Asthma Immunol 2015; 241-3.

FAILURE TO TREAT WITH ADEQUATE DOSE

TABLE IX. Probable effective dose range for standardized and nonstandardized US- licensed allergen extracts

Allergenic extract	Labeled potency or concentration	Probable effective dose range	Range of estimated major allergen content in US-licensed extracts
Dust mites: <i>D. farinae</i> and <i>D. pteronyssinus</i>	3,000, 5,000, 10,000, and 30,000 AU/mL	500-2,000 AU	10,000 AU/mL 20-160 µg/mL Der p 1, Der f 1* 2-180 µg/mL Der p 2, Der f 2* 78-206 µg/mL Der p 1, Der f 1† 13-147 µg/mL Der p 2, Der f 2†
Cat hair	5,000 and 10,000 BAU/mL	1,000-4,000 BAU	10,000 BAU/mL 20-50 µg/mL Fel d 1*† 30-100 µg/mL cat albumin§
Cat pelt	5,000-10,000 BAU/mL	1,000-4,000 BAU	10,000 BAU/mL 20-50 µg/mL Fel d 1*† 400-2,000 µg/mL cat albumin§
Grass, standardized	100,000 BAU/mL	1,000-4,000 BAU	100,000 BAU/mL 425-1,100 µg/mL Phl p 5* 506-2,346 µg/mL group 1
Bermuda	10,000 BAU/mL	300-1,500 BAU	10,000 BAU/mL 141-422 Cyn d 1 µg/mL*
Short ragweed	1:10, 1:20 wt/vol, 100,000 AU/mL	6-12 µg of Amb a 1 or 1,000-4,000 AU	1:10 wt/vol 300 µg/mL Amb a 1† Concentration of Amb a 1 is on the label of wt/vol extracts
Nonstandardized AP Dog	1:100 wt/vol	15 µg of Can f 1	80-400 µg/mL Can f 1† 10-20 µg/mL dog albumin¶
Nonstandardized extract, dog	1:10 and 1:20 wt/vol	15 µg of Can f 1	0.5 to 10 µg/mL Can f 1† <12-1,500 µg/mL dog albumin¶
Nonstandardized extracts: pollen	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	0.5 mL of 1:100 or 1:200 wt/vol	NA
Nonstandardized extracts: mold/fungi, cockroach	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose	NA
Hymenoptera venom	100 µg/mL single venom 300 µg/mL in mixed vespid extract	50-200 µg of each venom	100-300 µg/mL of venom protein
Imported fire ant	1:10 to 1:20 wt/vol whole-body extract	0.5 mL of a 1:100 wt/vol to 0.5 mL of a 1:10 wt/vol extract	NA

- Dust mite: 0.5 -2mL
- Cat 1-4mL
- Dog (depends)
- Bermuda 0.3 -1.5mL
- Timothy 0.1-0.4mL
- Non-standardized pollens 0.5mL

➤ Cox L et al. Allergen Immunotherapy: A practice parameter third update. J Allergy Clin Immunol 2011; 127(1): S1-S55.

"IMPROVEMENT"

- Retrospective review of 1,624 AIT patients with 1,519 matched patients not on AIT
- 30% improvement in CSMS
 - 84% vs 8%
- 60%+ improvement from baseline
 - 71% vs 6%

CSMS criteria (0-6)

Symptom scoring

Itchy nose	0-3	
Sneezing	0-3	
Runny nose	0-3	
Blocked nose	0-3	
Conjunctival symptoms	Itchy/red eyes	0-3
	Watery eyes	

- Add up and divide by 6 = daily symptom score (dSS)

PLUS

- Daily medication score (dMS) [0-3]
 - 1 = oral and/or topical H1
 - 2 = INCS and/or H1
 - 3 = OCS +/- INCS +/- H1

RELATIVE CONTRAINDICATIONS

- Partially controlled asthma (FEV1 <70%)
- Patient taking a beta-blocker or ACE-I
- Severe cardiovascular disease (e.g., arrhythmia, CAD, uncontrolled HTN)
- Primary or secondary immunodeficiency
- History of systemic reaction to SCIT
- Children under 5
- Low compliance

ABSOLUTE CONTRAINDICATIONS

- Uncontrolled or severe asthma
- Diagnosis of current malignancy or refractory autoimmune disorder
- Starting in a woman who is pregnant
- * Patient is unable or unwilling to communicate
- ** Patient tried to die after a SCIT injection

