

ACCURATE DIAGNOSIS OF ALLERGIC AIRWAY DISEASES

Prof Dr Philippe GEVAERT

DISCLOSURES

Phillipe Gevaert, MD, PhD, has disclosed the following relationships: Served as an advisor or speaker and received grant/research support from: 3NT, Ablynx, ALK, Argenx, Bekaert Textiles, Genentech, GSK, Hall Allergy, Medtronic, Novartis, Regeneron, Roche, Sanofi-Genzyme, Teva, and Thermo Fisher

ACCURATE DIAGNOSIS OF ALLERGIC AIRWAY DISEASES

History
Inspection
Clinical Examination

Sensitisation
Nasal patency
Nasal provocation

Precision medicine

SYMPTOMS OF ALLERGIC RHINITIS

4 MAJOR NASAL SYMPTOMS

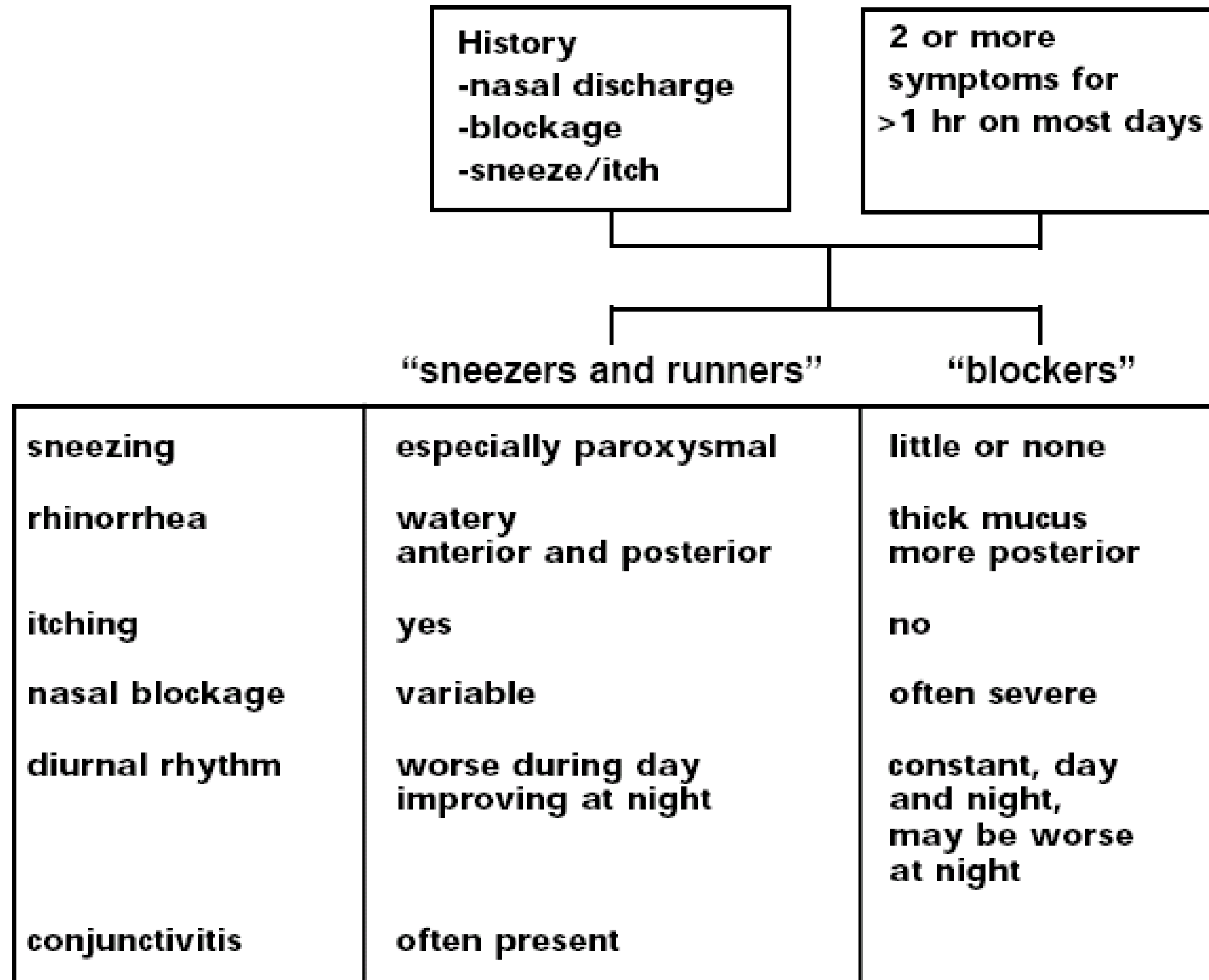
sneezing
itchy nose
rhinorrhoea

nasal obstruction



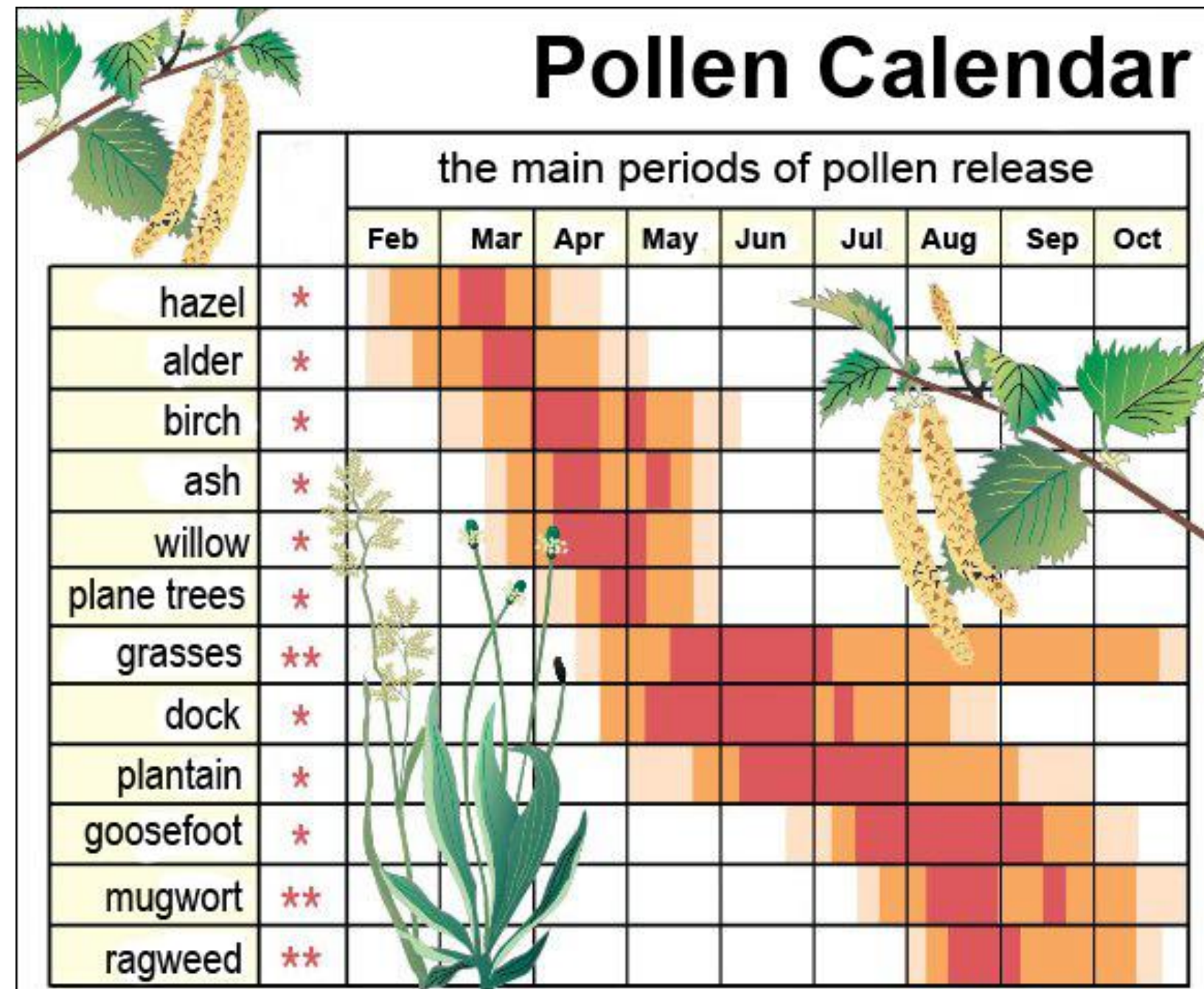
NOTE
most important
symptom !

Clinical assessment of rhinitis



HISTORY TAKING IN ALLERGIC RHINITIS

seasonality of symptoms

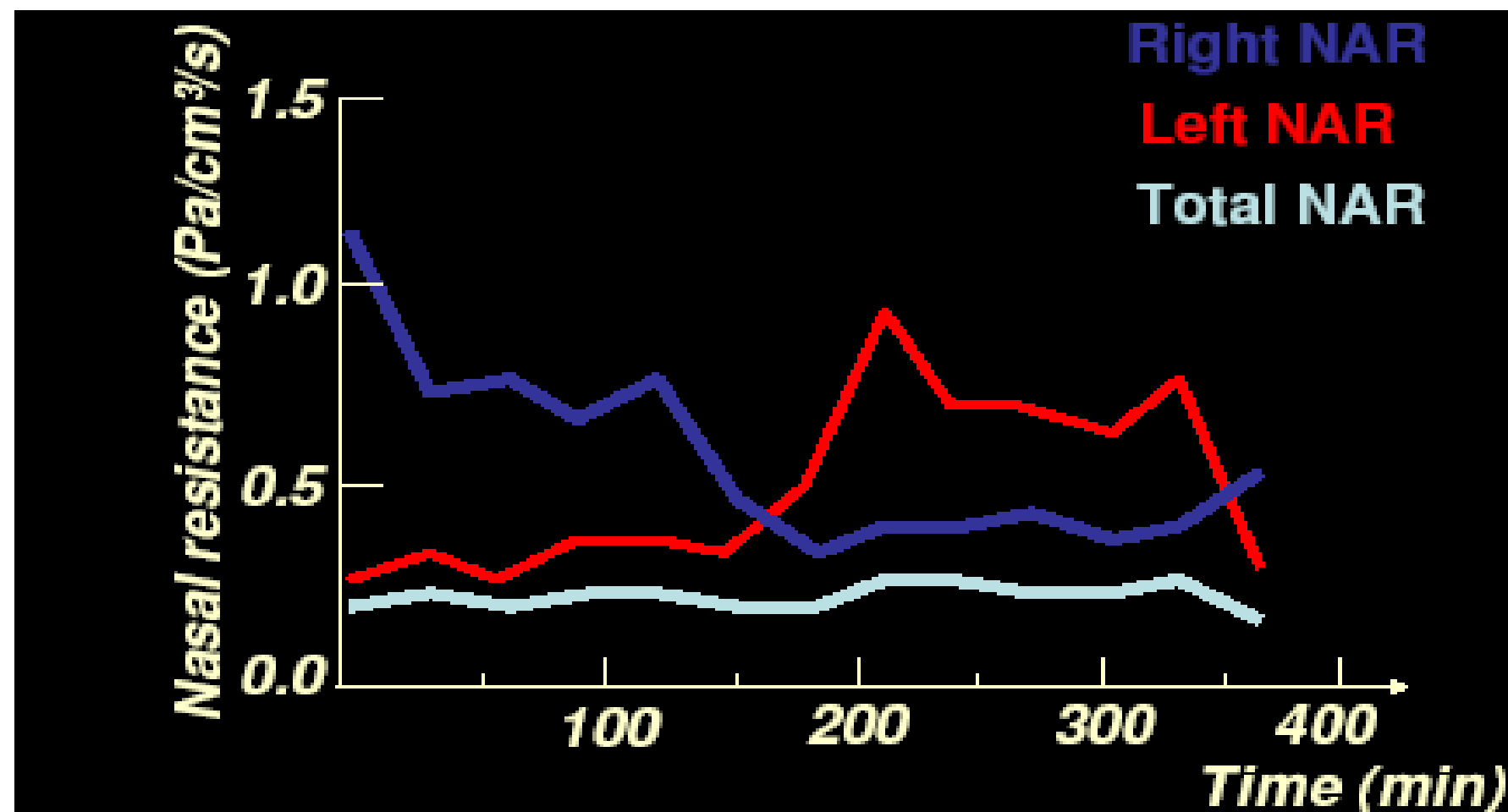


HISTORY TAKING IN ALLERGIC RHINITIS

seasonality of symptoms

influencing factors

aggravating vs alleviating factors



Cave: Nasal Cycle!

