


Ioana Agache
Transylvania University Brasov

Adult and pediatric asthma and related co-morbidities – from research to clinical practice and purposeful education

Part 1. Scientific and professional achievements

Part 2. Evolution and development plans for career development

1. Scientific and professional achievements

1a. Main research area – adult and pediatric asthma

Asthma as a major health problem (1)

- **300 million people** around the globe
- 10% in the EU
- increasing prevalence in developing countries
- projected increase to 400 millions in the upcoming three decades

- Majority children and adults < 45 years old affecting up to 25% of the pediatric population in some European countries
- the most frequent chronic disease of childhood
- the leading cause for hospitalization and ED consultations for the pediatric population

Asher M et al. Lancet 2006;368:733-43; Lai CK et al. Thorax 2009;64:476-83
Burney P et al. Int J Tuberc Lung Dis 2015;19:10-20; Sembajwe G, et al. Eur Respir J 2010;35:279-86; Anto JM et al. Allergy 2010;65:1021-30

Asthma as a major health problem (2)

- Significant direct and indirect costs = 72.2 billion Euro/year

- Uncontrolled asthma with frequent exacerbations, hospitalisations together with medications costs are the leading determinants of direct costs

- 75% of the economic burden is due to indirect costs resulting from absenteeism and decreased productivity at the workplace

Masoli M, et al. Allergy 2004;59:469-78; Bahadori K et al. BMC Pulm Med 2009;9:24; Sullivan PW, et al. J Asthma 2016;10; Tavakoli H et al. Allergy. 2017;72(2):291-299; Beran D et al. Lancet Respir Med 2015;3:159-70

An efficient approach to tackle the "asthma epidemics"

1. Research and development programmes focused on:

a. prevention
b. disease mechanisms and biomarkers
c. personalised approaches
d. new treatments curing the disease.

An efficient approach to tackle the "asthma epidemics"

2. Integrative management of asthma patients

a. Next generation guidelines
b. Registries for asthma
c. Improved access to early diagnosis and quality treatment
d. Environment and co-morbidities control
e. Patient and general public education
f. Cost-efficient use of resources
g. Patient-centered care models

An efficient approach to tackle the "asthma epidemics"

3. Strategic partnership between all stakeholders

A community approach to a community problem

4. Recognition of asthma as a major health problem

Increasing awareness

Description and validation of pediatric and adults asthma phenotypes, endotypes and biomarkers

Endotype driven asthma treatment and new potential curative approaches

Tackling environment (infections, pollution), lifestyle (diet, exercise) and co-morbidities (allergic rhinitis, obesity, food allergy)

Asthma prevention and control

Development and implementation of new models for cost-efficient disease management.

My research in asthma

Asthma is extremely heterogeneous

- Asthma phenotypes and endotypes

Disease phenotypes

- describe clinical, physiolologic and morphologic characteristics as well as unique responses to treatment

Visible properties

Agache I, Akdis C, Jutel M, Virchow JC. Allergy. 2012;67(7):835-46

Age, gender, race

Onset

Triggers

Co-morbidities

Long-term outcome

Inflammation type

Asthma visible properties

Vital risk

Remodeling

Response to treatment

Lung physiology

Agache I, et al. Allergy. 2012;67(7):835-46

ANA as a visible property

Table 1: Independent risk factors for severe evolution of asthma (multiple regression analysis)		
End-point	Risk factor	p value
Death	ANA	p=0.037
	NSAID intolerance	p<0.001
	low FEV1 at inclusion	p=0.021
Severe exacerbations	ANA	p=0.011
	sputum eosinophils	p<0.001
	smoke	p=0.044
	NSAID intolerance	p=0.022
High inhaled corticosteroid intake	ANA	p=0.036
	sputum eosinophils	p=0.026
	FEV1 at inclusion < 30%	p=0.006
FEV1 decline > 100 ml/year	ANA	p=0.006
	sputum eosinophils	p=0.037
	BMI>25	p=0.046
	NSAID intolerance	p=0.017

Agache I et al. Iran J Allergy Asthma Immunol 2009;8:49-52

Predictive value of lung function trend and FeNO for difficult asthma in children

Table 3. Logistic Regression Analysis for Independent Risk Factors for Difficult Asthma

	Wald Statisic	Odds Ratio	CIs		*P* Level
			Lower	Upper	
Male	0.4469	0.2564	0.0047	13.8647	.5038
Atopy	0.0069	1.1638	0.0327	41.4673	.9337
Obesity	3.9913	0.0233	0.0006	0.9312	.0457*
Exposure to tobacco smoke	0.1214	0.5266	0.0143	19.4270	.7275
Low socio-economic status	0.1504	0.4998	0.0150	16.6372	.6982
Severe rhinitis	4.3544	0.0209	0.0006	0.7907	.0369[a]
Psycho-pathology	0.1787	0.5526	0.0353	8.6479	.6725
Low adherence to treatment	0.8200	0.2239	0.0088	5.7110	.3652
Persistent bronchodilator response	0.2230	1.8668	0.1399	24.9027	.6368
Unfavorable lung function trend	3.2596	0.0247	0.0004	1.3729	.0710
Persistently high FeNO	4.1397	0.0297	0.0010	0.8790	.0419[a]

Agache I et al. J Investig Allergol Clin Immunol 2012;22:419-26

Longitudinal evaluation and risk prediction

Persistent high FeNO as prognostic factor

	Children			Adults		
	With persistent high FeNO n = 9	Without persistent high FeNO n = 82	p value	With persistent high FeNO n = 31	Without persistent high FeNO n = 134	p value
ACT mean	9.4	10.47	0.57	9.6	24	0.0001*
Persistent airway obstruc-tion	4(44.4%)	10(12.2%)	0.01*	6(19.4%)	10(7.5%)	0.04*
Fast FEV1 decline	3(33.33%)	1(1.22%)	0.0001*	10(32.3%)	13(9.7%)	0.001*

Agache I et al. submitted

Linking asthma phenotypes with endotypes

Phenotype	Endotype
Allergic asthma	Eosinophilic
	Th2 driven inflammation
	Steroid-responsive
	Anti IgE responsive
	Anti IL-5 responsive
	Anti IL-4/IL-13 responsive
Intrinsic asthma	Eosinophilic
	Neutrophilic
	Associated with autoantibodies/ superantigens
	Steroid-responsive
	Steroid-resistant
Neutrophilic asthma	Activation of innate immune response
	HDAC2 abnormal recruitment
	Increased neutrophil survival
	Steroid-resistant
	Responsive to antioxidants/antibiotics
	Anti TNF-a responsive
	Responsive to HDAC regulators (theophylline)
Aspirin intolerant asthma	Eosinophilic
	Alteration in the eicosanoid metabolism/ sensitivity to leukotrienes C4, D4, and E4
	Steroid-responsive
	LTRA-responsive
Extensive remodeling asthma	Lack of inflammation/extensive remodeling
	Abnormal EMTU activation
	Abnormalities of ASM
	Defective repair mechanisms
	Steroid-resistant
	ASM-targeted treatment responsive
	MMP-targeted treatment responsive
	Antiangiogenic responsive