WAO SCIT SYSTEMIC REACTION GRADING

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<i>Symptom(s)/ sign(s) of one organ system presentⁱ</i> <u>Cutaneous</u> Generalized pruritus, urticaria, flushing or sensation of heat or warmthⁱⁱ or Angioedema (not laryngeal, tongue or uvular) or <u>Upper respiratory</u> Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to come from the upper airway, not the lung, larynx, or trachea or <u>Conjunctival</u> Conjunctival erythema, pruritus or tearing <u>Other</u> Nausea, metallic taste, or headache	<i>Symptom(s)/ sign(s) of more than one organ system present</i> or <u>Lower respiratory</u> Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) or <u>Gastrointestinal</u> Abdominal cramps, vomiting, or diarrhea or <u>Other</u> Uterine cramps	<u>Lower respiratory</u> Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) or <u>Upper respiratory</u> Laryngeal, uvula or tongue edema with or without stridor	<u>Lower or Upper respiratory</u> Respiratory failure with or without loss of consciousness or <u>Cardiovascular</u> Hypotension with or without loss of consciousness	Death

IMMUNOLOGIC EFFECTS OF AIT

- Increase in CD4+CD25+ regulatory T cells
- Increase in CD10 and TGF-B
- Deviation from Th2 -> Th1
- sIgE response – initially increases and then decreases
- Increase in specific IgG1, IgG4, and IgA (but does not correlate with clinical improvement)
- ?Changes in avidity, affinity for allergen may play a role.

BIOMARKERS

- EAACI reviewed 7 domains
 - Total IgE
 - sIgE
 - sIgE/total IgE ratio
 - IgG subclasses (IgG1, sIgG4, sIgE/IgG4 ratio)
 - Serum inhibitory activity for IgE
 - Basophil activation
 - Cytokines and chemokines
 - Cellular markers
 - *In vivo* markers

BIOMARKERS

- No validated or generally accepted biomarkers which are predictive of SCIT response¹
- Although one study in HDM-allergic patients with asthma who demonstrated continued improvement had reduced skin test reactivity with titrated HDM extract²

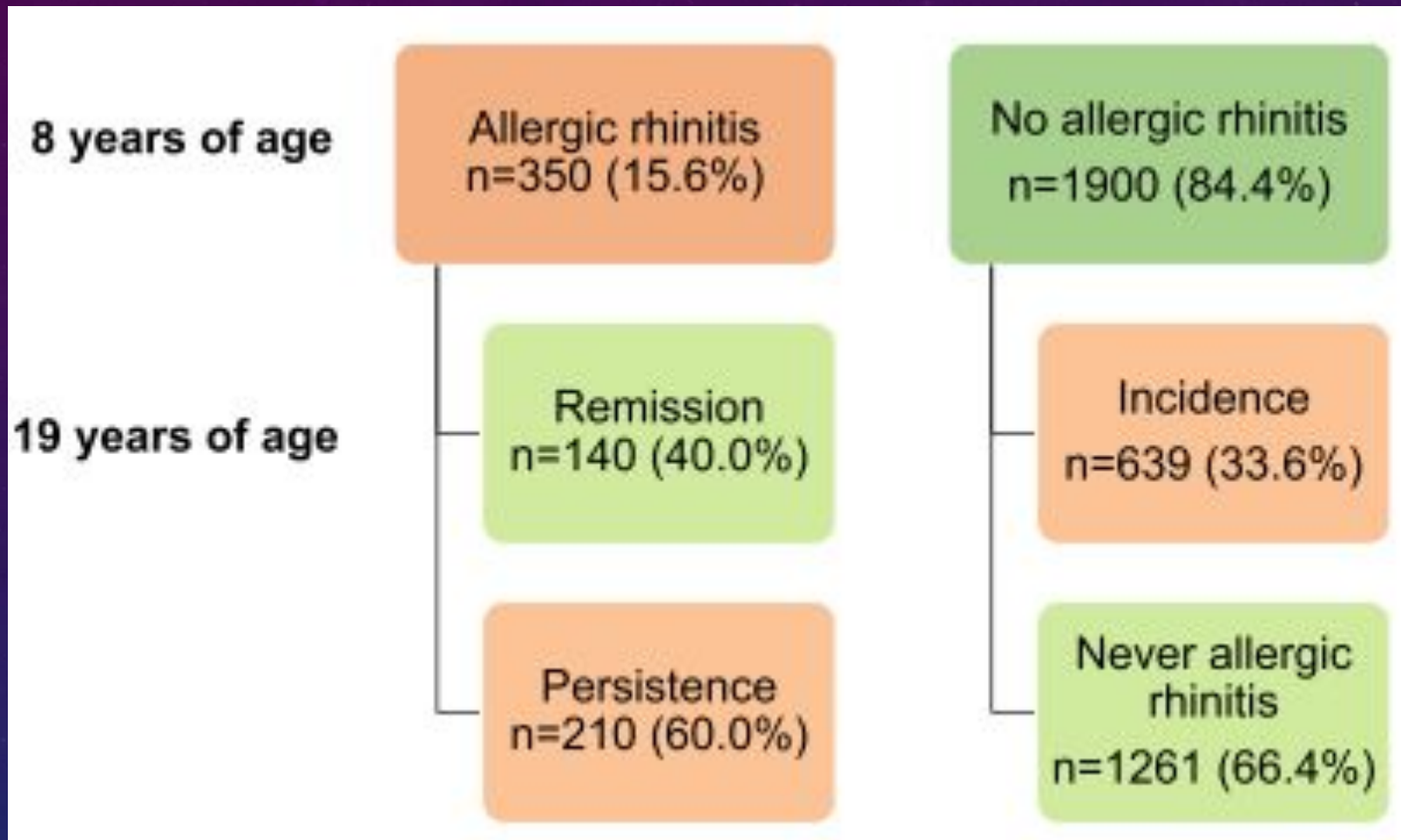
¹Shamji MH, Kappen JH, Akdis M et al. Allergy 2017 (72): 1156-1173.