HISTORY TAKING IN ALLERGIC RHINITIS

seasonality of symptoms

influencing factors

aggravating vs alleviating factors

duration of symptoms

Intermittent

- . < 4 days per week
- . or < 4 weeks

Persistent

- . \geq 4 days per week
- . and \geq 4 weeks

HISTORY TAKING IN ALLERGIC RHINITIS

seasonality of symptoms

influencing factors
aggravating vs alleviating factors

duration of symptoms

effects on **general well-being**
Quality of life

ARIA CLASSIFICATION

Intermittent

- . < 4 days per week
- . or < 4 weeks

Persistent

- . ≥ 4 days per week
- . and ≥ 4 weeks

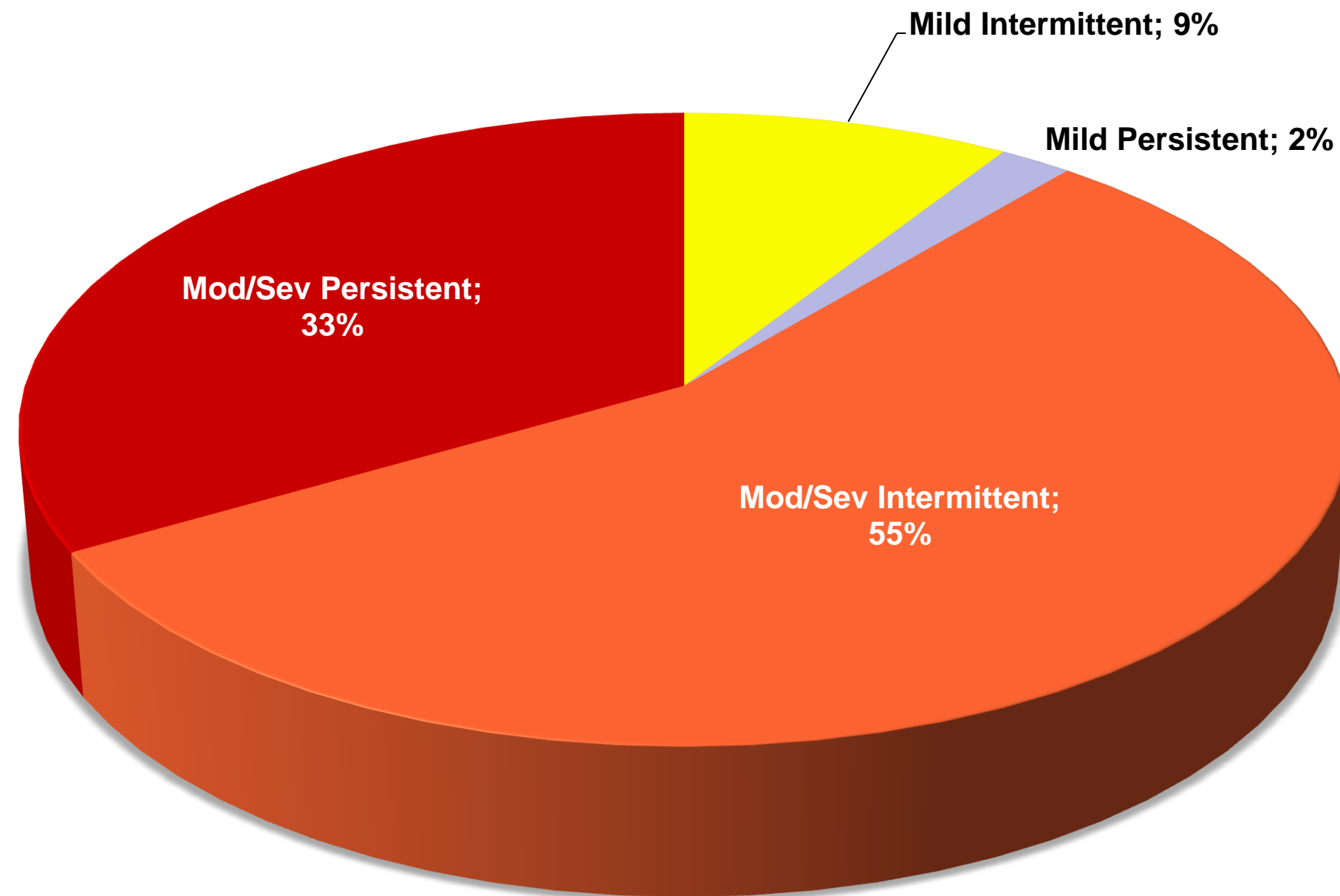
Mild

normal sleep
& no impairment of daily
activities, sport, leisure
& normal work and
school
& no troublesome
symptoms

Moderate-severe *one or more items*

- . abnormal sleep
- . impairment of daily activities,
sport, leisure
- . abnormal work and school
- . troublesome symptoms

CLASSIFICATION OF AR PATIENTS IN GENERAL PRACTICE DURING POLLEN SEASON

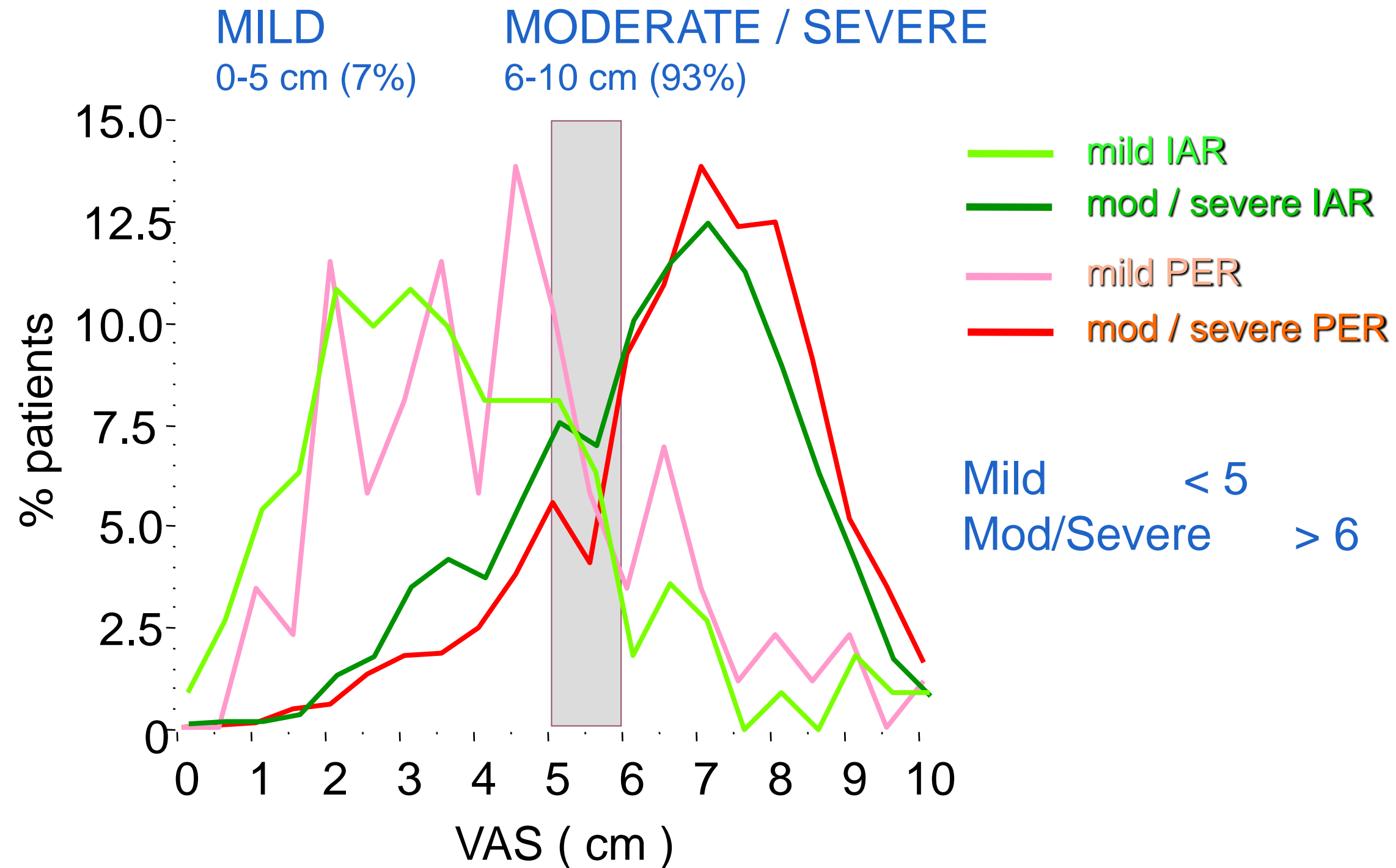


N=804 subjects with GP-based diagnosis

Van Hoecke et al, 2005

ARIA classification

SEVERITY



HISTORY TAKING IN ALLERGIC RHINITIS

Family history of allergy: Eczema

Food allergy: Oral allergy syndrome (birch – apple)