Agache I. et al. et al. Allergy. 2012;67(7):835-46

The use of inflammometry – induced sputum

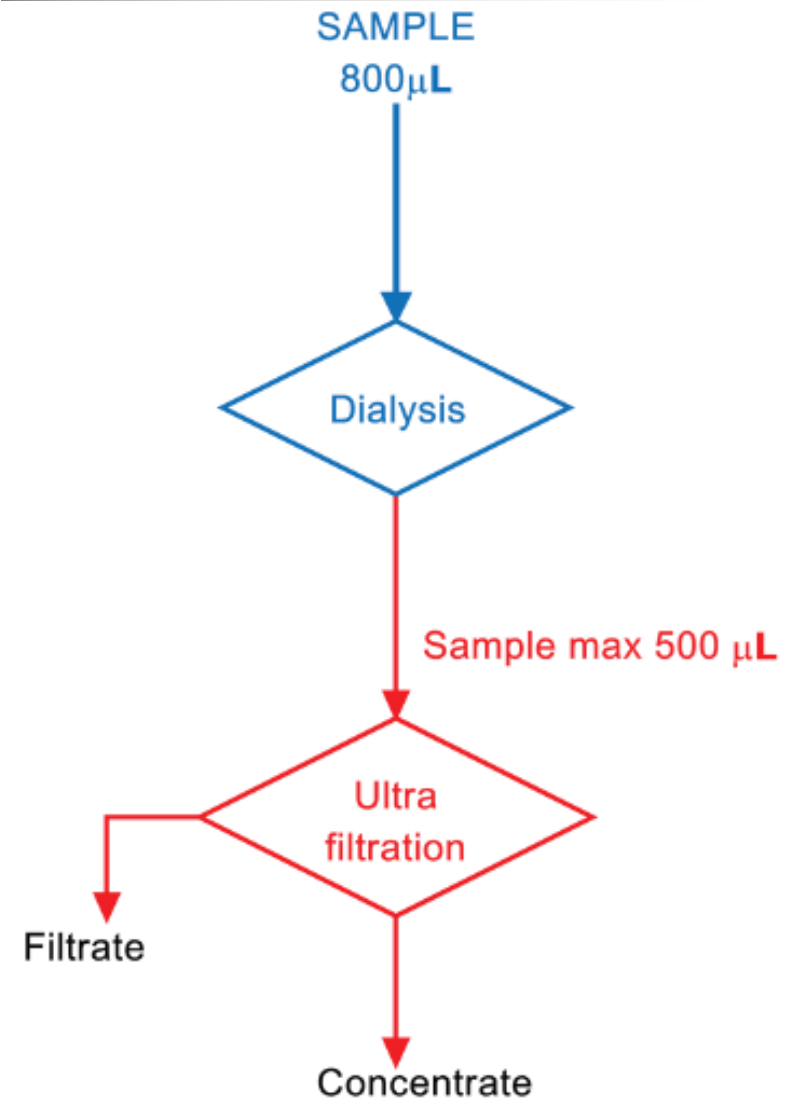


Figure 2

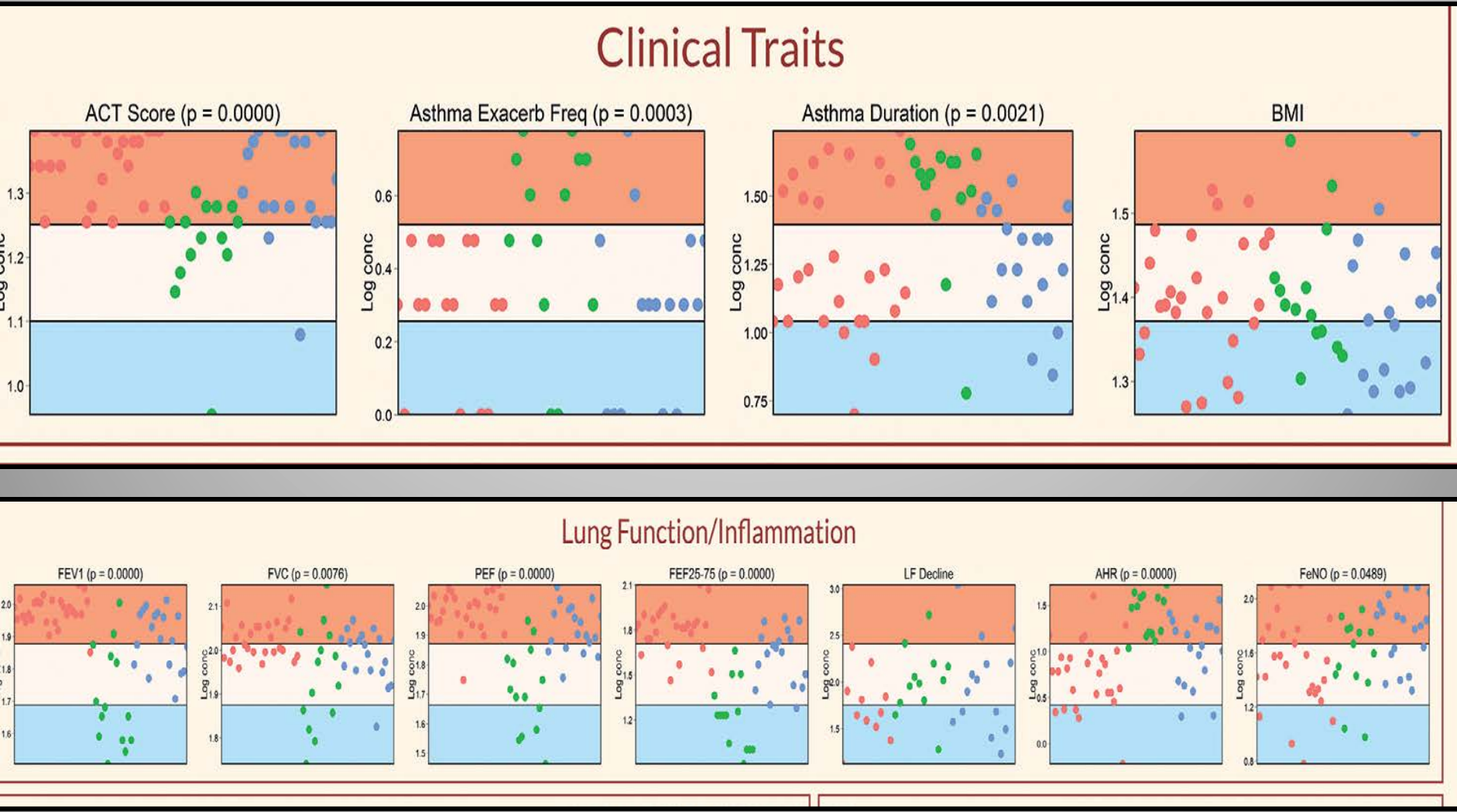
The dialysis-ultrafiltration method patented together with the SIAF asthma research team for measurement of sputum cytokines. *(reproduced from Agache C et al. European Respiratory International Congress, Barcelona, 2013)*

	Sputum Cluster 1	Sputum Cluster 2	Sputum Cluster 3	p
N	27	14	19	
Age	39.04 ± 12.71	57.50 ± 12.37	40.68 ± 11.76	0.0000
	19 ÷ 63	29 ÷ 77	20 ÷ 71	
Gender (% female)	37	64.3	63.2	0.1257

	Sputum Cluster 1	Sputum Cluster 2	Sputum Cluster 3	p
Asthma classification (GINA)				0.0000
mild persistent, %	63.0	0.0	31.6	
moderate persistent, %	29.6	21.4	42.1	
severe persistent, %	7.4	78.6	26.3	
Atopic asthma, %	70.4	50.0	73.7	0.3222
Smokers, %	14.8	28.6	10.5	0.3785
Chronic_rhinosinusitis, %	25.9	28.6	26.3	0.9836
Aspirin_Sensitivity, %	40.7	57.1	31.6	0.3475
CS_resistant, %	3.7	57.1	0	0.0000
Exercise_induced_asthma, %	33.3	28.6	31.6	0.9551
Near_fatal_asthma, %	3.7	64.3	5.3	0.0000

Agache I, Akdis CA et al. in preparation

Asthma visible properties



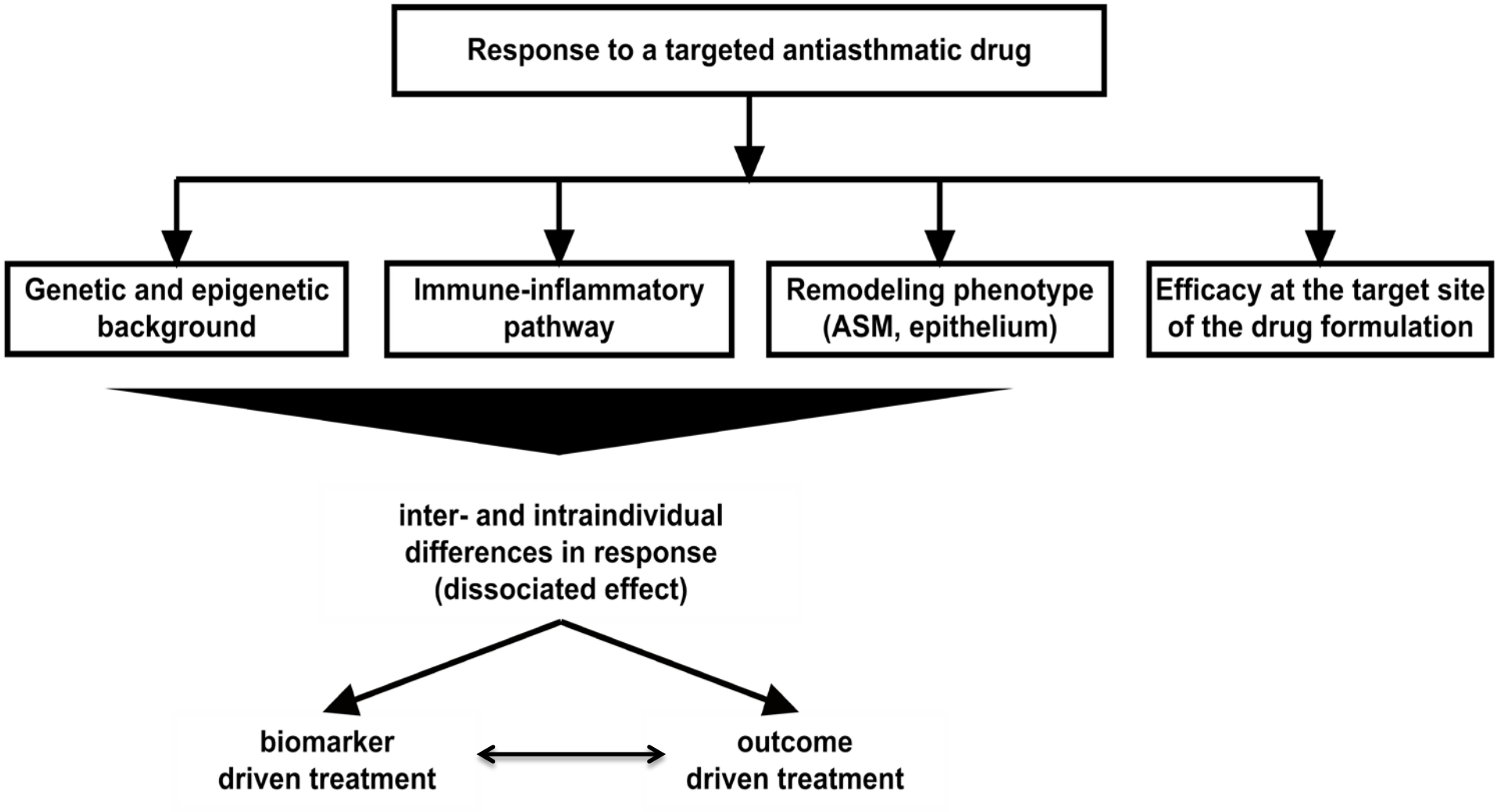
Agache I, Akdis CA et al. in preparation