² A Des Roches, L Paradis, J Knani et al. Allergy 1996; 51(6): 430-3.

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- 2006 longitudinal study in Sweden from age 8 -> 19yrs
 - 2,250 completed questionnaire; 1,338 had skin testing at 8 and again at 19
 - pet dander, HDM, birch, timothy, alternaria, cladosporium, mugwort
 - "Remission" defined as having a +questionnaire at 8yrs but not at 19 yrs
 - No immunotherapy

	2006				2016-2017			
	Total % (n = 2250)	Boys % (n = 1153)	Girls % (n = 1097)	Difference by sex, p-value	Total % (n = 2250)	Boys % (n = 1153)	Girls % (n = 1097)	Difference by sex, p-value
Symptoms and diseases								
Current AR symptoms	15.1 (339)	17.5 (202)	12.5 (137)	<.001	35.6 (800)	31.7 (366)	39.6 (434)	<.001
Current AR medication	10.2 (229)	11.4 (132)	8.8 (97)	.043	22.2 (499)	18.9 (218)	25.6 (281)	<.001
Current AR	15.6 (350)	18.0 (207)	13.0 (143)	.001	37.7 (849)	34.3 (395)	41.4 (454)	<.001
Physician-diagnosed AR	7.8 (175)	8.9 (103)	6.6 (72)	.040	8.9 (201)	8.1 (93)	9.8 (108)	.140
Physician-diagnosed asthma	7.1 (160)	9.1 (105)	5.0 (55)	<.001	17.6 (395)	17.6 (203)	17.5 (192)	.956
Physician-diagnosed eczema	15.4 (346)	16.4 (189)	14.3 (157)	.179	14.7 (331)	11.6 (134)	18.0 (197)	<.001
Sensitisation								
At least one positive skin prick test	30.9 (413/1338)	34.3 (244/654)	27.6 (189/684)	.009	46.8 (626/1338)	50.8 (332/654)	43.0 (294/684)	.004



WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- Prevalence of allergic rhinitis ranges from 15-30%
- Clinical remission of AR up to 25% of patients
- Previous factors:
 - Absence of IgE sensitization
 - Older age
 - No asthma at baseline

Heldin J, Malinovschi A, Johannessen A, et al. J Asthma and Allergy 2022; 15: 1569-1578.

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- Longitudinal questionnaire study in Sweden, Norway, Iceland, Denmark, and Estonia
- 1989-1992 (RHINE I), 1989-2001 (RHINE II), and 2010-2012 (RHINE III)
- 20-44yrs (n=21,595), 30-54yrs (n = 16,049), and 38-66yrs (n=13,053 [60%])

Heldin J, Malinovschi A, Johannessen A, et al. J Asthma and Allergy 2022; 15: 1569-1578.