Asthma: cough - dyspnea

Occupation: exposure to allergens / irritants
relation to symptoms

Medication use: reactions to medication e.g. aspirin
use of decongestant sprays

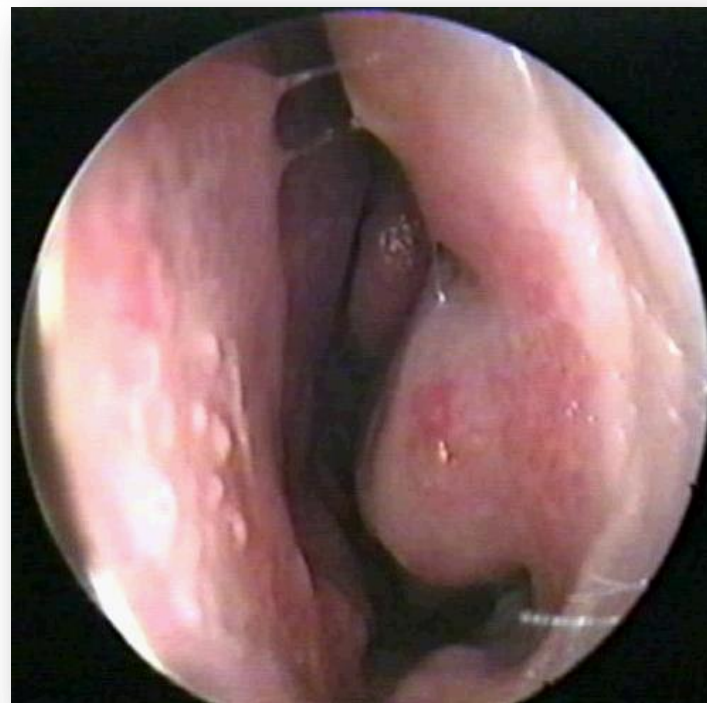
INSPECTION OF THE NOSE

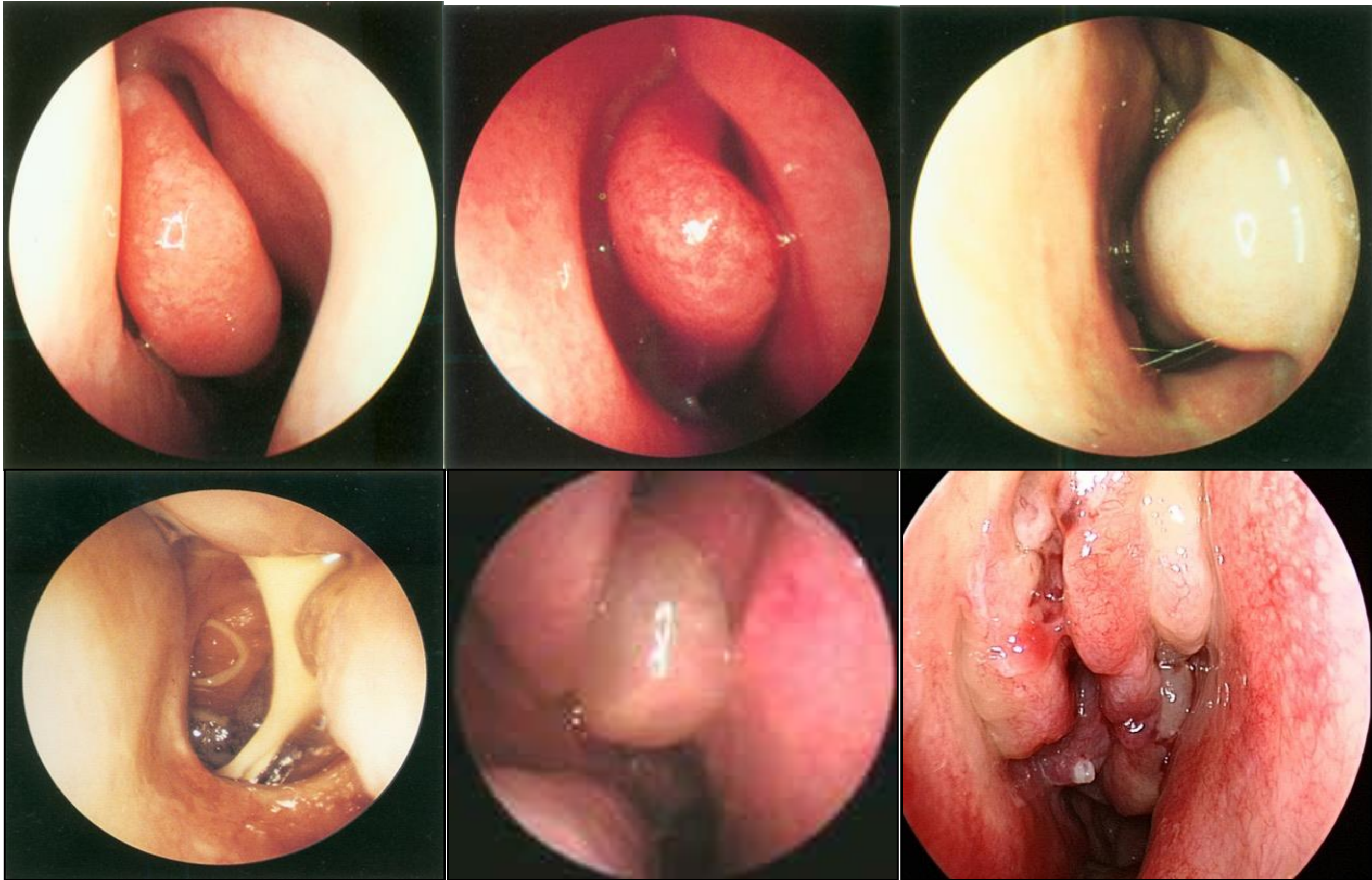
SIGNS OF ALLERGIC RHINITIS in children

- Open mouth breathing: adenoids?

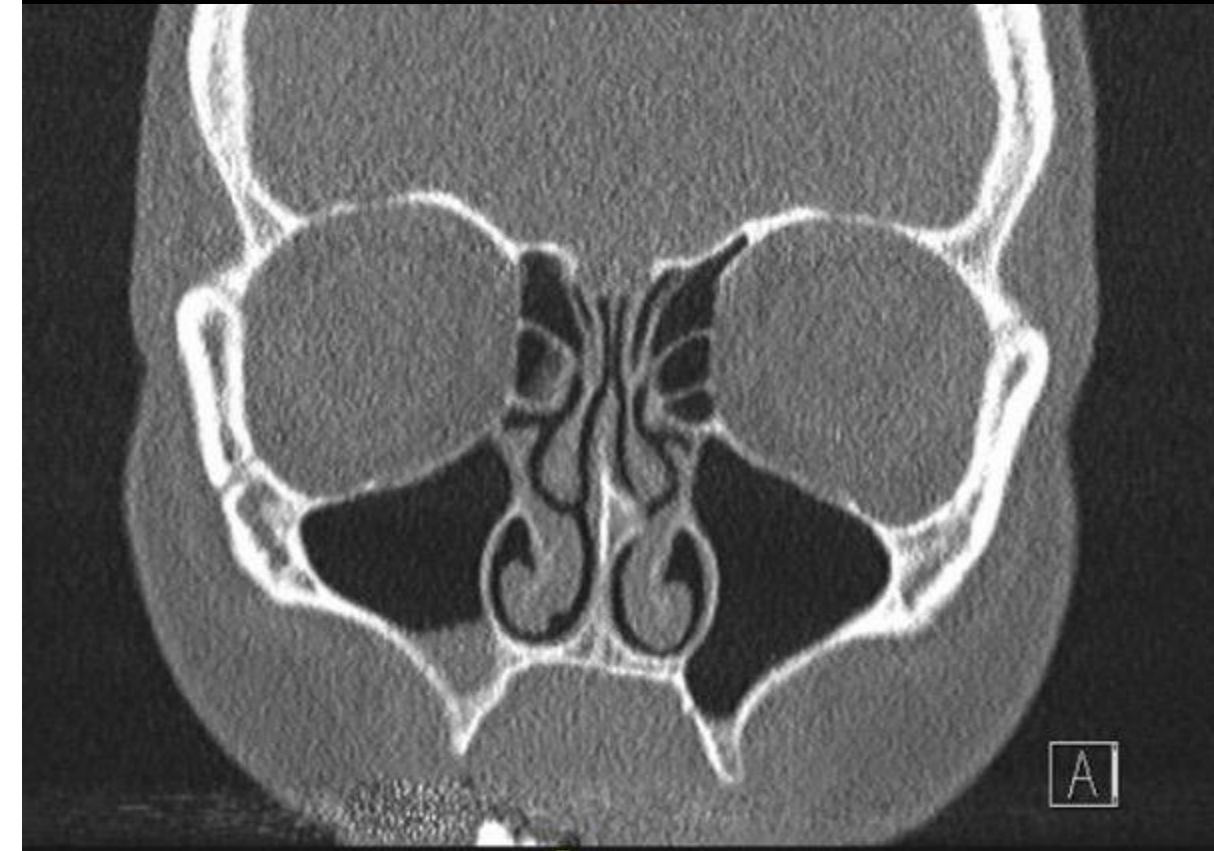
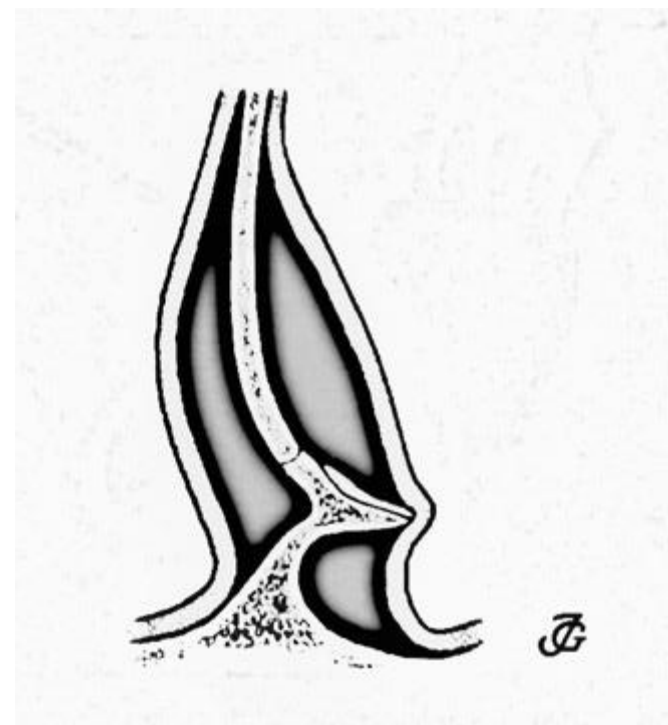
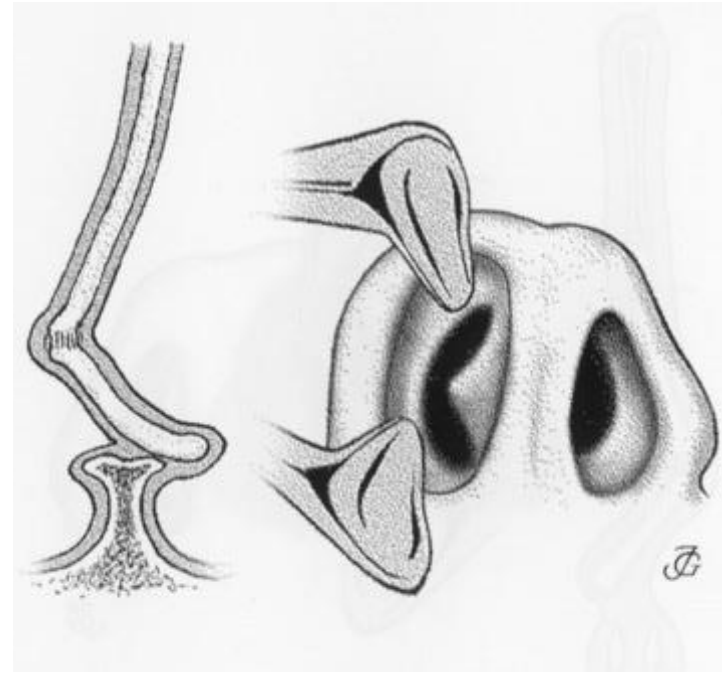
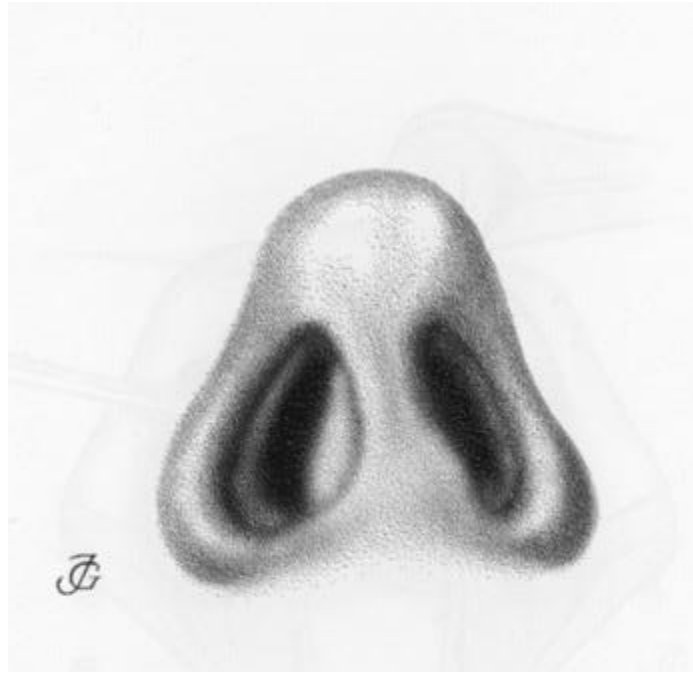


ANTERIOR RHINOSCOPY & NASAL ENDOSCOPY





SEPTAL PATHOLOGY



ACCURATE DIAGNOSIS OF ALLERGIC AIRWAY DISEASES

History
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Nasal provocation

Precision medicine

SKIN PRICK TESTING VERSUS ALLERGIC SYMPTOMS

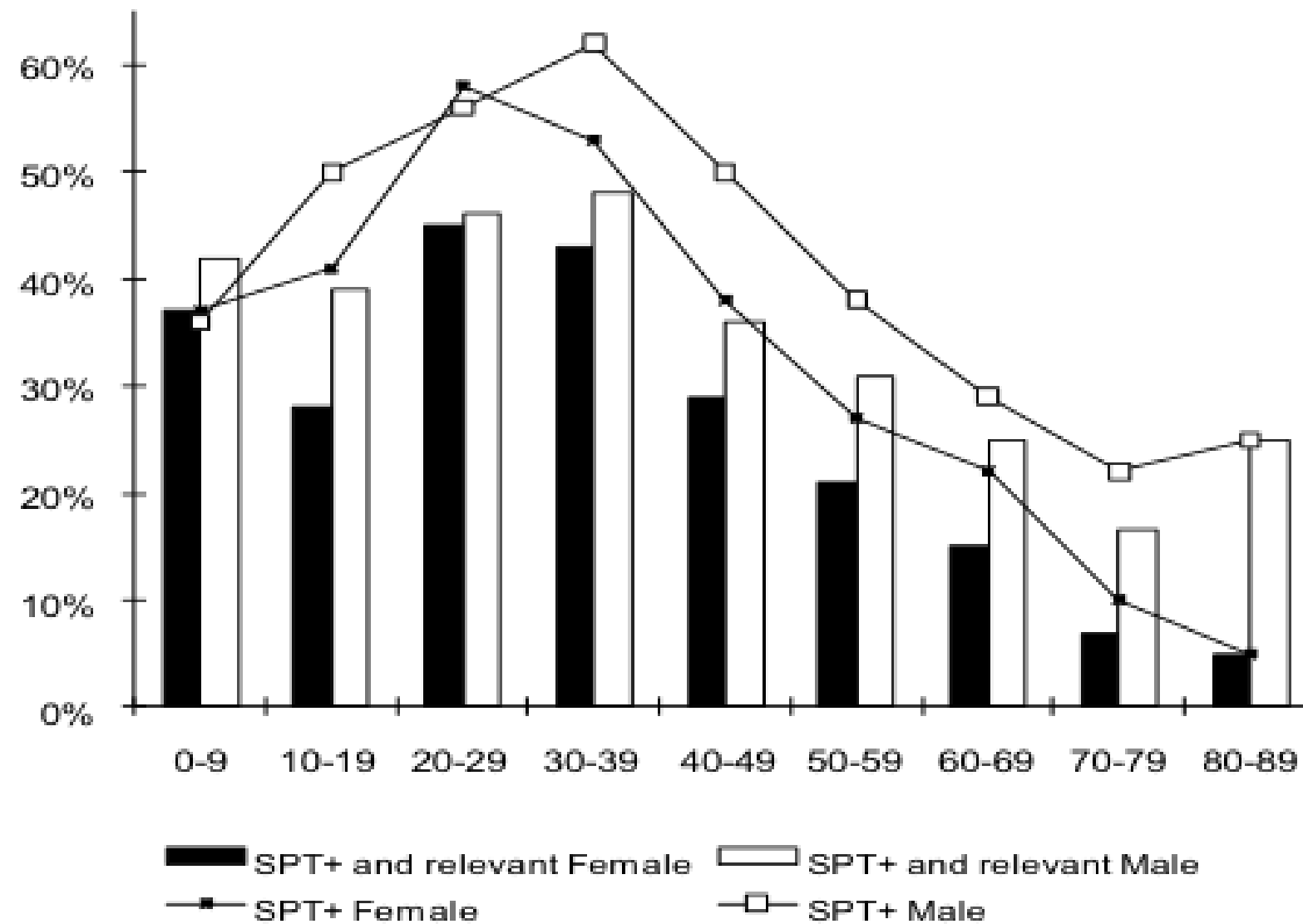
40% SENSITISATION
29.8% SPT+ AR SYMPTOMS