New pathogenetic mechanisms in asthma

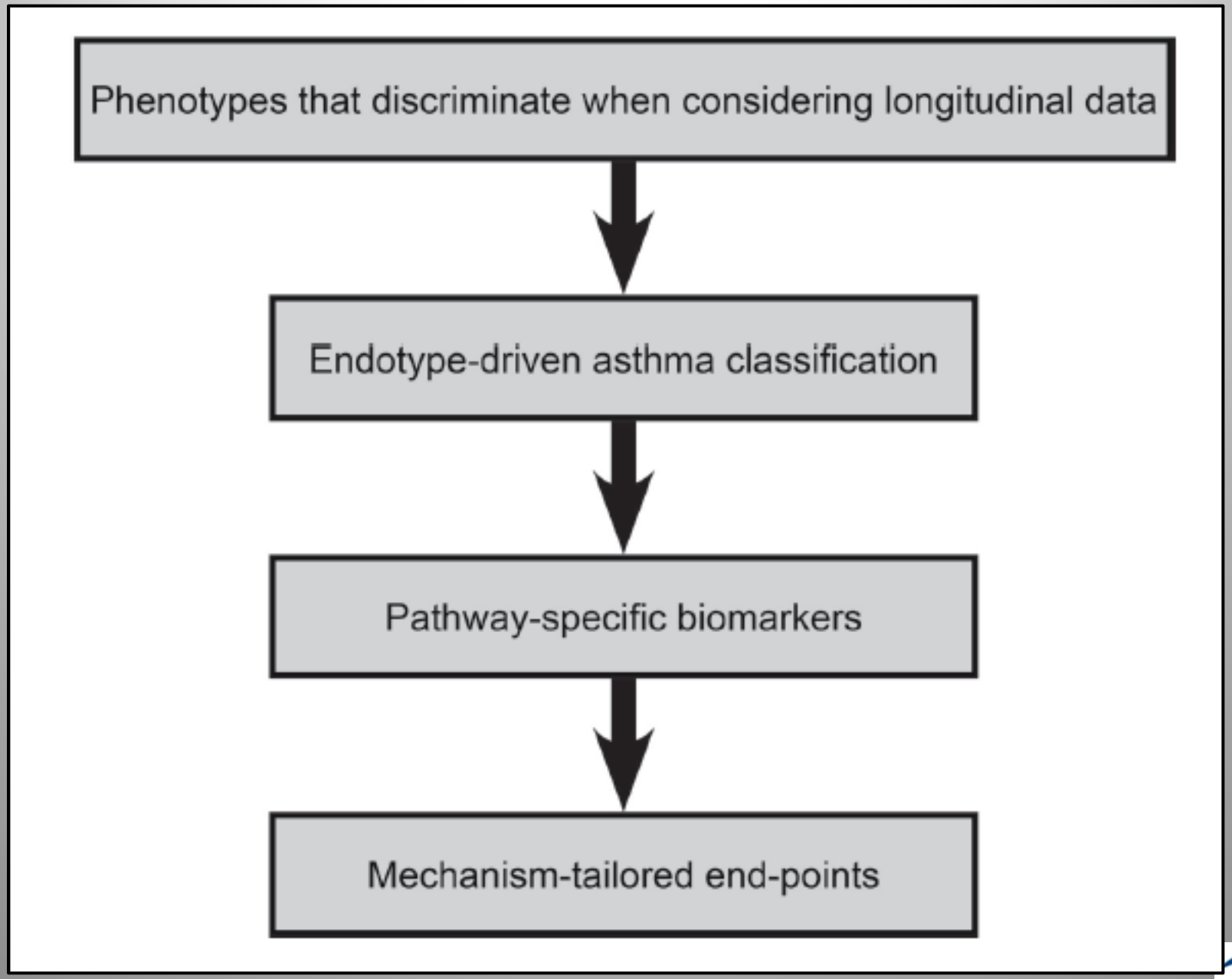
- Increased eotaxin and RANTES in smokers with asthma
- IL-6 and lung function decline
- IL-2 and brittle asthma
- VEGF and near-fatal asthma
- IP-10 and frequent exacerbators
- IL-10 and response to steroids