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- AR defined as "Do you have any nasal allergies, including hay fever?"
- Remission defined as +response in Rhine I or II with a negative response in RHINE III

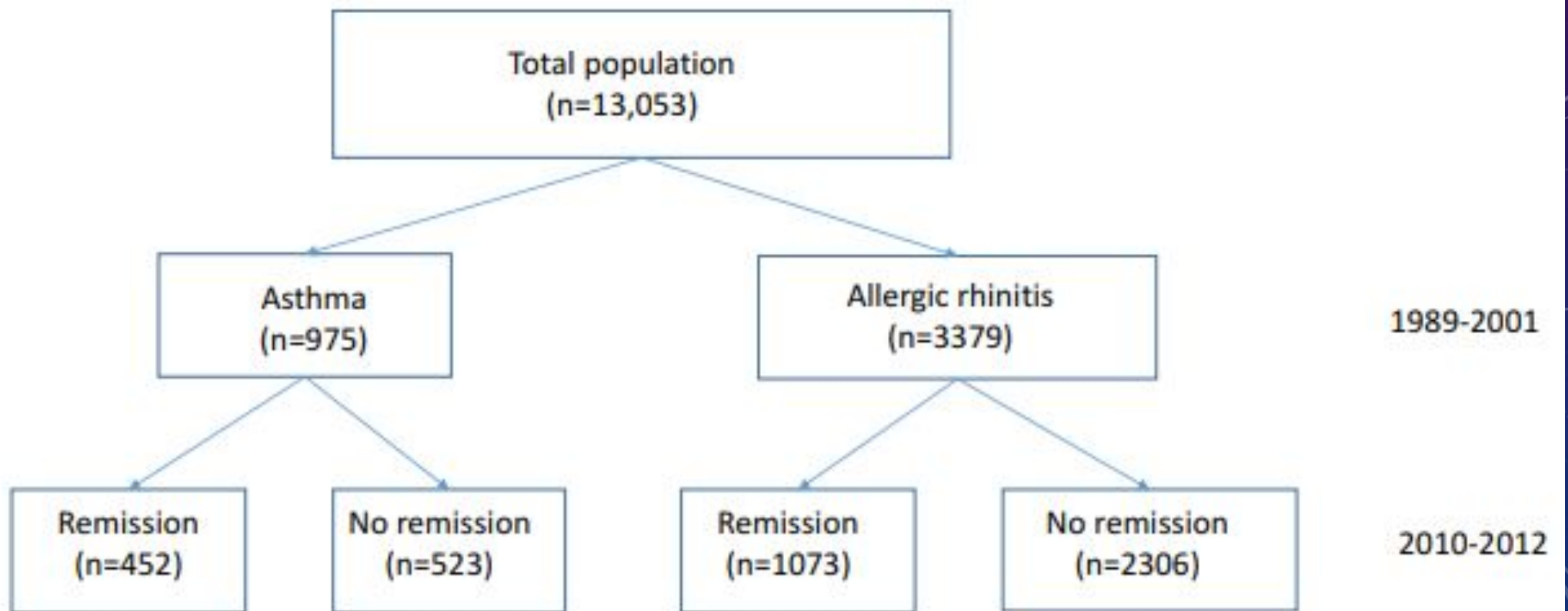


Figure 1 Study flow and number of participants with and without a clinical remission of asthma and allergic rhinitis.

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- 3,378 reported allergic rhinitis
- 1,078 (31.8%) had remission by RHINE III
- Factors related to clinical remission
 - AR onset after age 12yrs
 - Living on a farm or rural area
 - Absence of asthma

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- Both sensitization and allergic rhinitis (AR) are considered chronic conditions
- Remission of "sensitization [skin test responses] in adult and pediatric populations is reported to be 1-20%
- Few studies also included sIgE responses

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- Mailed survey to participants 15-69 yrs old followed by health exam
 - 6,998 responded to survey
 - Random group selected (n=793) and symptom group (n=788)
 - slgE was "positive" if ≥ 0.7 kU_a/L (class 2)
- AR defined as +slgE with +clinical response
- "Remission" defined as absence of symptoms/response

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- Follow up 94 months (range 82-104)

TABLE I. Remission of AR from 1990 to 1998 (n = 198)

Disease status 1990	Total, % (n)	Disease status 1998: Symptoms			
		Absent		Present	
		s-IgE ≥ 0.7 kU _A /L		s-IgE ≥ 0.7 kU _A /L	
		Absent, % (n)	Present, % (n)	Absent, % (n)	Present, % (n)
Pollen AR*	100 (170)	2.4 (4)	9.4 (16)	4.1 (7)	84.1 (143)
Furry animal AR*	100 (53)	1.9 (1)	17.0 (9)	9.4 (5)	71.7 (38)
HDM AR*	100 (34)	5.8 (2)	32.4 (11)	0 (0)	61.8 (21)

*Definition: self-reported rhinitis symptoms on allergen exposure within the last 12 months and relevant allergen-specific IgE levels of 0.7 kU_A/L or greater.