Skin prick tests

+

AR symptoms

N=2320



Blomme K Int Arch Allergy Immunol 2013;160:200–207



Geographical variation in the prevalence of sensitization to common aeroallergens in adults: the GA²LEN survey

R. B. Newson¹, R. van Ree^{2,3}, B. Forsberg⁴, C. Janson⁵, J. Lötvalld⁶, S.-E. Dahlén⁷, E. M. Toskala^{8,9}, J. Bælum¹⁰, G. M. Brożek¹¹, L. Kasper¹², M. L. Kowalski¹³, P. H. Howarth¹⁴, W. J. Fokkens¹⁵, C. Bachert^{16,17}, T. Keil^{18,19}, U. Krämer^{20,21}, J. Bislimovska²², M. Gjomarkaj²³, C. Loureiro²⁴, P. G. J. Burney^{1,25} & D. Jarvis^{1,25}

Table 2 Population prevalence (95% CI) of sensitization to each allergen and population geometric mean total immunoglobulin E (IgE; 95% CI) in each area

Subpopulation	Any allergen in list (%)	Grass mix (%)	Timothy grass (%)	Cat (%)	Dog (%)
Umea	39.9 (32.3, 48.1)	21.0 (15.2, 28.3)	21.3 (15.5, 28.5)	17.1 (12.2, 23.5)	19.5 (14.2, 26.2)
South Sweden	44.7 (39.5, 49.9)	23.4 (19.4, 28.1)	24.2 (20.1, 28.9)	18.8 (15.2, 23.0)	19.9 (16.1, 24.2)
Helsinki	44.7 (35.1, 54.6)	22.1 (15.1, 31.2)	18.6 (12.3, 27.3)	11.1 (6.7, 17.7)	20.8 (14.2, 29.4)
Odense	31.4 (24.6, 39.1)	16.9 (11.8, 23.5)	17.3 (12.2, 23.9)	8.3 (5.1, 13.2)	13.1 (8.8, 19.0)
Poland	34.6 (25.8, 44.6)	10.2 (6.2, 16.3)	9.9 (5.9, 16.0)	7.1 (4.0, 12.5)	11.1 (6.8, 17.5)
UK	37.1 (27.1, 48.2)	22.5 (14.8, 32.7)	26.9 (18.3, 37.7)	10.0 (5.7, 17.0)	16.5 (10.1, 25.8)
Amsterdam	46.2 (36.9, 55.8)	22.1 (15.4, 30.8)	19.5 (13.2, 27.8)	15.1 (9.7, 22.8)	17.2 (11.5, 25.1)
Ghent	43.5 (33.8, 53.7)	24.3 (16.9, 33.6)	18.5 (12.2, 26.9)	11.4 (6.7, 18.8)	15.7 (9.7, 24.5)
Brandenburg	49.9 (39.7, 60.2)	29.7 (21.2, 39.8)	28.5 (20.2, 38.5)	17.7 (11.3, 26.8)	20.6 (13.5, 30.1)
Duisburg	52.9 (45.1, 60.6)	28.5 (22.1, 35.9)	28.3 (21.9, 35.7)	13.8 (9.4, 19.9)	12.5 (8.3, 18.5)
Skopje	n/a†	23.8 (15.0, 35.7)	n/a	16.6 (9.3, 27.7)	8.3 (3.6, 17.7)
Palermo	n/a†	12.5 (4.9, 28.4)	n/a	9.7 (3.3, 25.1)	6.4 (1.8, 20.7)
Coimbra	50.4 (42.6, 58.2)	18.2 (13.3, 24.3)	18.6 (13.6, 24.8)	18.3 (13.2, 24.7)	13.8 (9.5, 19.7)

Subpopulation	Any house dust mite (%)	<i>Dermatophagoides pteronyssinus</i> (%)	<i>Dermatophagoides farinae</i> (%)	Birch (%)	Artemisia (%)
Umea	9.3 (5.6, 15.1)	8.2 (4.7, 13.7)	5.4 (2.7, 10.5)	22.3 (16.4, 29.5)	4.3 (2.2, 8.5)
South Sweden	10.2 (7.5, 13.7)	8.6 (6.1, 11.9)	6.4 (4.4, 9.3)	21.7 (17.8, 26.2)	9.6 (7.0, 13.1)
Helsinki	13.9 (8.4, 22.1)	10.4 (5.8, 17.9)	8.8 (4.6, 16.2)	18.7 (12.4, 27.2)	13.4 (8.7, 21.4)
Odense	9.9 (6.3, 15.3)	7.9 (4.7, 12.8)	8.2 (5.0, 13.1)	8.7 (5.3, 13.9)	10.8 (6.9, 16.6)
Poland	13.6 (8.7, 20.5)	11.2 (6.9, 17.6)	10.0 (6.0, 16.1)	8.8 (5.0, 15.0)	11.3 (6.9, 18.1)
UK	22.3 (14.6, 32.5)	21.8 (14.1, 32.0)	17.3 (10.5, 27.0)	9.9 (5.2, 17.9)	3.4 (1.3, 8.6)
Amsterdam	20.8 (14.4, 29.0)	20.0 (13.7, 28.3)	14.2 (9.2, 21.2)	11.5 (6.9, 18.7)	7.9 (4.2, 14.5)
Ghent	27.3 (19.4, 36.9)	27.3 (19.4, 36.9)	20.3 (13.5, 29.2)	9.7 (5.1, 17.8)	4.9 (2.2, 10.7)
Brandenburg	13.0 (7.5, 21.5)	10.4 (5.7, 18.4)	7.9 (3.9, 15.0)	24.8 (17.0, 34.5)	12.8 (7.3, 21.3)
Duisburg	20.5 (14.9, 27.4)	17.2 (12.2, 23.8)	18.7 (13.4, 25.6)	25.5 (19.5, 32.7)	11.4 (7.2, 17.5)
Skopje	21.2 (12.8, 32.9)	15.5 (8.5, 26.7)	13.7 (7.2, 24.5)	11.5 (5.7, 21.7)	11.3 (5.5, 21.9)
Palermo	15.3 (6.8, 31.1)	13.1 (5.3, 28.7)	8.7 (2.9, 22.9)	n/a*	9.1 (2.9, 24.9)
Coimbra	30.6 (24.2, 37.9)	26.9 (20.8, 33.9)	21.7 (16.4, 28.0)	6.8 (3.8, 12.0)	9.6 (5.9, 15.2)

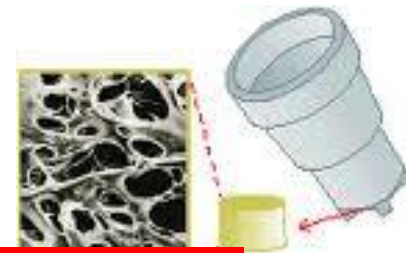
Subpopulation	Olive (%)	Parietaria (%)	Blattella (%)	Alternaria (%)	Total IgE (kU/l; geometric mean)
Umea	3.7 (1.8, 7.1)	2.8 (1.2, 6.6)	3.1 (1.4, 6.7)	2.0 (0.8, 4.8)	28.3 (21.8, 36.7)
South Sweden	3.1 (1.9, 5.3)	1.2 (0.5, 2.6)	4.2 (2.7, 6.7)	2.8 (1.6, 5.0)	33.3 (28.8, 38.6)
Helsinki	4.7 (1.9, 11.3)	1.4 (0.3, 6.6)	2.6 (0.8, 8.2)	3.9 (1.5, 9.9)	41.1 (31.1, 54.2)
Odense	1.2 (0.3, 4.3)	0.2 (0.1, 0.5)	3.0 (1.2, 7.0)	2.5 (1.1, 5.9)	30.9 (25.5, 37.5)
Poland	2.2 (0.8, 5.8)	0.7 (0.3, 1.8)	5.6 (2.5, 12.0)	2.1 (0.7, 5.7)	39.0 (31.2, 48.8)
UK	3.4 (1.3, 8.6)	2.6 (0.8, 8.5)	2.6 (0.8, 8.5)	4.7 (1.8, 11.6)	33.3 (24.3, 45.7)
Amsterdam	8.8 (5.0, 15.3)	0.6 (0.2, 1.6)	5.9 (2.8, 12.2)	2.3 (0.8, 6.3)	40.8 (31.9, 52.2)
Ghent	4.0 (1.5, 9.9)	0.3 (0.0, 1.8)	5.6 (2.2, 13.3)	4.3 (1.5, 11.6)	38.7 (29.4, 51.1)
Brandenburg	4.2 (1.6, 10.9)	0.3 (0.1, 1.0)	5.5 (2.3, 12.6)	3.5 (1.3, 9.1)	37.6 (28.1, 50.3)
Duisburg	13.2 (8.8, 19.5)	2.7 (1.1, 6.3)	6.0 (3.2, 11.0)	5.4 (2.8, 10.2)	43.5 (34.4, 55.0)
Skopje	14.1 (7.6, 24.7)	4.0 (1.2, 12.3)	14.7 (8.0, 25.6)	12.1 (6.1, 22.6)	n/a
Palermo	21.2 (10.7, 37.7)	17.6 (8.3, 33.5)	2.9 (0.4, 18.4)	3.0 (0.4, 18.8)	n/a
Coimbra	9.6 (5.9, 15.2)	9.6 (6.0, 15.0)	12.5 (8.2, 18.6)	8.9 (5.6, 14.0)	38.5 (30.7, 48.2)

Region specific extracts

RAST – MOLECULAR ALLERGOLOGY - MULTIPLEX

RAST

classical ImmunoCAP assay



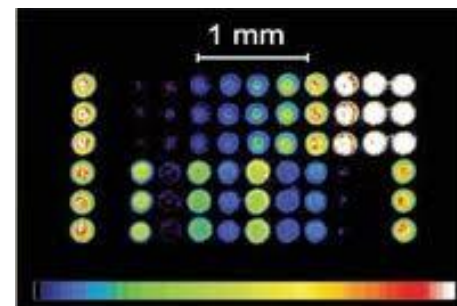
RAST₁

40 µL

Single-analyte assay: single analysis of specific IgE directed against single allergens, single allergen components or mixtures of allergens

ISAC (Immuno Solid-phase Allergy Chip)

ImmunoCAP ISAC (16 spots per mm²)