Agache I, Akdis CA et al. in preparation

New concept – the dissociated effect

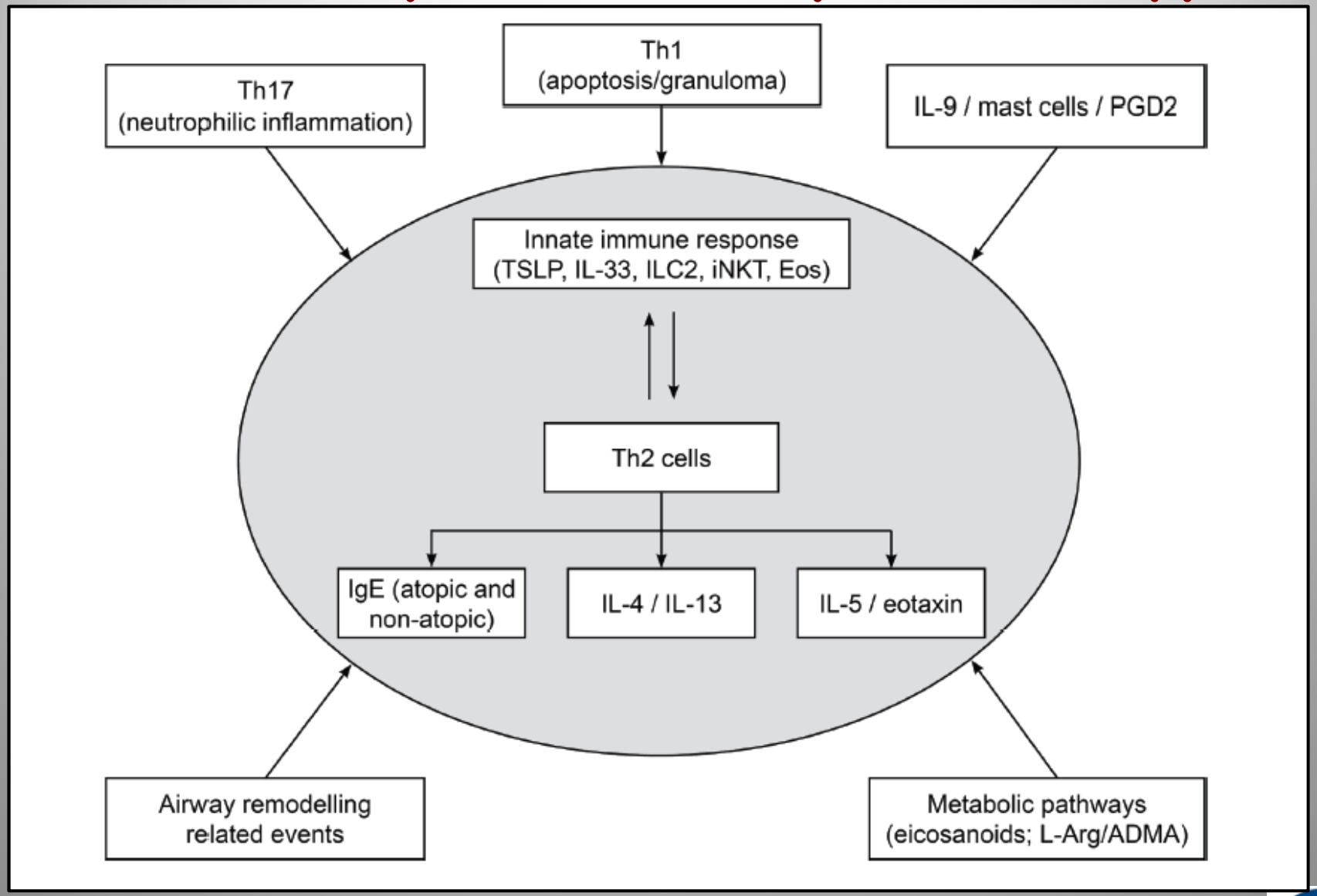


Agache I. Curr Opin Allergy Clin Immunol. 2013; 13(3):249-256



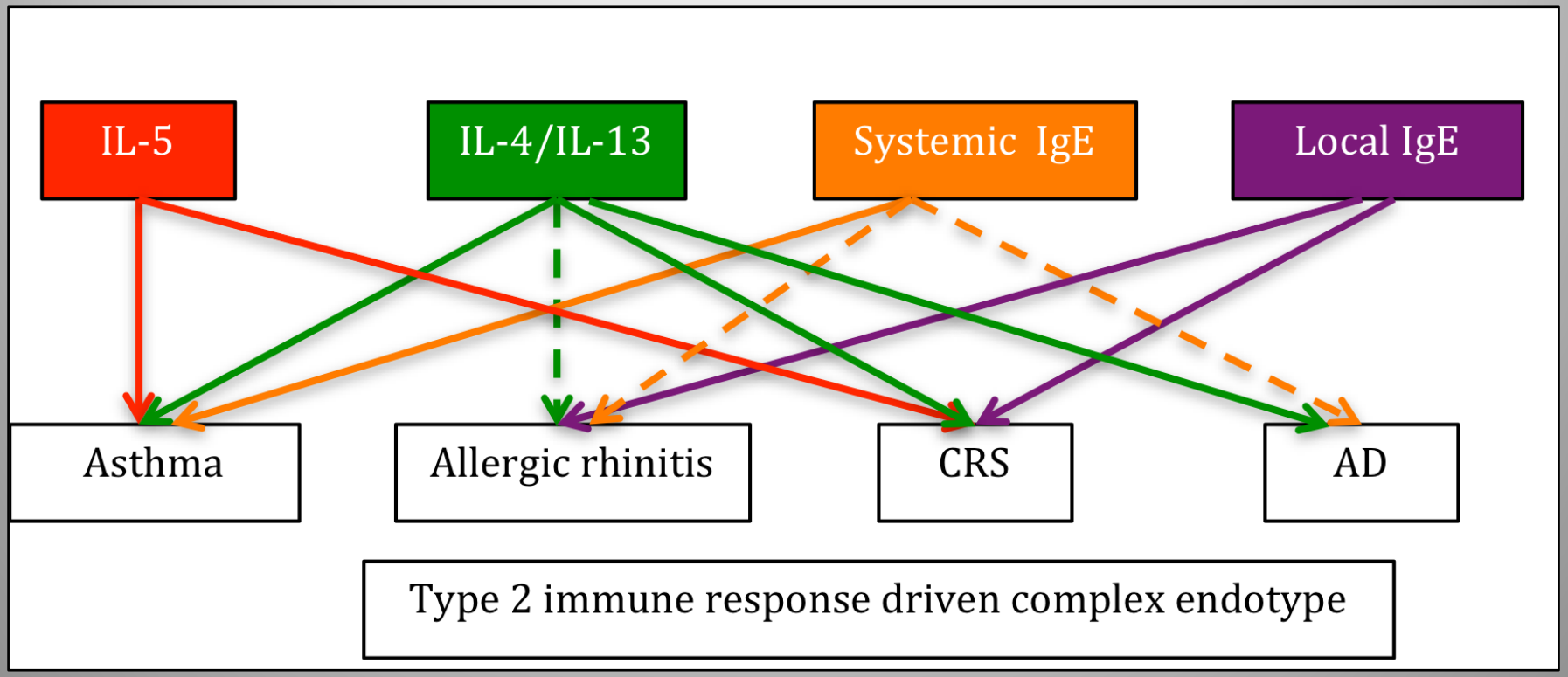
Agache I. WAO Congress 2011

New concept – the complex endotype



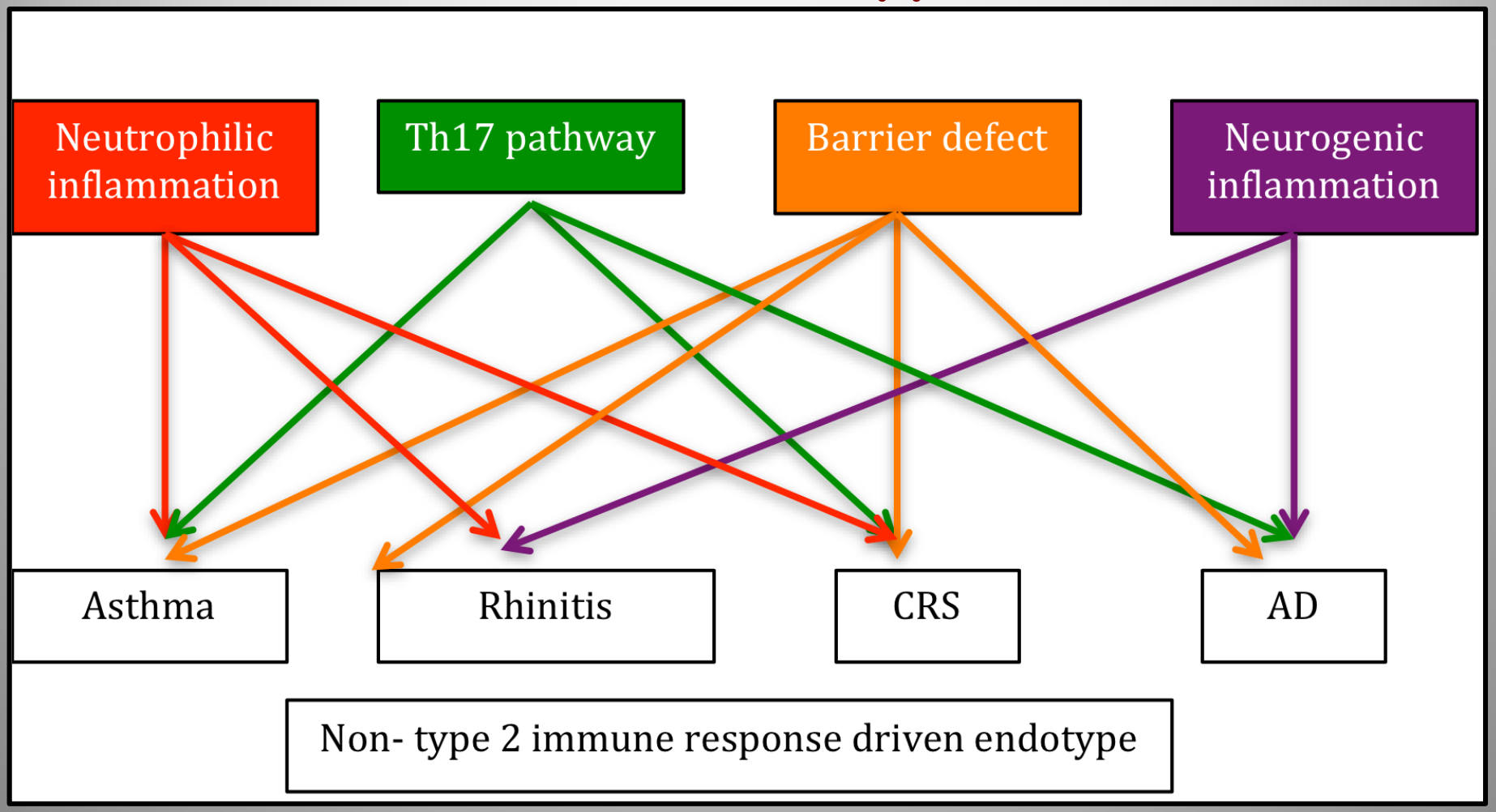
Agache I et al. Curr Allergy Asthma Rep 2015;15:29.

Multiple type 2-driven molecular sub-endotypes



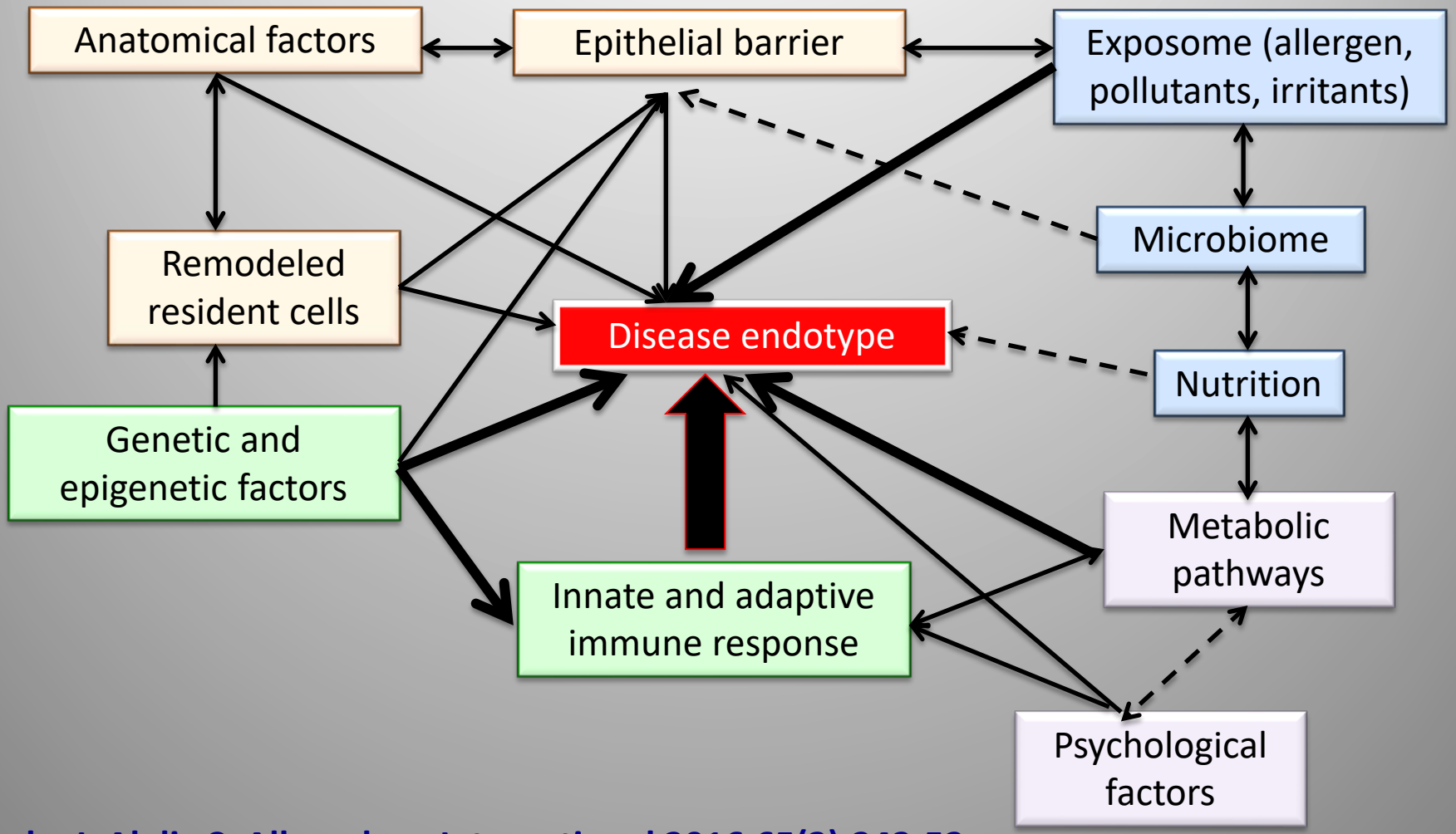
Agache I, Akdis CA. Allergol Int. 2016 ;65(3):243-52

Multiple non-type 2-driven molecular sub-endotypes



Agache I, Akdis C. Allergology International 2016,65(3):243-52

Factors modulating the disease endotype



Agache I, Akdis C. Allergology International 2016,65(3):243-52

The value of a biomarker

Marker for the endotype ⟷ **Key mechanism for the endotype**

↓ **Guides treatment**

↓ **Therapeutic target**

Variable across age, asthma severity and in time →

Agache I. Current Treatment Options in Allergy 2014 ; 1:198–212
Agache I. Curr Opin Allergy Clin Immunol. 2013; 13(3):249-256

The ideal biomarker

Validity

- Reproducible (inter- and intra- coefficient of variability)
- Usable as diagnostic test (easily measurable, affordable)

Relevance

- Pathway specific
- Related to a relevant clinical end point (surrogate end points)

Agache I. Curr Opin Allergy Clin Immunol. 2013;13(3):249-56

Current biomarkers in severe asthma

- The majority predict treatment response, very few forecast disease risk and progression
- Suitable for research settings
- Need to be validated and qualified

Agache I, Akdis C. Allergology International 2016,65(3):243-52

IL-5 (serum, saliva) (ref 27, 28, 29, 30,31,32,33,34, 35	✔	✔	✔
IL-13 (serum, sputum) (ref 27, 36, 37,38)	✔	✔	✔
IgE (serum) (ref 39, 40,41)	✔	✔	✔
IL-4 (serum, sputum) (ref 38,42)	✔	✔	✔
Periostin (serum, lung biopsies, BAL, tears) (ref 43,44,45)	✔	✔	✔
Type 2 gene expression (periostin, serpin B2, CLCA-1) in bronchial biopsies/sputum cells (ref 19,22,46)	✔	✔	–
DPP-4 (serum) (ref 47)	✔	–	✔
Eotaxin, RANTES, GM-CSF (serum, saliva) (ref 48,49)	✔	✔	-
IL-9 (serum) (ref 50)	✔	✔	?
IL-25 (bronchial epithelium, serum) (ref 51,52)	✔	✔	?
TSLP; CRTH2 and DP1 receptors (ref 52,53,54,55,56,57)	✔	✔	Under investigation
CCR8; TARC; IL-31; IL-32 and T1/ST-2; IL-19; NKT cells (ref 58, 59,60)	✔	✔	-
IL-33, proangiogenic BM precursors, osteopontin, galectin 9 (ref 61,62,63)	✔	✔	-
CD48, leptin, lactoferin, IL-23 (ref 64,65,66)	✔	-	-
IL-7 (serum, PBMCs) (ref 67)	✔	✔	-
ICOS/ICOS-L; IL-22; H4 receptors (ref 68,69,70)	✔	-	-
Il-5 and IL-13 producing Innate lymphoid cells in serum and sputum (ref 71)	✔	✔	-
DNA methylation profile (ref 72)		✔	

Type 2 asthma biomarkers

Agache I, Rogozea L. In press

Validation and qualification of biomarkers

- **Validation** is the process of assessing the measurement performance of the biomarker (reproducible and accurate data)

- **Qualification** is the evidentiary process of linking a biomarker with biological processes and clinical end points

Wagner JA, Williams SA, Webster CJ. Clin Pharmacol Ther. 2007;81:104–7
Goodsaid FM, Frueh FW, Mattes W. Toxicology. 2008;245:219–23