- Remission rate 16.7% (11.8-38.2%)

Bodtger U and Linneberg. Remission of allergic rhinitis: An 8-year observational study. J Allergy Clin Immunol 2004; 144(6): 1384-1388.

WILL ALLERGIC RHINITIS GO AWAY ON ITS OWN?

- 78% of patients with clinical remission had stable sIgE levels
- 22% of remitting vs 7.4% of non-remitting) had a sIgE reduce by one s-IgE class
- Patients receiving AIT (n=13) had remission of 18.8% vs non-AIT patients with 14.7% ($P = 0.6$)
- Conclusion: AR to aeroallergens is a chronic disease

FACTORS WHICH INFLUENCE SUBCUTANEOUS IMMUNOTHERAPY (SCIT)

- Age
- Mono vs polysensitized
- Smoking status
- Level of allergen exposure
- Dose of allergen used
- Duration of SCIT

- What do the guidelines say

Follow-up every 6 to 12 months while on immunotherapy or more frequently for evaluation/management of immunotherapy reactions and/or underlying allergic disease or co-morbid conditions

Assess at follow up

Clinical response to immunotherapy (e.g., symptoms, medication use)

Immunotherapy schedule, reactions, compliance

Continuation of immunotherapy treatment

12

BOX 12

- Reassess symptoms and medication use
- Medical hx since last visit
- Evaluation of immunotherapy response
- IT schedule
- Patient compliance
- Make adjustments in schedule or dose

<https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=32553>

BOX 12

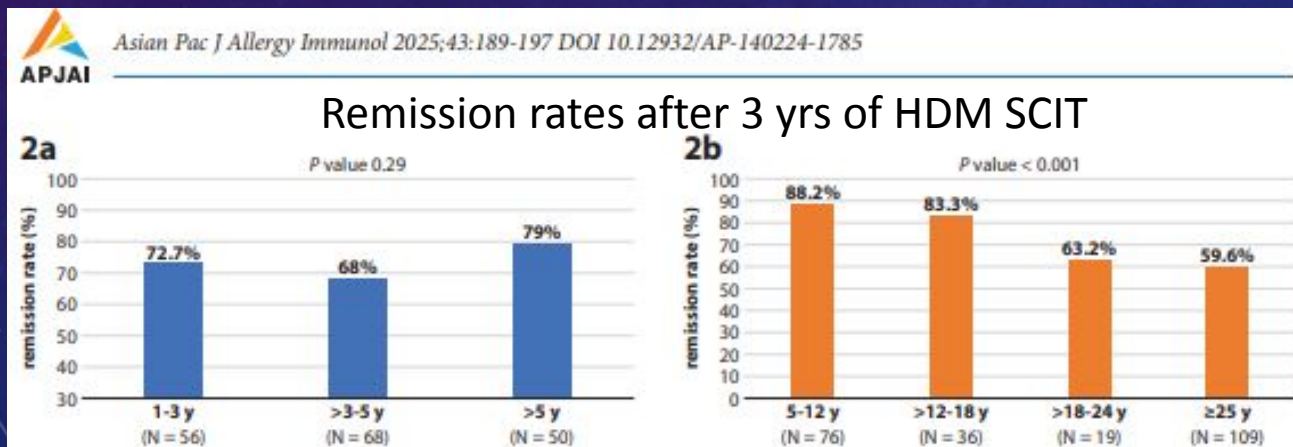
- There are no specific markers that will predict who will remain in clinical remission after discontinuing effective allergen immunotherapy (AIT).

BOX 12 - CONSIDERATIONS

- Decision is individualized
- Factors to consider
 - Severity of illness prior to starting AIT
 - Cost/Inconvenience of AIT

PRACTICAL CONSIDERATIONS

- Starting sooner is likely better, especially if monosensitized
- n=240 who completed HDM AIT > 3yrs and off for 1+yrs
- Ages 11-36 (mean 21 yrs)
- "Remission" defined as no longer requiring oral antihistamines or nasal sprays to control symptoms





Machine learning

Cillufo G, Bajowala S, Elliott T et al. JACI In Pract 2025; 13(11): 2877-2889.