ISAC₁₁₂

30 µL

Multiplex assay: multiple analysis of specific IgE directed against allergen components in one single run

rBet v 1

rCor a 1.01
rCor a 1.04



rPyr c 1



rMal d 1

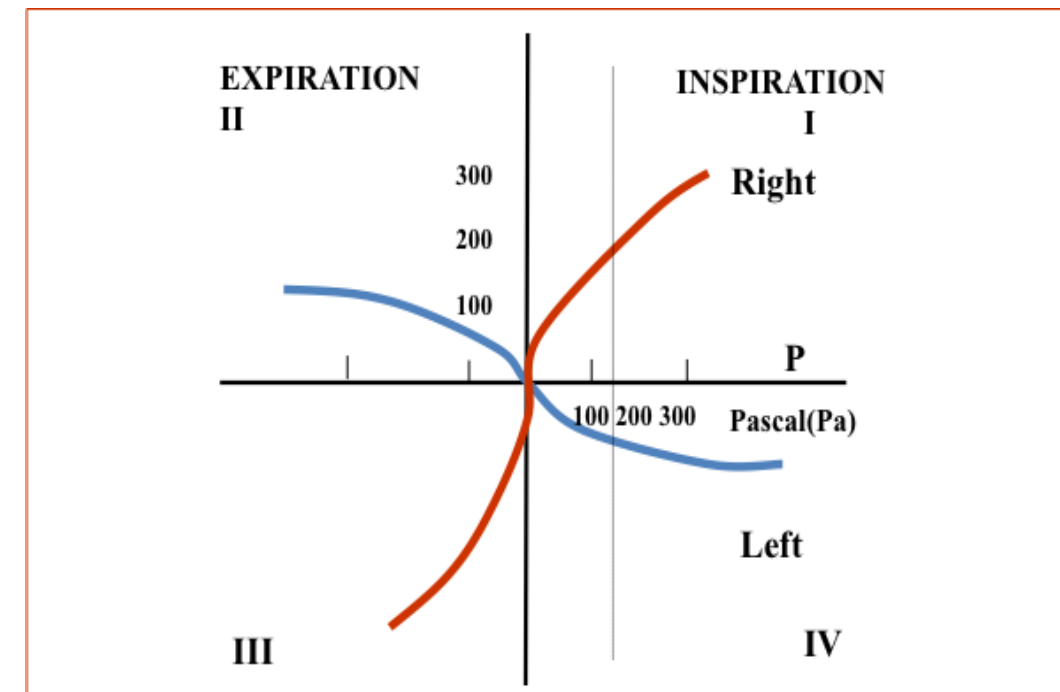
NASAL PATENCY AND AIRFLOW

— Mirror test



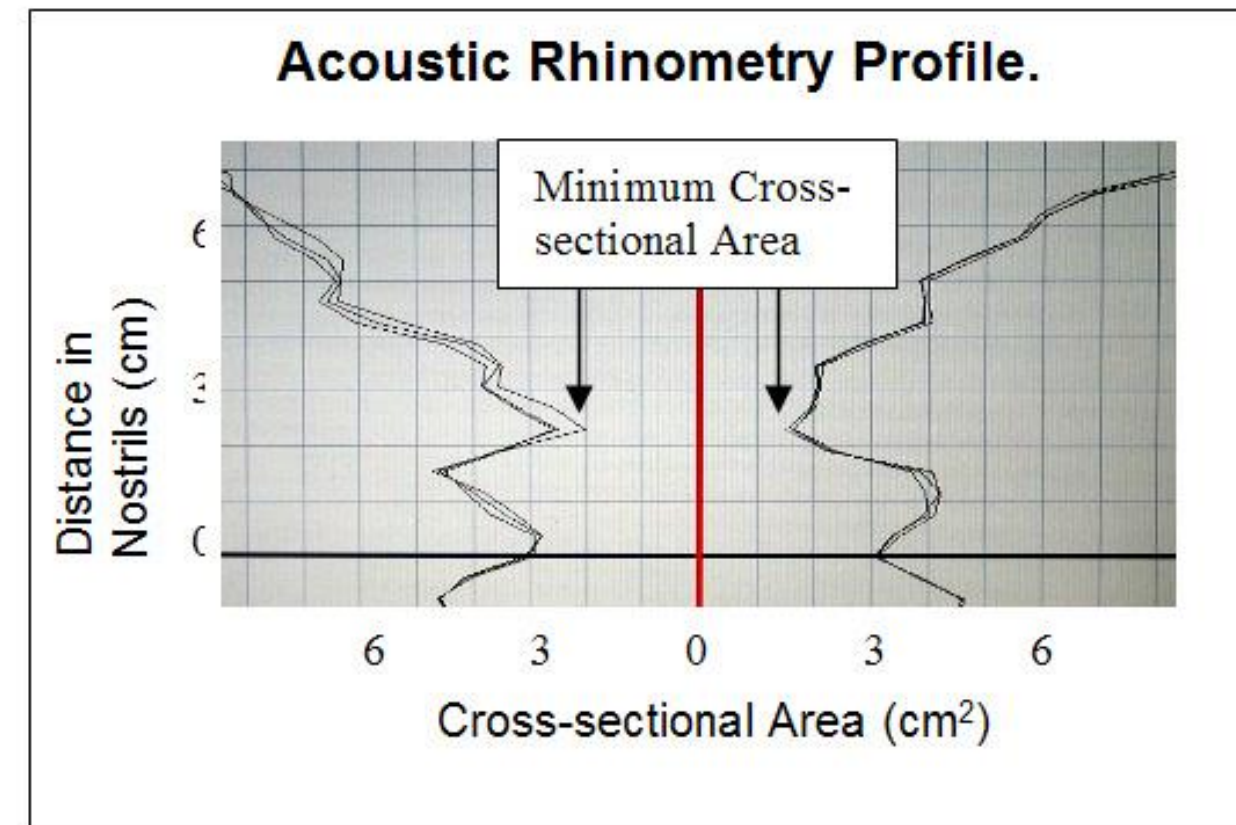
NASAL PATENCY AND AIRFLOW

- Mirror test
- Rhinomanometry



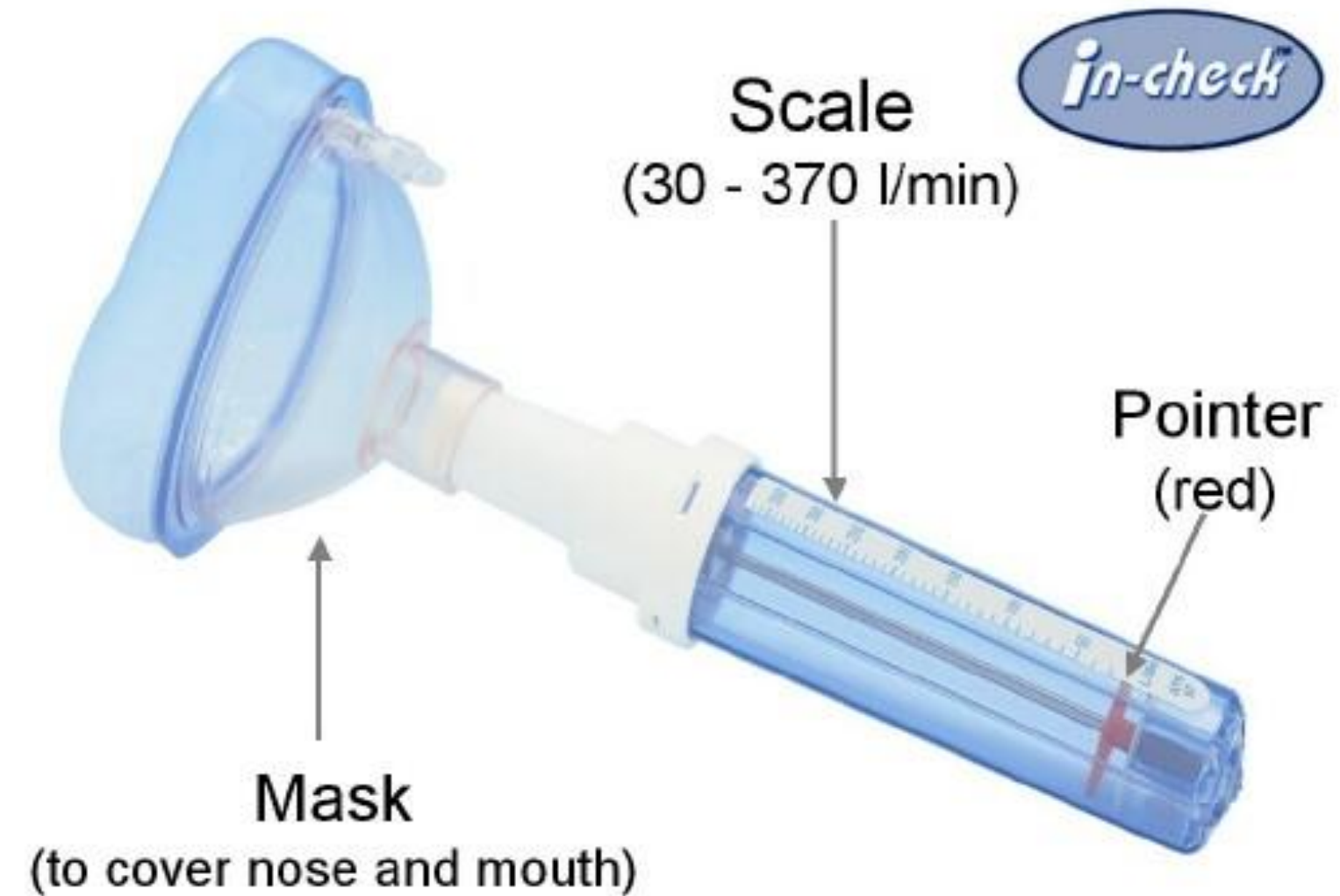
NASAL PATENCY AND AIRFLOW

- Mirror test
- Rhinomanometry
- Acoustic rhinometry



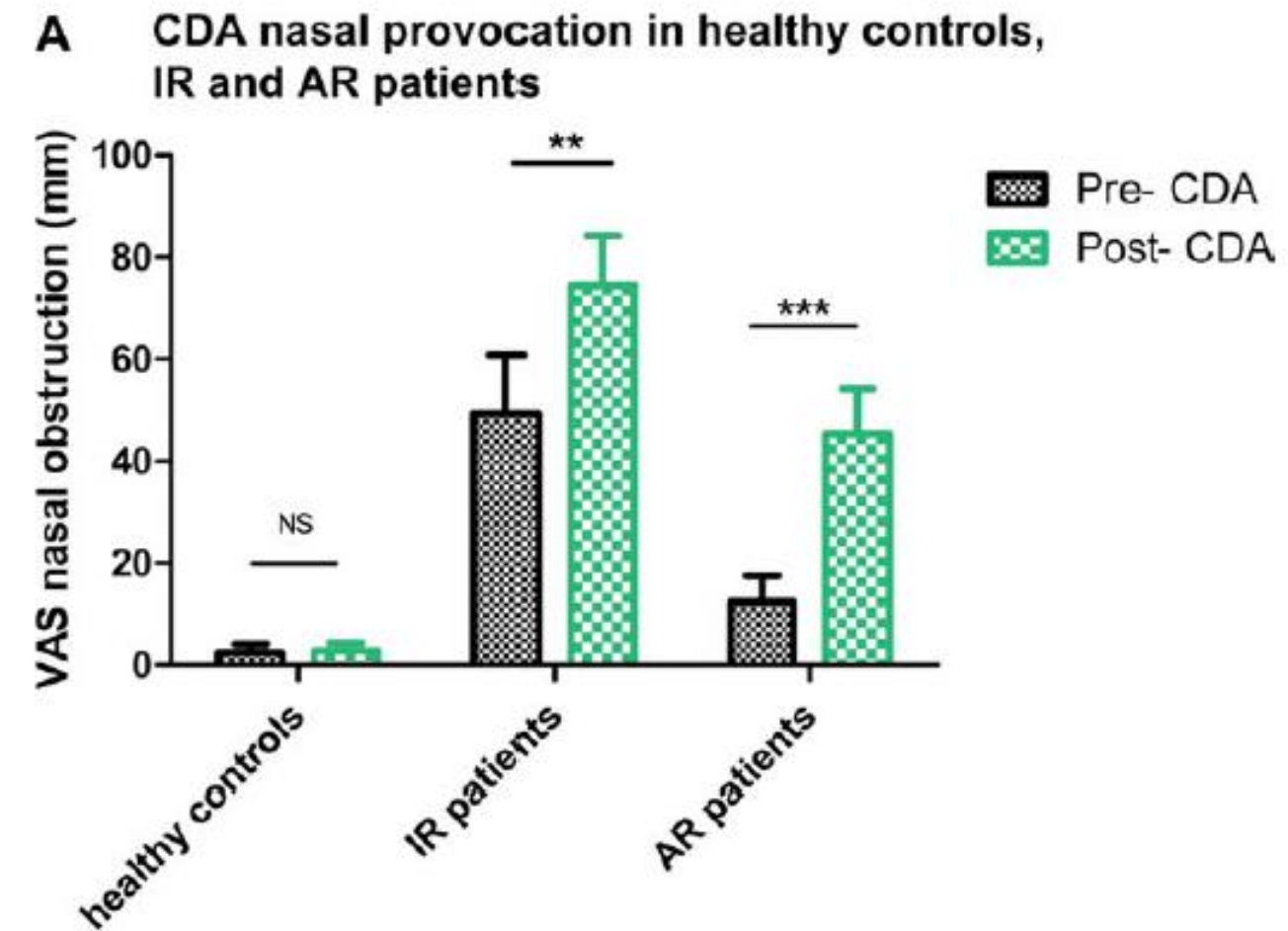
NASAL PATENCY AND AIRFLOW

- Mirror test
- Rhinomanometry
- Acoustic rhinometry
- Nasal inspiratory / expiratory peak flow