Serum IL-17 as a biomarker for severe asthma

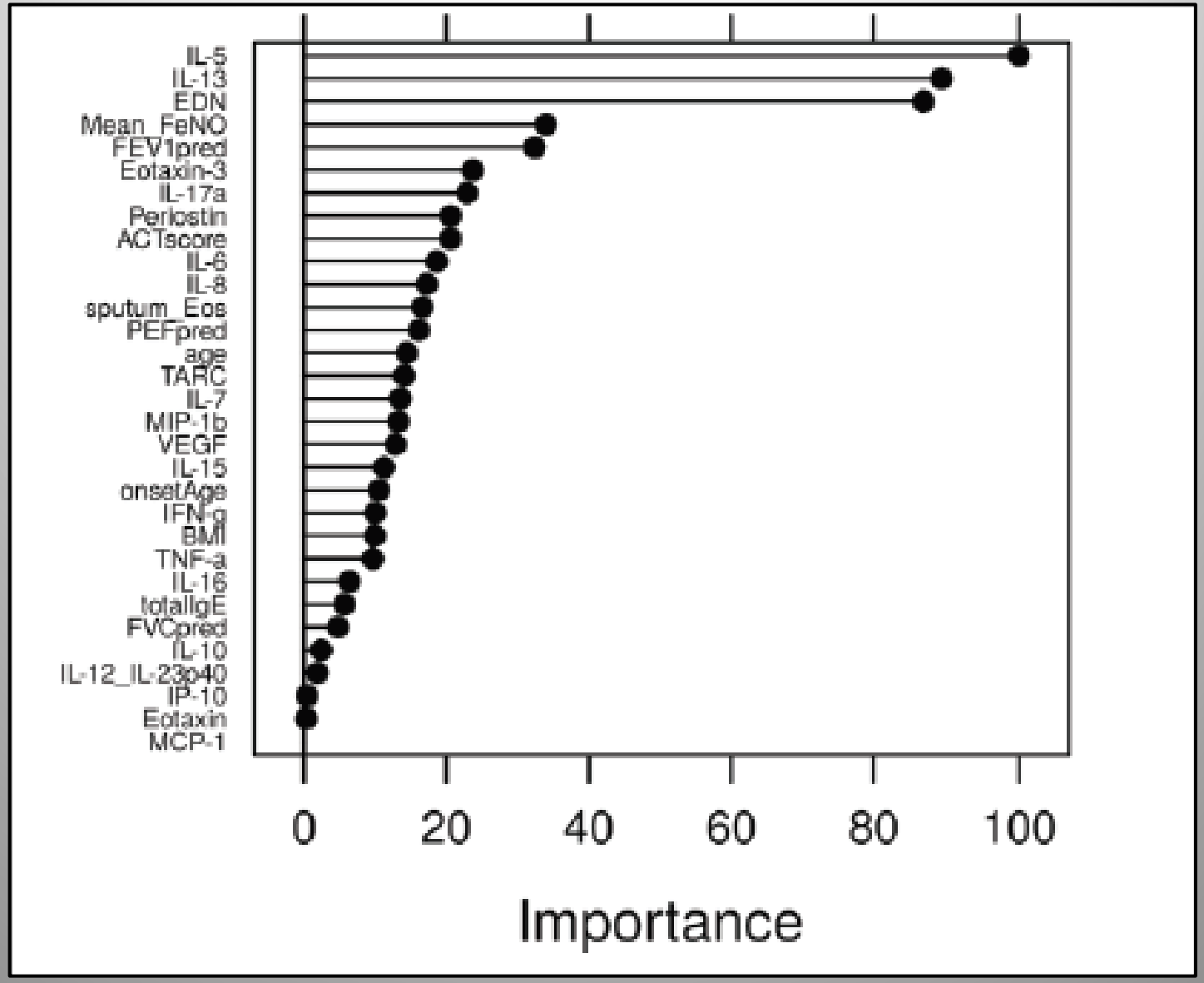
120

	Beta	Standard Error of Beta	B	Standard Error of B	t(73)	p-level
Smoke	0.010273	0.092371	0.010370	0.093245	0.11121	0.911746
NSAID intolerance	0.346923	0.097467	0.345615	0.097099	3.55940	0.000649
Atopy	-0.076304	0.098527	-0.075581	0.097593	-0.77445	0.441099
Obesity	-0.002673	0.104863	-0.002714	0.106457	-0.02549	0.979728
Moderate/severe persistent rhinitis/ chronic rhinosinusitis	-0.028323	0.097938	-0.041392	0.143129	-0.28919	0.773233
Blood eosinophilia	-0.094935	0.093798	-0.093847	0.092722	-1.01213	0.314731
FEV1 < 50% predicted	0.400498	0.092198	0.609701	0.140359	4.34388	0.000043
IL-17 > 20 pg/ml	0.352762	0.091920	0.442894	0.115406	3.83770	0.000257

(23 patients) (26 patients) (36 patients)

Agache I et al. Respir Med 2010;104:1131-7

Biomarkers for eosinophilic asthma

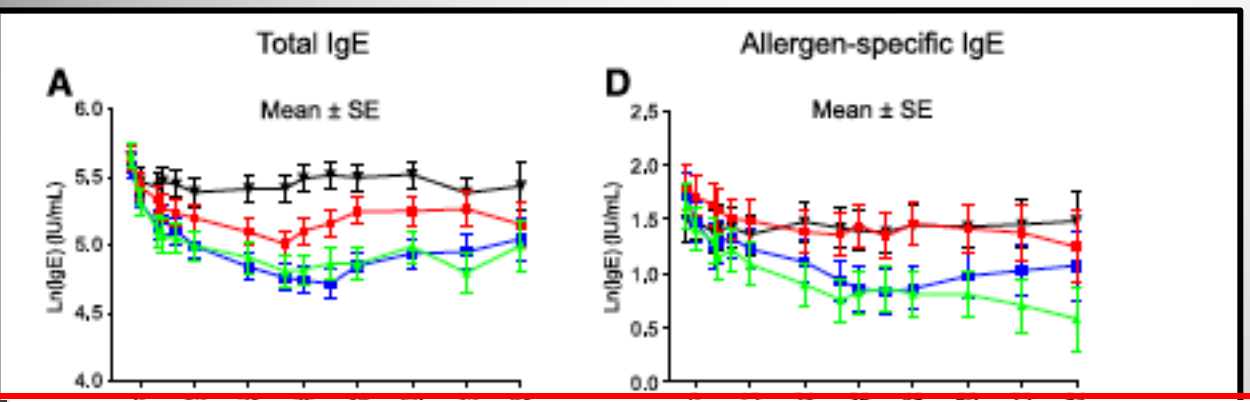


Agache I et al. Allergy 2016;71:1192-202

Endotype driven treatment in type 2 asthma

Predictive biomarker	Drug	Target	Effects	Regulatory status
Blood eos Periostin FeNO	Omalizumab	IgE	Reduces exacerbations Improves symptoms and quality of life	FDA- and EMA-approved
Blood/sputum eos FeNO	Mepolizumab	IL-5	Reduces eos, exacerbations and OCS	FDA and EMA approved
Blood eos	Reslizumab	IL-5	Reduces eos, exacerbations Improves FEV_1	FDA and EMA approved
Blood eos	Benralizumab	IL-5Rα	Reduces eos and bas, exacerbations Improves FEV_1	Phase III
Blood eos	Dupilumab	IL-4Rα	Reduces exacerbations, Improves FEV_1	Phase III
Periostin DPP-4	Tralokinumab	IL-13	Reduces eos Improves FEV_1	Phase II
Periostin	Lebrikizumab	IL-13	Reduces exacerbations Improves FEV_1	Phase III

Muraro A, et al. J Allergy Clin Immunol. 2016;137(5):1347-58



Treatment	n	Number of Exacerbations	Exacerbation Rate	Rate Reduction (%)	90% CI
	145	60	0.62		
150 mg Q	145	63	0.66	-5.7	-54.7 to 27.8
450 mg Q	145	63	0.69	-11.2	-62.7 to 24
300 mg M	143	47	0.5	19.6	-21.3 to 46.8