Short-Time Cold Dry Air Exposure: A Useful Diagnostic Tool for Nasal Hyperresponsiveness

Laura Van Gerven, MD; Guy Boeckxstaens, MD, PhD; Mark Jorissen, MD, PhD;
Wytske Fokkens, MD, PhD; Peter W. Hellings, MD, PhD

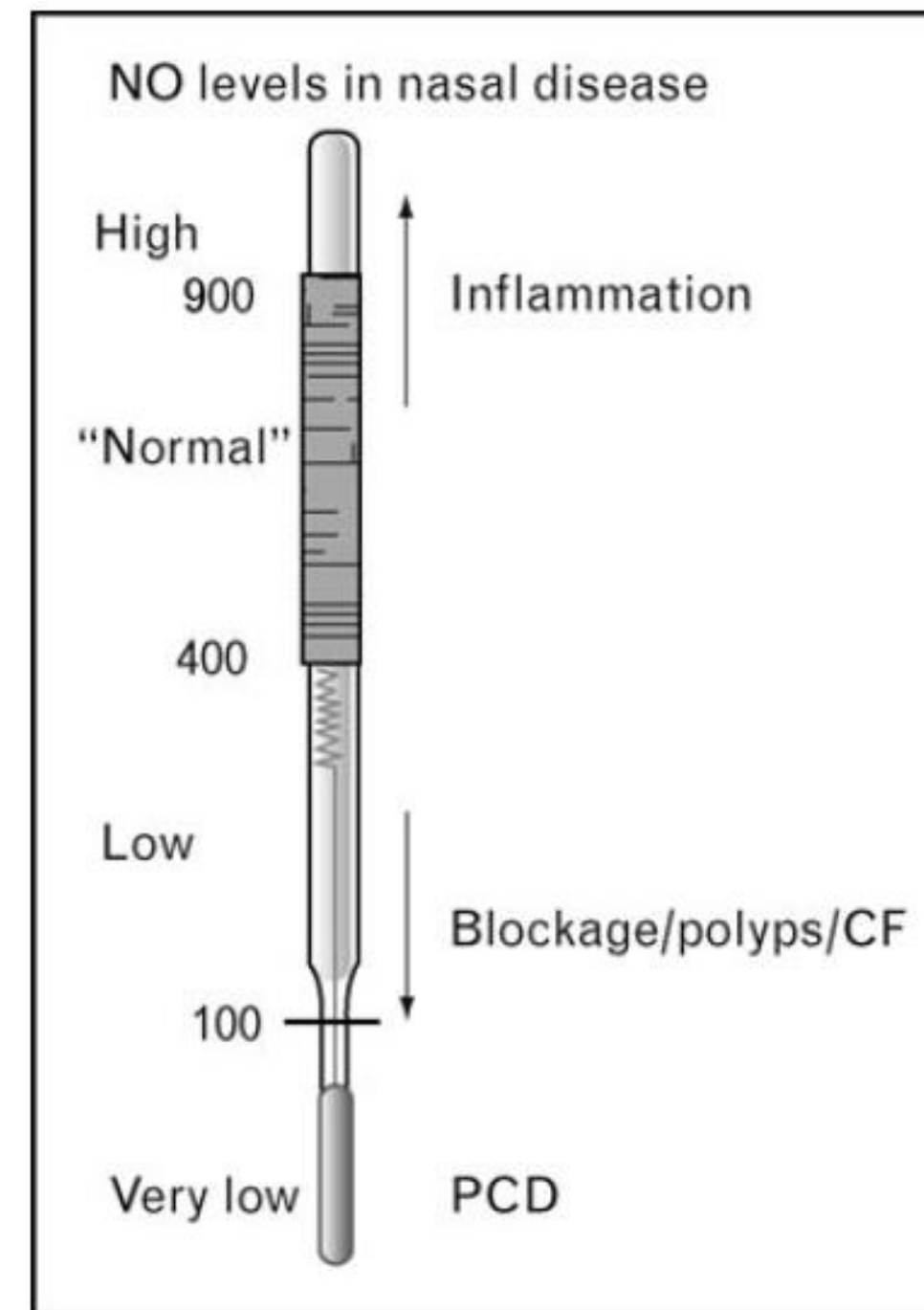
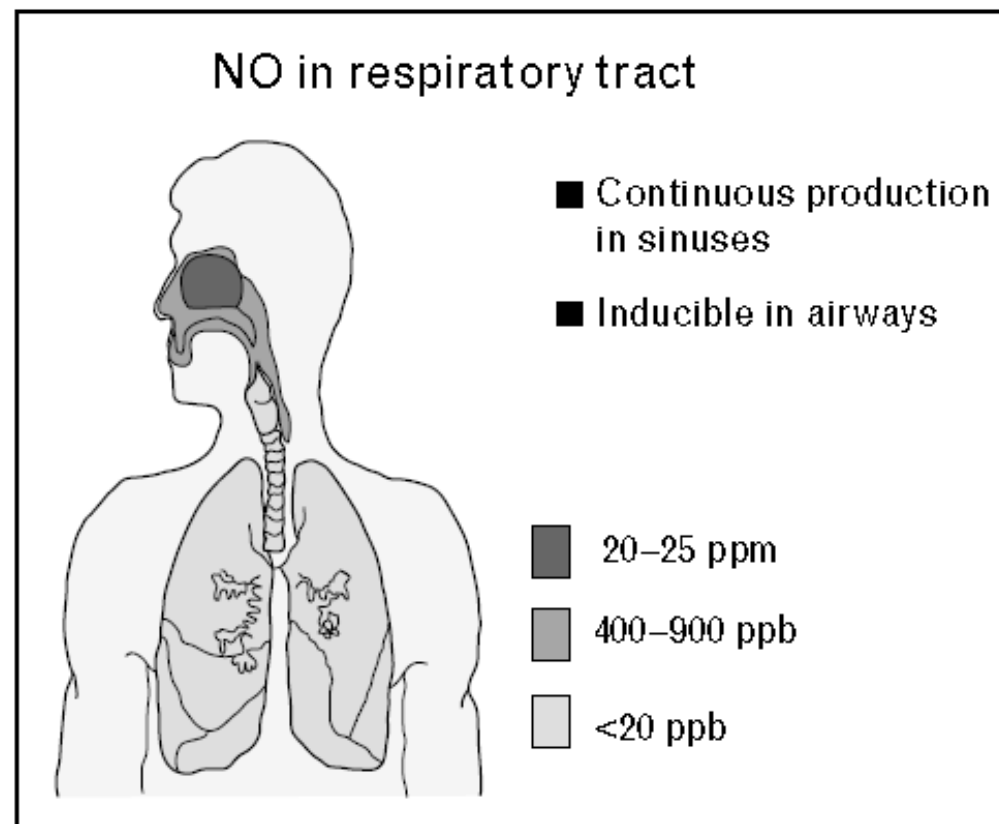


NASAL NITRIC OXIDE

(G SCADDING, CURR OPIN OTOLARYNGOL HEAD NECK SURG. 2007)

- main source = paranasal sinuses
- 100-fold higher relative to lower airways
- Useful in PCD

Figure 1 The very different levels of nitric oxide in sinuses, upper and lower airways



EAACI Position paper on the standardization of nasal allergen challenges

Unmet needs in the **Methodology**

Allergen **dose** and quality

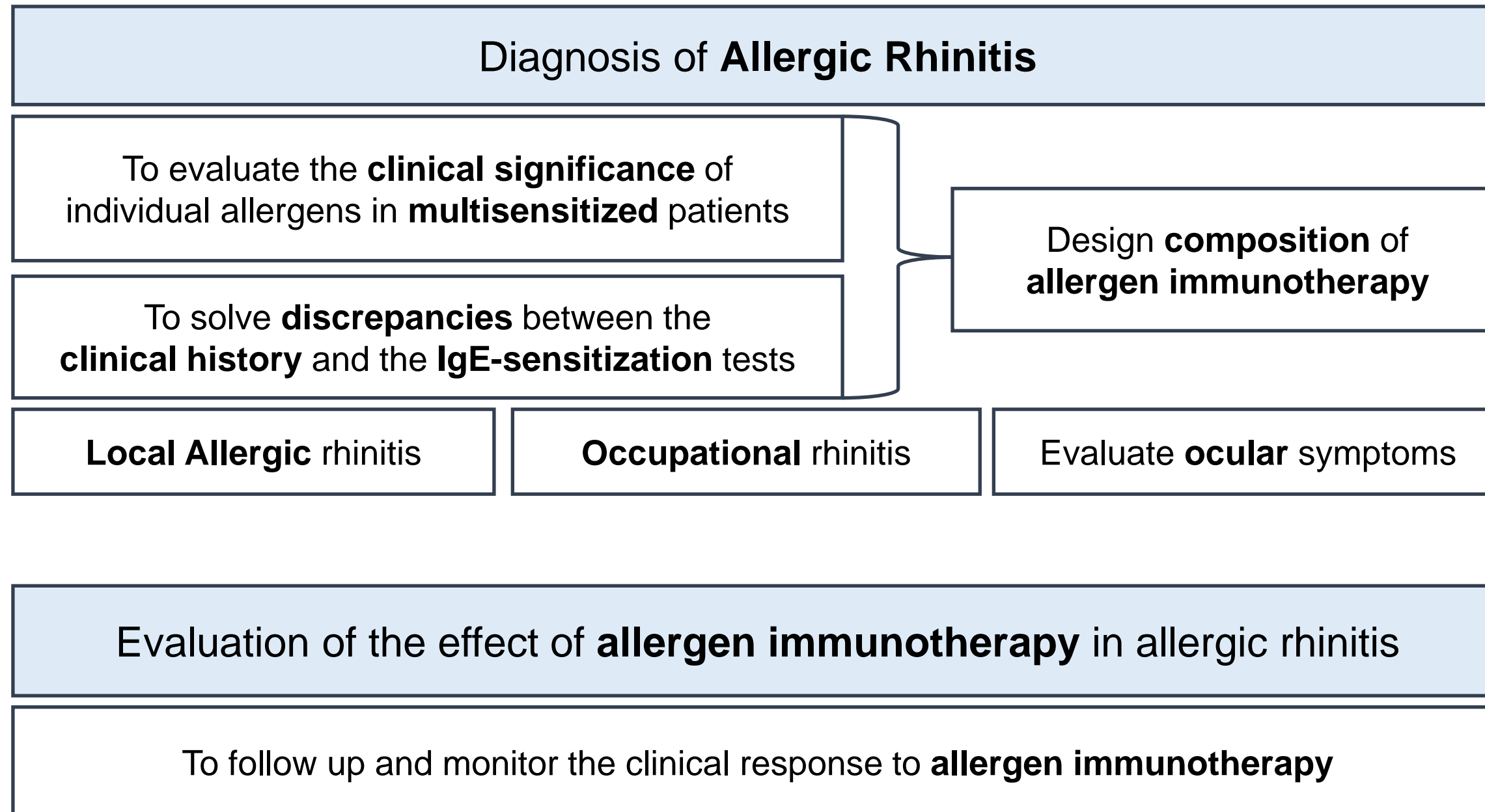
Allergen **application** technique

The need of a **titration** process

Provocation of either **one** or **two nostrils**

The method to **assess** subjective and objective **outcome**

ALLERGEN CHALLENGE: INDICATIONS FOR THE CLINICAL PRACTICE



APPLICATION TECHNIQUE FOR SPRAY DEVICES

EAACI
PP 2018

Bilateral application by **spray** vial with a **50 µl** nozzle



Test puff prior to the challenge

Two puffs of 50 µl/each per **nostril**

Patient's collaboration

Breathe deeply before

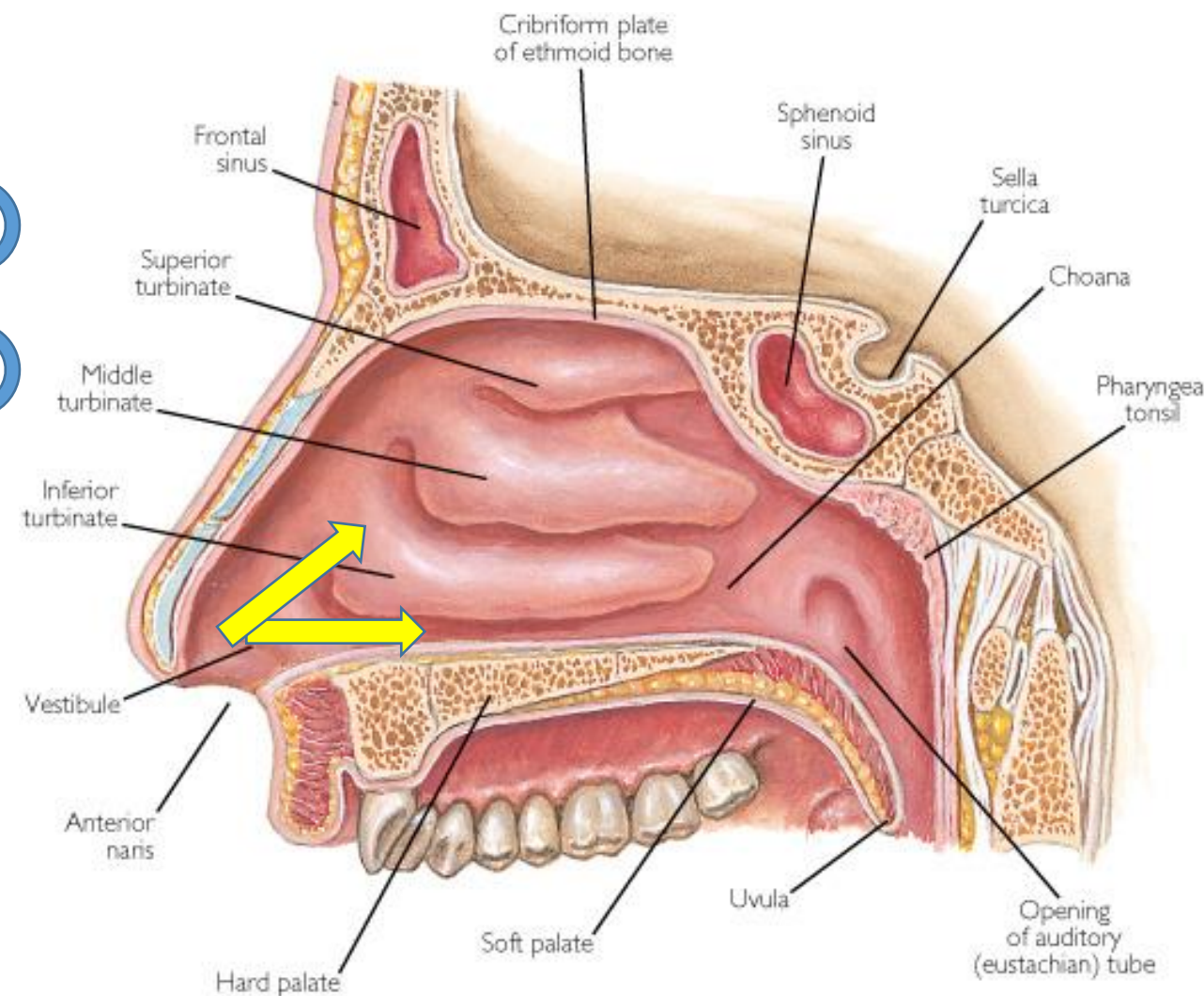
Hold breath during

Exhale profoundly after

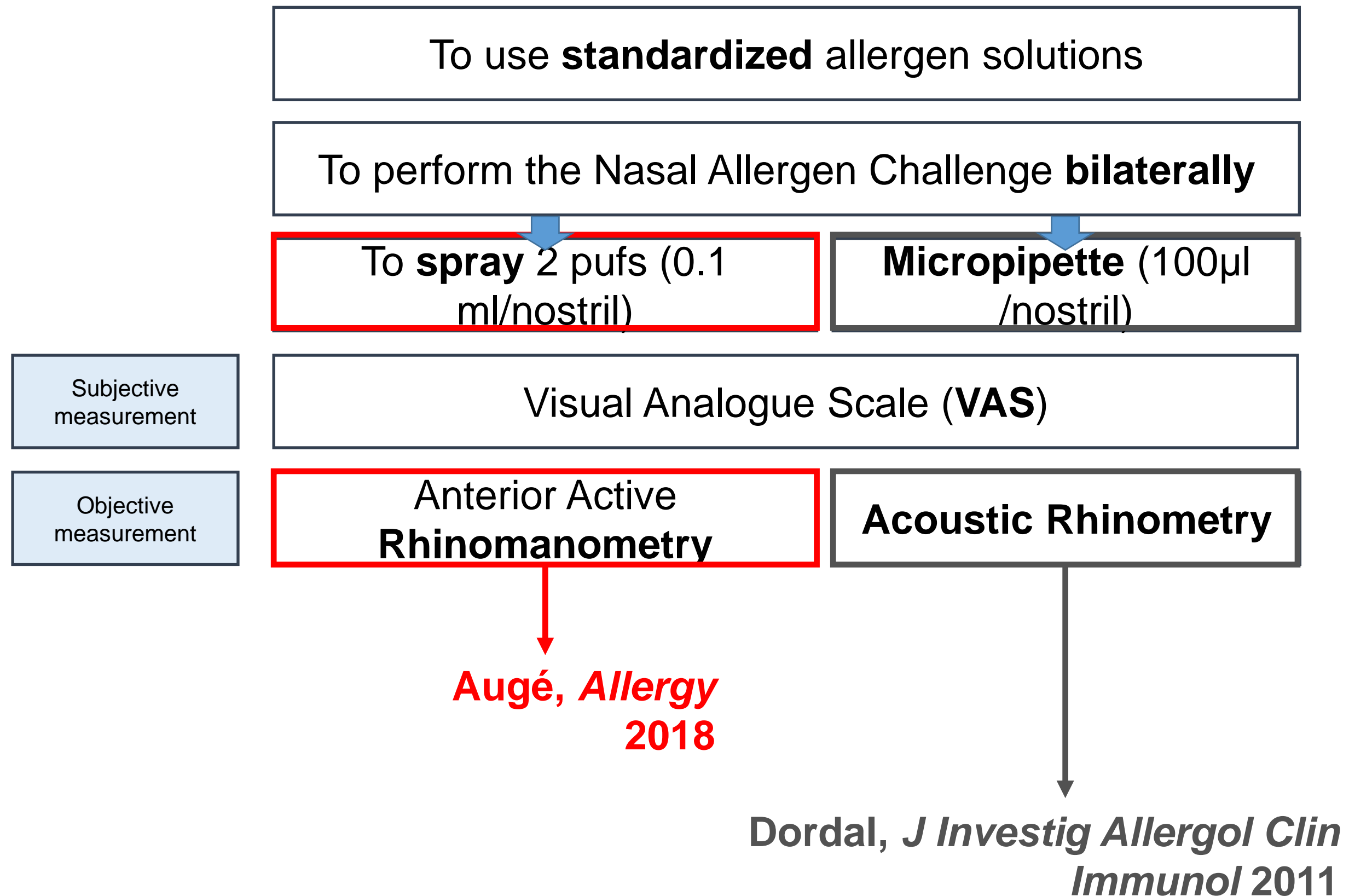


To **prevent** aerosol **penetration** of the lower airways

Avoid to spray towards the nasal **septum**



SUMMARY OF METHODOLOGICAL RECOMMENDATIONS



ACCURATE DIAGNOSIS OF ALLERGIC AIRWAY DISEASES

History
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Clinical Examination

Sensitisation
Nasal patency
Nasal provocation

Precision medicine

WE HAD A DREAM (AND STILL HAVE A DREAM)



Sample



Diagnosis



Personalized treatment

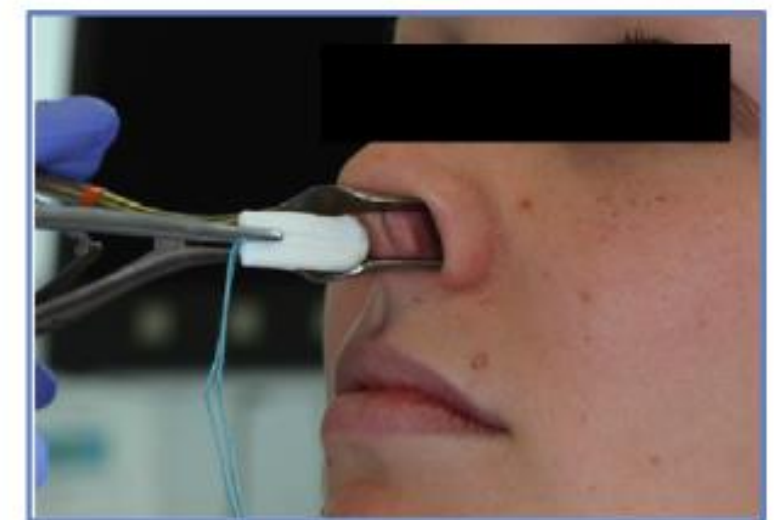
RELIABLE MITE-SPECIFIC IGE TESTING IN NASAL SECRETIONS BY MEANS OF ALLERGEN MICROARRAY.

Berings M1, Arasi S2, De Ruyck N3, Perna S4, Resch Y5, Lupinek C5, Chen KW5, Vrtala S6, Pajno GB7, Bachert C3, Lambrecht BN8, Dullaers M9, Valenta R5, Matricardi PM4, Gevaert P3.

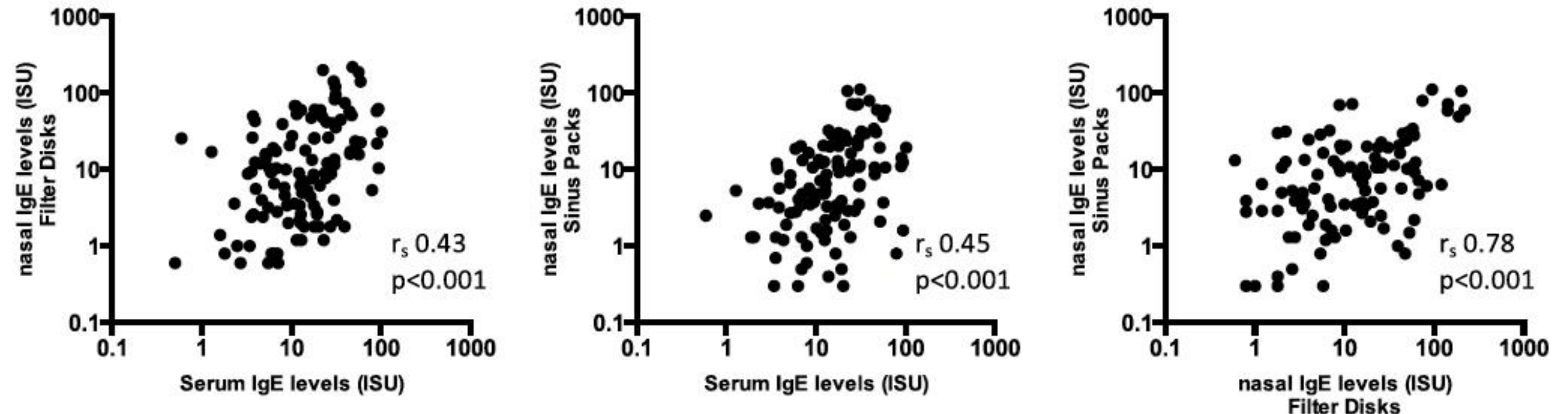
A



B

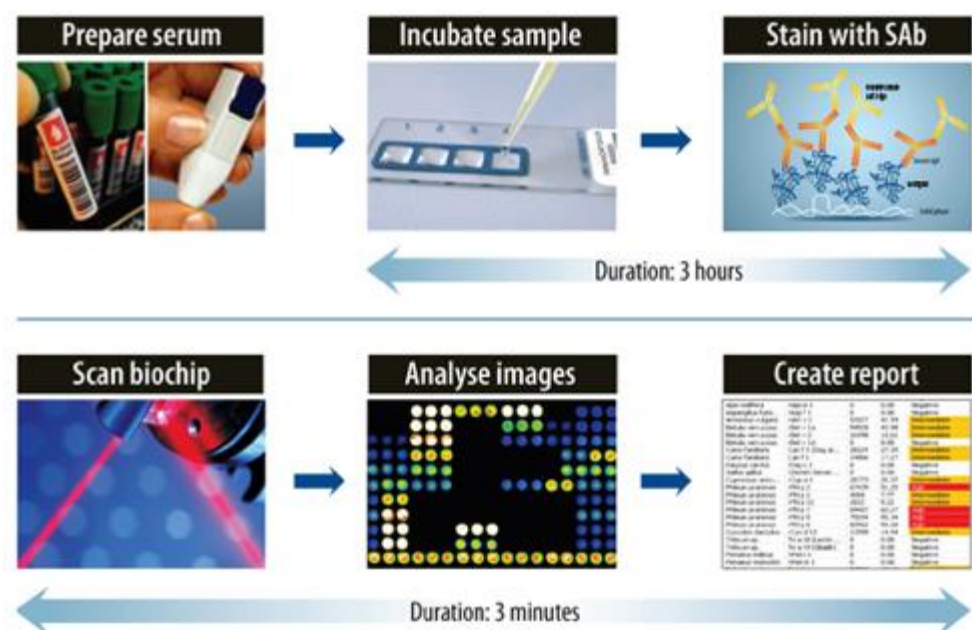


C



RELIABLE MITE-SPECIFIC IGE TESTING IN NASAL SECRETIONS BY MEANS OF ALLERGEN MICROARRAY.