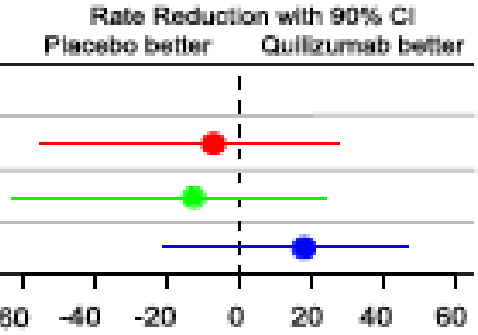
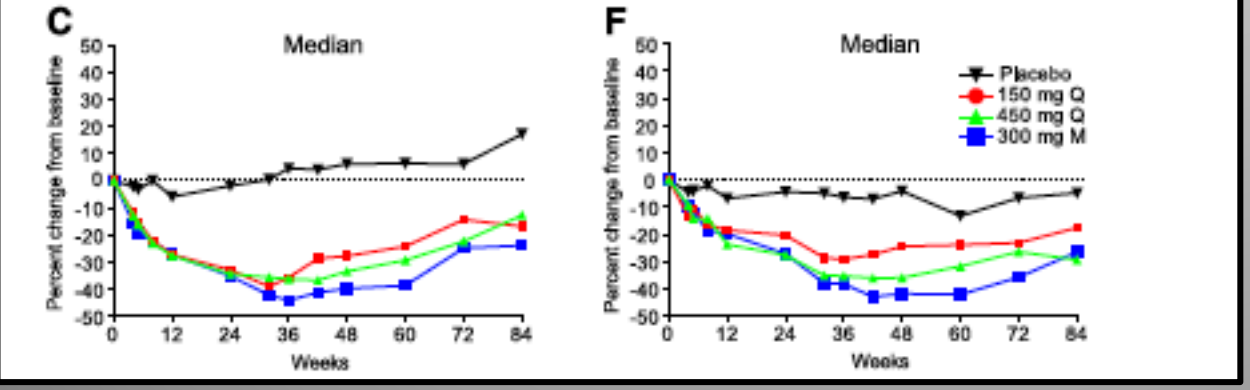
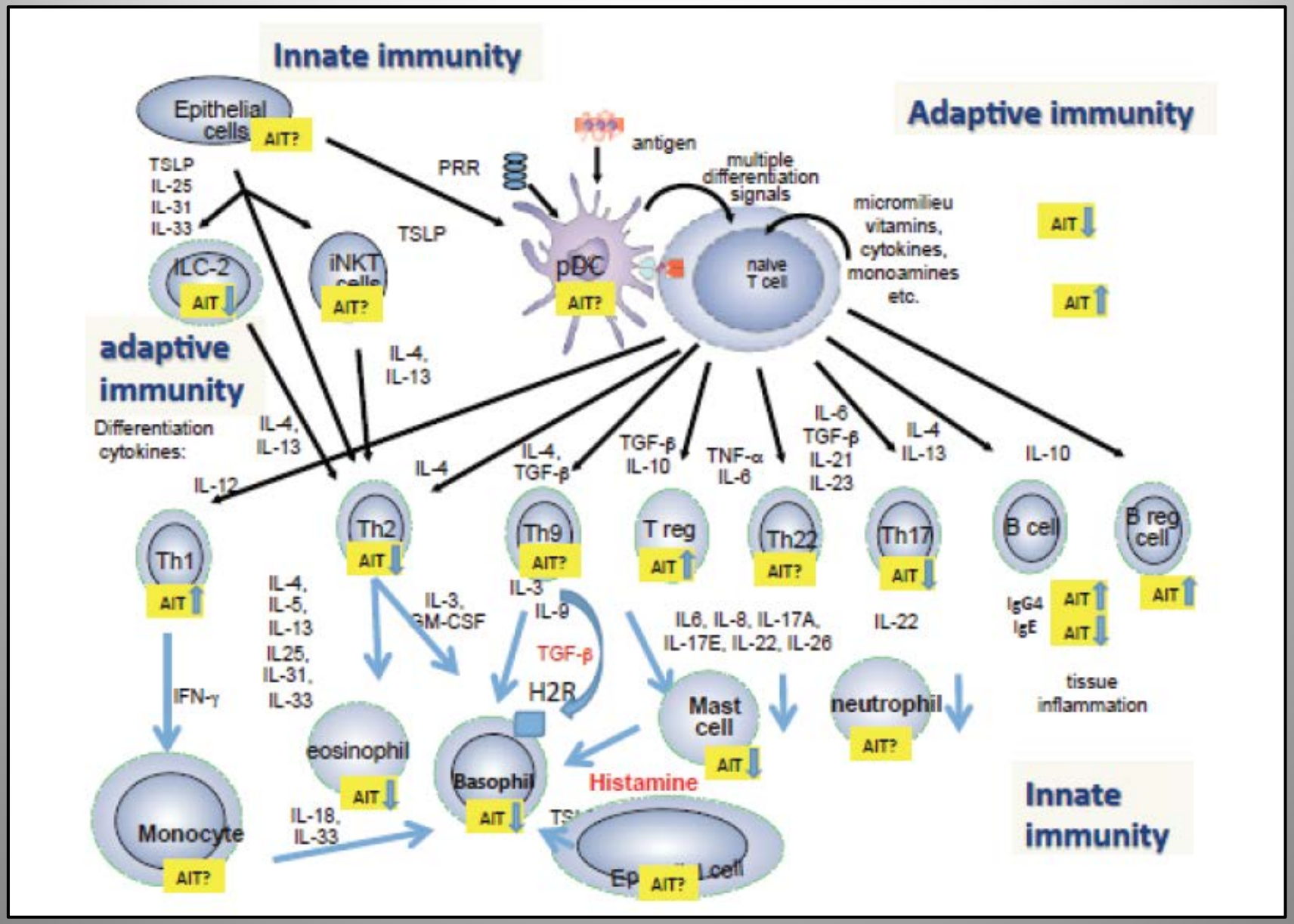


Fig. 3 Rate of protocol-defined asthma exacerbations through Week 36 for all patients. M, monthly; Q, quarterly



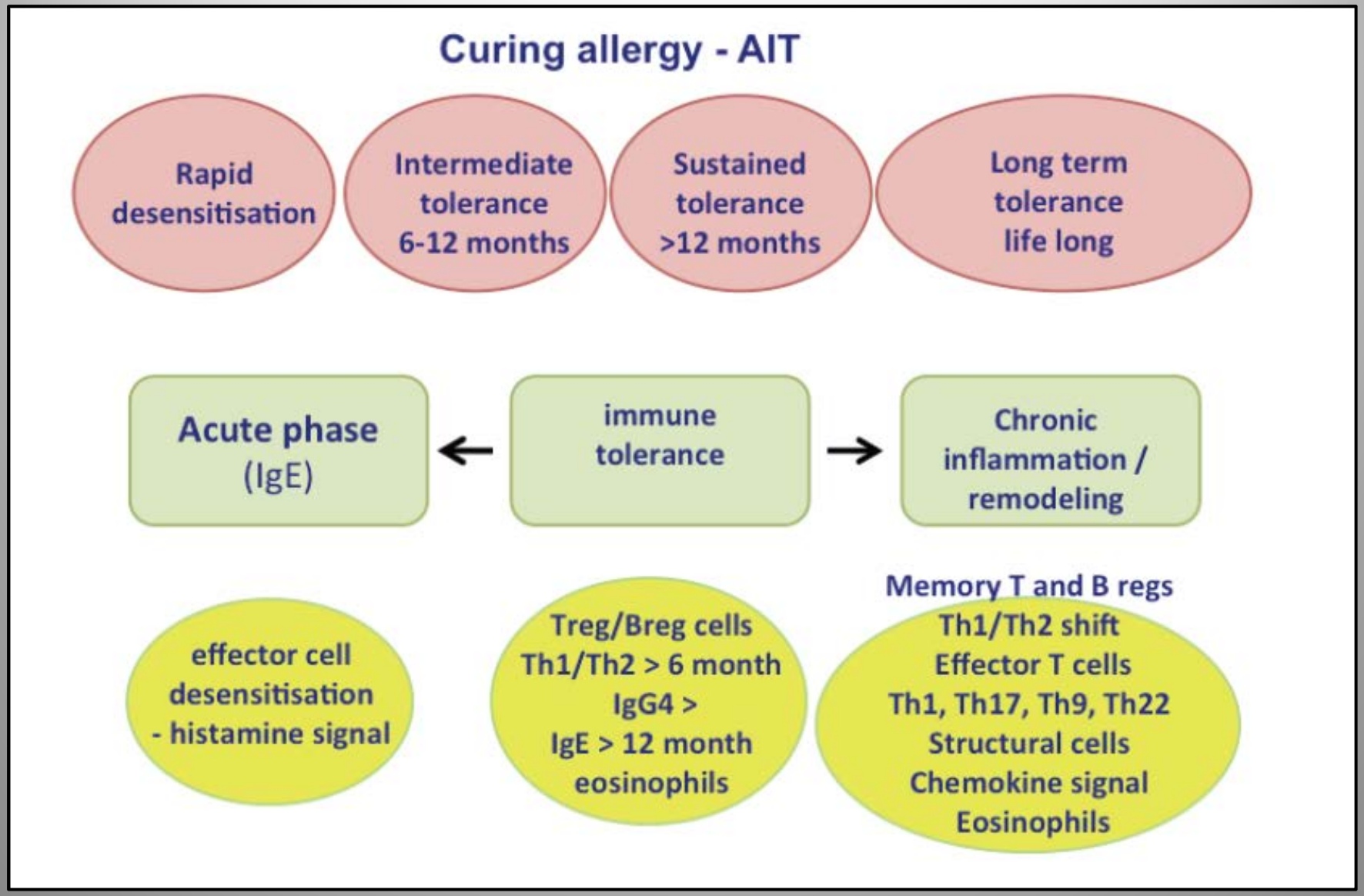
Harris JM, et al. Respir Res. 2016;17:29

Allergen immunotherapy in asthma



Jutel M, Agache I et al. J Allergy Clin Immunol 2016;137:358-68

Allergen immunotherapy in asthma



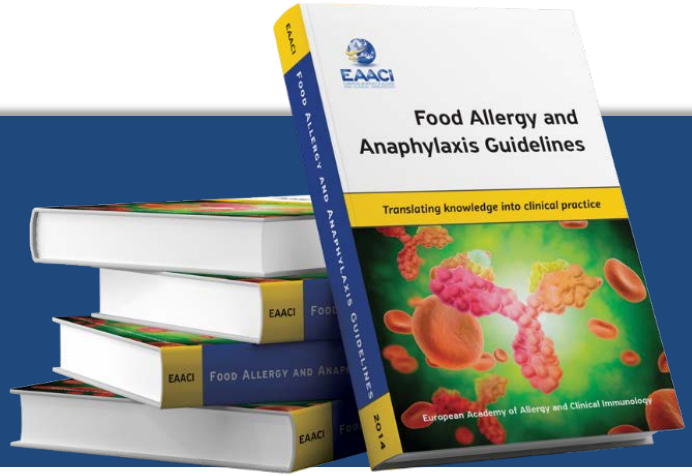
Jutel M, Agache I et al. J Allergy Clin Immunol 2016;137:358-68

Allergen immunotherapy in asthma

Primary outcomes	1. Effectiveness	Short term (during treatment)	Symptom score
		Long term (at least one year after discontinuation of treatment)	Medication score
			Symptom and medication score
	2. Cost-effectiveness		
	3. Safety		
Secondary outcomes	1. Asthma control		
	2. Asthma specific quality of life		
	3. Exacerbations		
	4. Lung function		
	5. Response to environmental exposure chamber or bronchial allergen challenge		
	6. Safety as assessed by local and systemic reactions		
	7. Health economic analysis from the perspective of the health system/payer		

Dhami S et al. Clin Transl Allergy. 2016;6:5.