Berings M1, Arasi S2, De Ruyck N3, Perna S4, Resch Y5, Lupinek C5, Chen KW5, Vrtala S6, Pajno GB7, Bachert C3, Lambrecht BN8, Dullaers M9, Valenta R5, Matricardi PM4, Gevaert P3.

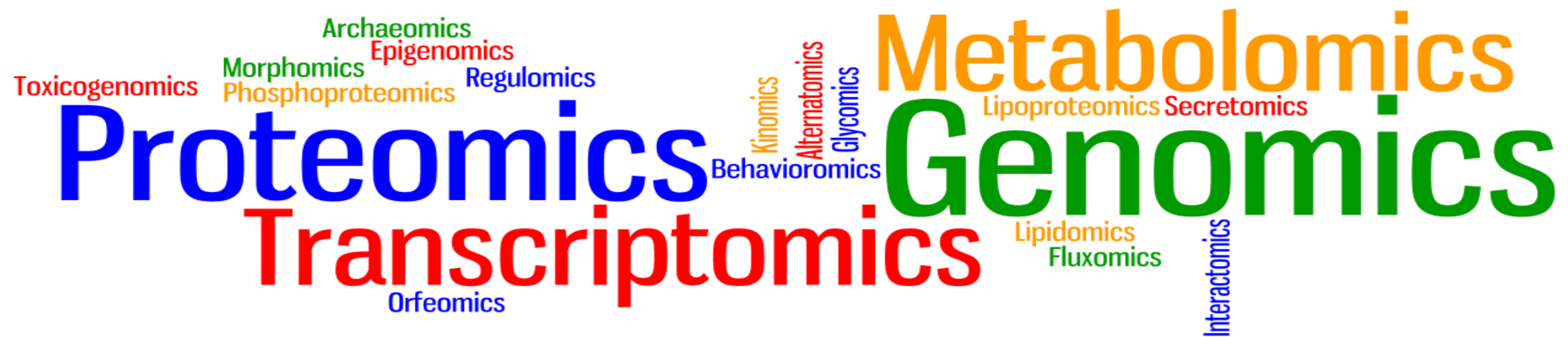


ImmunoCap ISAC



	FD										
	Sensitivity		Specificity		PPV		NPV		Accuracy, %	LR+	LR–
	%	95% CI*	%	95% CI*	%	95% CI*	%	95% CI*			
Any major molecules†	90	73-98	100	83-100	100	82-100	91	75-98	95	∞	0.1
nDer p 1	46	26-66	100	85-100	100	62-100	73	58-85	78	∞	0.5
nDer f 1	68	46-85	100	85-100	100	73-100	81	66-91	86	∞	0.3
rDer p 2	90	73-98	100	83-100	100	81-100	91	76-98	95	∞	0.1
rDer f 2	90	73-98	100	83-100	100	81-100	91	76-98	95	∞	0.1
rDer p 23	81	61-93	100	85-100	100	77-100	87	72-96	92	∞	0.2
Other molecules											
rDer p 4	0	0-53	98	90-100	0	0-99	88	77-95	86	0.0	1.0
rDer p 5	80	44-97	100	89-100	100	52-100	96	87-100	97	∞	0.2
rDer p 7	78	40-97	100	90-100	100	47-100	96	87-100	97	∞	0.2
rDer p 21	57	18-90	100	90-100	100	28-100	95	85-99	95	∞	0.4
All molecules‡	71	63-77	100	99-100	98	93-100	93	91-95	94	167.4	0.3

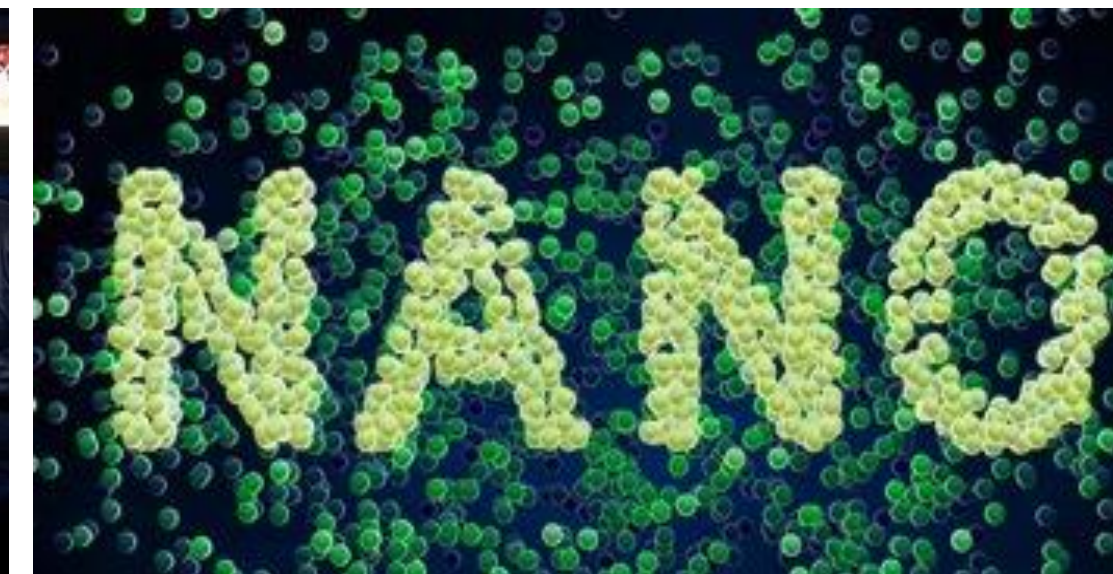
	SP										
	Sensitivity		Specificity		PPV		NPV		Accuracy, %	LR+	LR–
	%	95% CI*	%	95% CI*	%	95% CI*	%	95% CI*			
Any major molecules†	87	69-96	100	83-100	100	81-100	88	72-97	93	∞	0.1
nDer p 1	58	37-78	100	85-100	100	68-100	78	63-89	83	∞	0.4
nDer f 1	48	28-69	100	85-100	100	64-100	72	57-84	78	∞	0.5
rDer p 2	86	68-96	100	83-100	100	80-100	88	73-97	93	∞	0.1
rDer f 2	86	68-96	100	83-100	100	80-100	88	73-97	93	∞	0.1
rDer p 23	81	61-93	100	85-100	100	77-100	87	72-96	92	∞	0.2
Other molecules											
rDer p 4	14	0-58	98	90-100	50	1-99	89	78-96	88	7.4	0.9
rDer p 5	70	35-93	90	78-97	58	28-85	94	82-99	86	6.9	0.3
rDer p 7	67	30-93	100	90-100	100	42-100	94	84-99	95	∞	0.3
rDer p 21	57	18-90	100	90-100	100	28-100	95	85-99	95	∞	0.4
All molecules‡	68	60-75	99	98-100	95	90-98	93	91-94	94	80.3	0.3



- Genomics: all the genes
 - pharmacogenomics : choice of personalized medicine
 - nutrigenomics : choice of best diet
 - toxicogenomics : prediction of toxicity
- Epigenomics: all epigenetic changes in genome
- Transcriptomics: all the mRNAs → microarrays
- Proteomics : all the proteins
- Interactomics : all interactions between all proteins
- Metabolomics (or metabonomics) : all metabolites
- ...



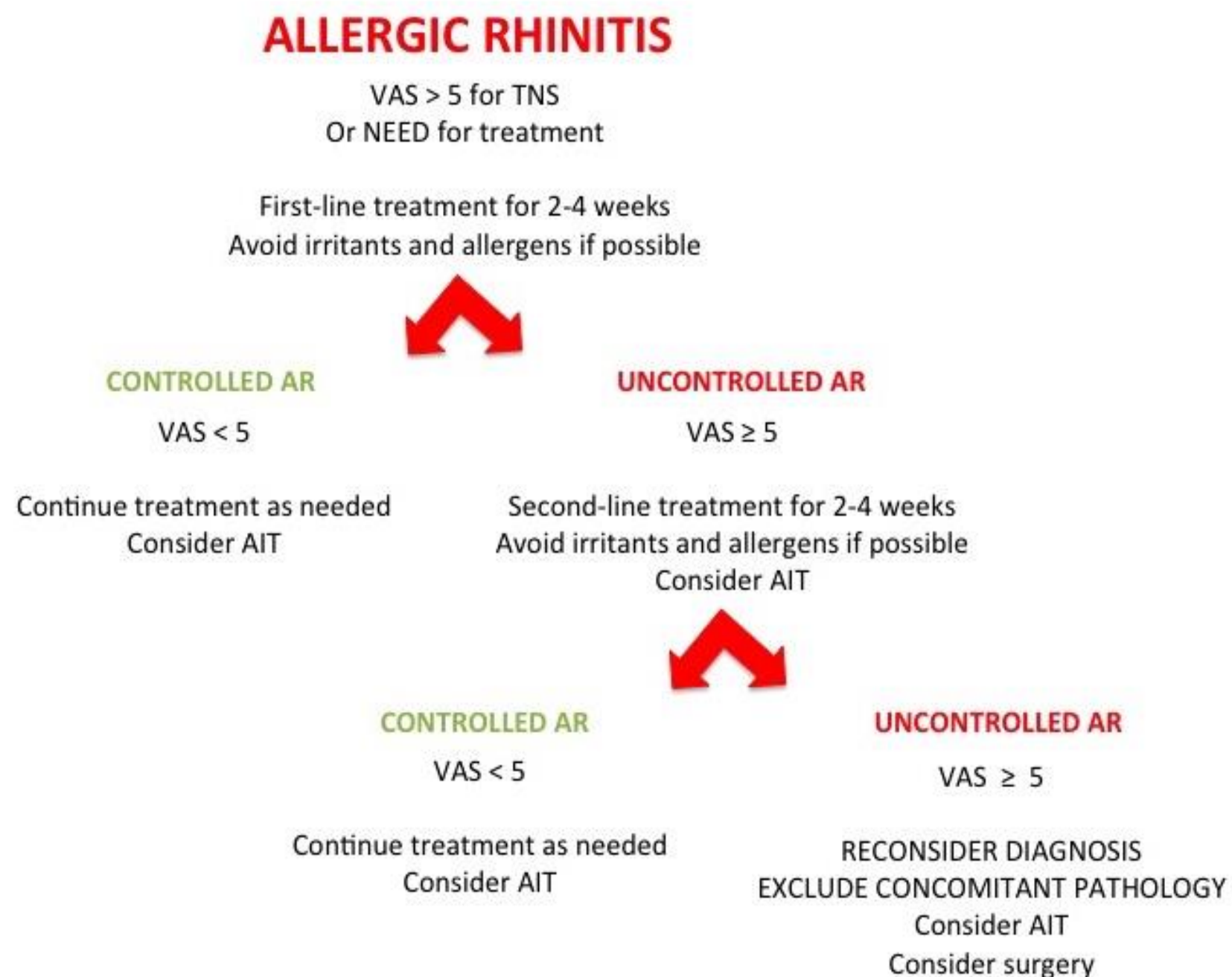
CURRENT TECHNOLOGICAL REVOLUTION ...





POSITIONING THE PRINCIPLES OF PRECISION MEDICINE IN CARE PATHWAYS FOR ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I, Bernal-Sprekelsen M, Canonica GW, Gevaert P, Joos G, Lund V, Muraro A, Onerci M, Zuberbier T, Pugin B, Seys SF, Bousquet Allergy. 2017 Mar 17



GRADED IMPLEMENTATION of PRECISION MEDICINE

← Prediction of success
Participation

← Prediction of success
Prevention strategy
Participation

← Personalized care
Prediction of success
Prevention strategy
Participation

PRECISION MEDICINE PRINCIPLES

ALLERGIC RHINITIS



ACCURATE DIAGNOSIS OF ALLERGIC AIRWAY DISEASES

History
Inspection
Clinical Examination

Sensitisation
Nasal patency
Nasal provocation

Precision medicine