Guidelines



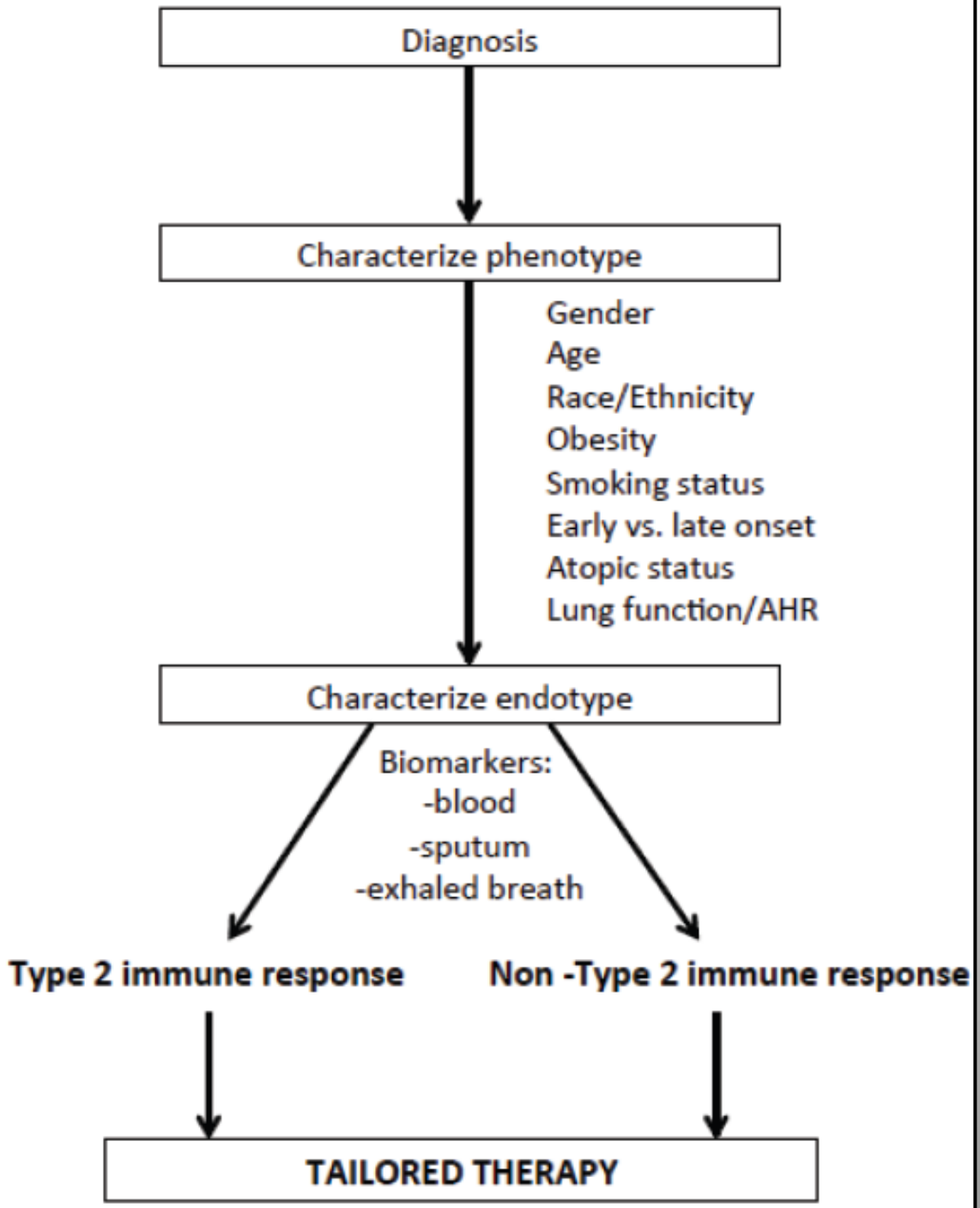
To be launched in 2017

Available for members on **www.eaaci.org**

EAACI Molecular Allergology User's Guide

Straightforward guide on molecular allergology describing what are components, the clinical benefits of testing for components as well as how to interpret results including understanding cross-reactions

Available on www.eaaci.org

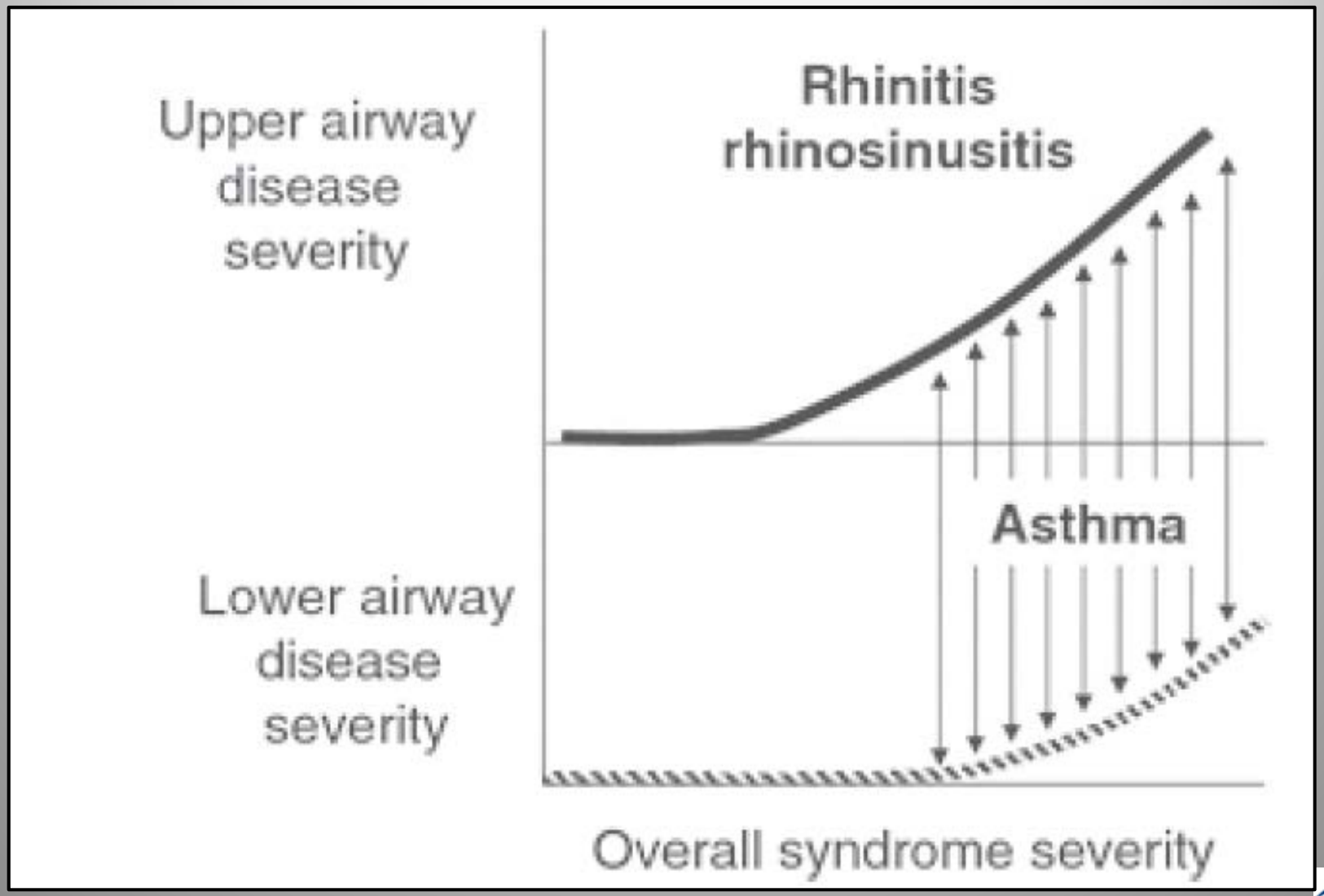


Precision medicine in asthma

Muraro A, et al. J Allergy Clin Immunol. 2016;137(5):1347-58

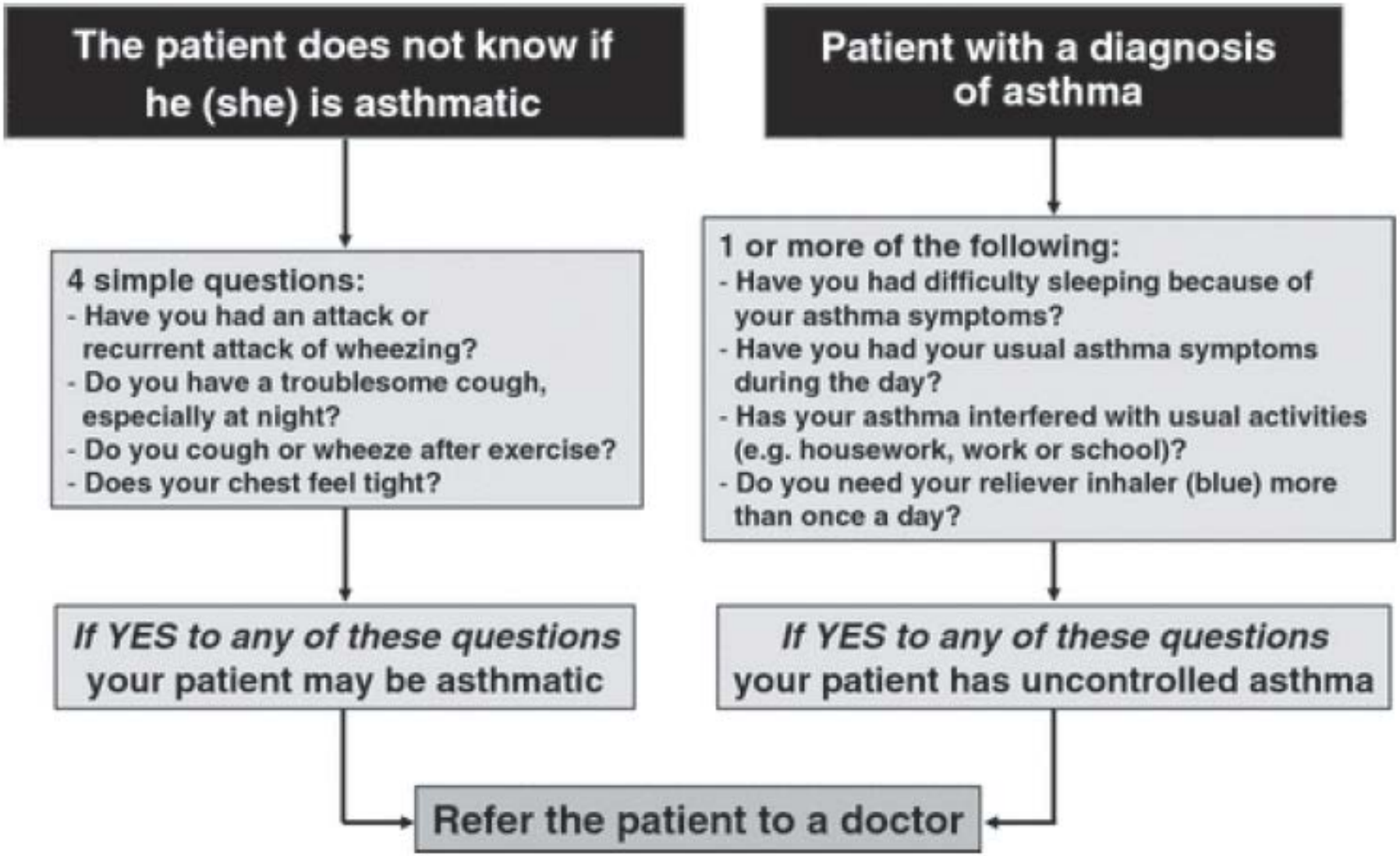
1b. Main research area – asthma co-morbidities

One airways disease concept - ARIA



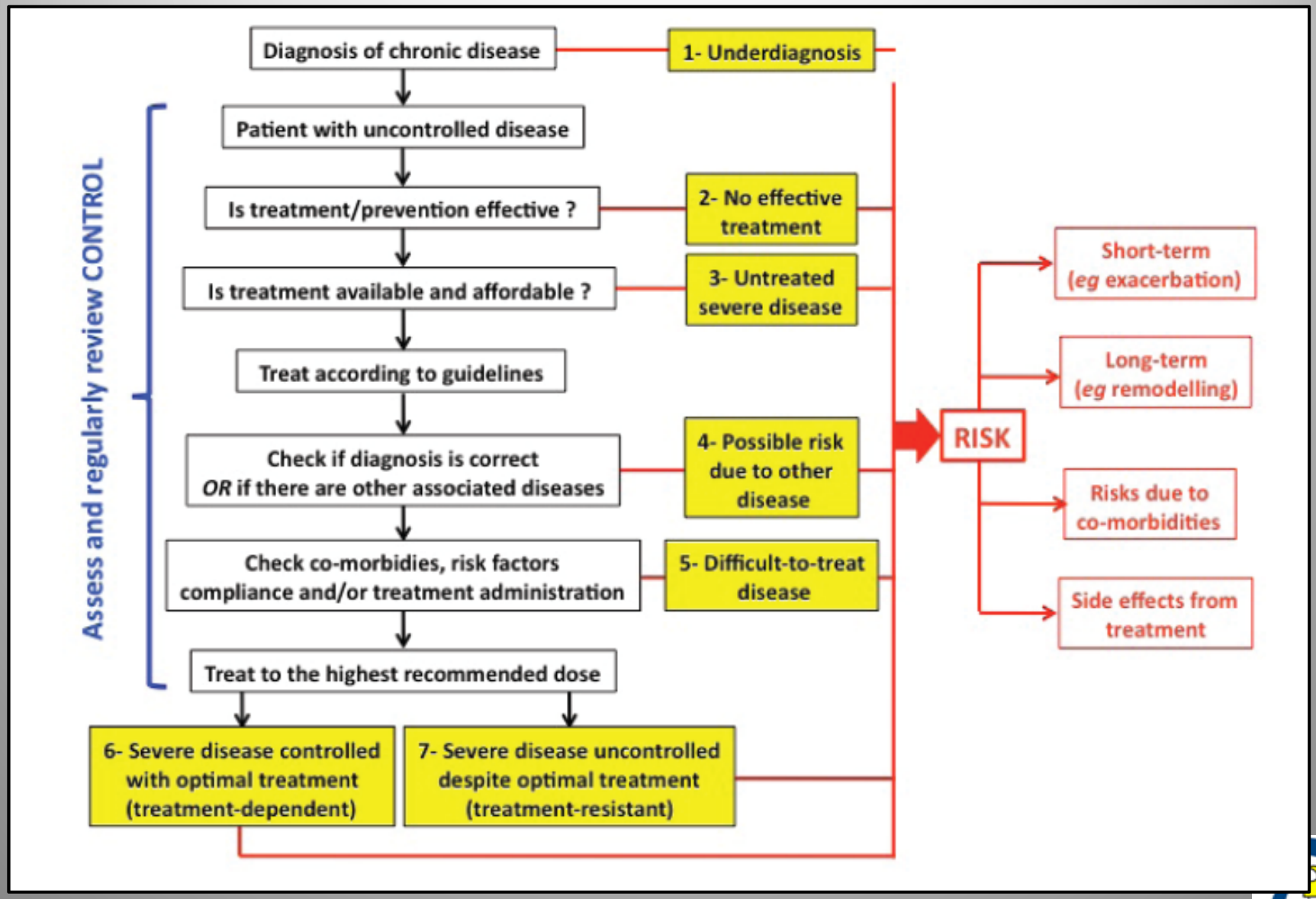
Bousquet J et al. Allergy. 2008;63 Suppl 86:8-160

One airways disease concept - ARIA



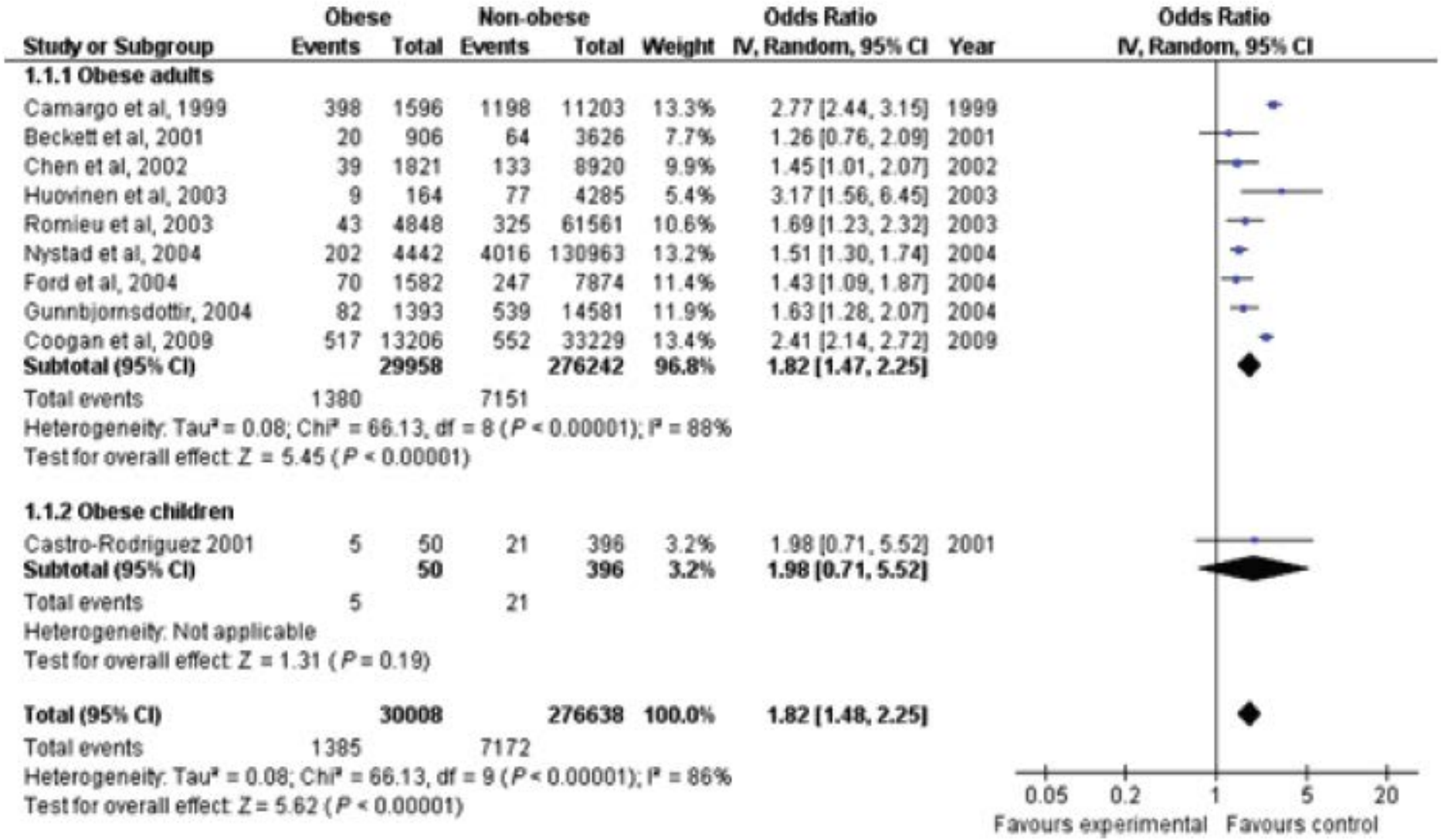
Bousquet J et al. Allergy. 2008;63 Suppl 86:8-160

Uniform approach for severe allergic diseases



Bousquet J et al. Int Arch Allergy Immunol. 2012;158(3):216-31

Asthma and obesity



Study or Subgroup	Obese Events	Obese Total	Non-obese Events	Non-obese Total	Weight	Odds Ratio IV, Random, 95% CI	Year
1.1.1 Obese adults							
Camargo et al, 1999	398	1596	1198	11203	13.3%	2.77 [2.44, 3.15]	1999
Beckett et al, 2001	20	906	64	3626	7.7%	1.26 [0.76, 2.09]	2001
Chen et al, 2002	39	1821	133	8920	9.9%	1.45 [1.01, 2.07]	2002
Huovinen et al, 2003	9	164	77	4285	5.4%	3.17 [1.56, 6.45]	2003
Romieu et al, 2003	43	4848	325	61561	10.6%	1.69 [1.23, 2.32]	2003
Nystad et al, 2004	202	4442	4016	130963	13.2%	1.51 [1.30, 1.74]	2004
Ford et al, 2004	70	1582	247	7874	11.4%	1.43 [1.09, 1.87]	2004
Gunnbjornsdottir, 2004	82	1393	539	14581	11.9%	1.63 [1.28, 2.07]	2004
Coogan et al, 2009	517	13206	552	33229	13.4%	2.41 [2.14, 2.72]	2009
Subtotal (95% CI)		**29958**		**276242**	**96.8%**	**1.82 [1.47, 2.25]**	
Total events	1380		7151				
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 66.13$, df = 8 ($P < 0.00001$); $I^2 = 88\%$							
Test for overall effect: $Z = 5.45$ ($P < 0.00001$)							
1.1.2 Obese children							
Castro-Rodriguez 2001	5	50	21	396	3.2%	1.98 [0.71, 5.52]	2001
Subtotal (95% CI)		**50**		**396**	**3.2%**	**1.98 [0.71, 5.52]**	
Total events	5		21				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 1.31$ ($P = 0.19$)							
Total (95% CI)		**30008**		**276638**	**100.0%**	**1.82 [1.48, 2.25]**	
Total events	1385		7172				
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 66.13$, df = 9 ($P < 0.00001$); $I^2 = 86\%$							
Test for overall effect: $Z = 5.62$ ($P < 0.00001$)							

Moreira A et al. Allergy. 2013;68(4):425-39.

1c. Asthma management plans and new models of care

New generation guidelines

New generation guidelines

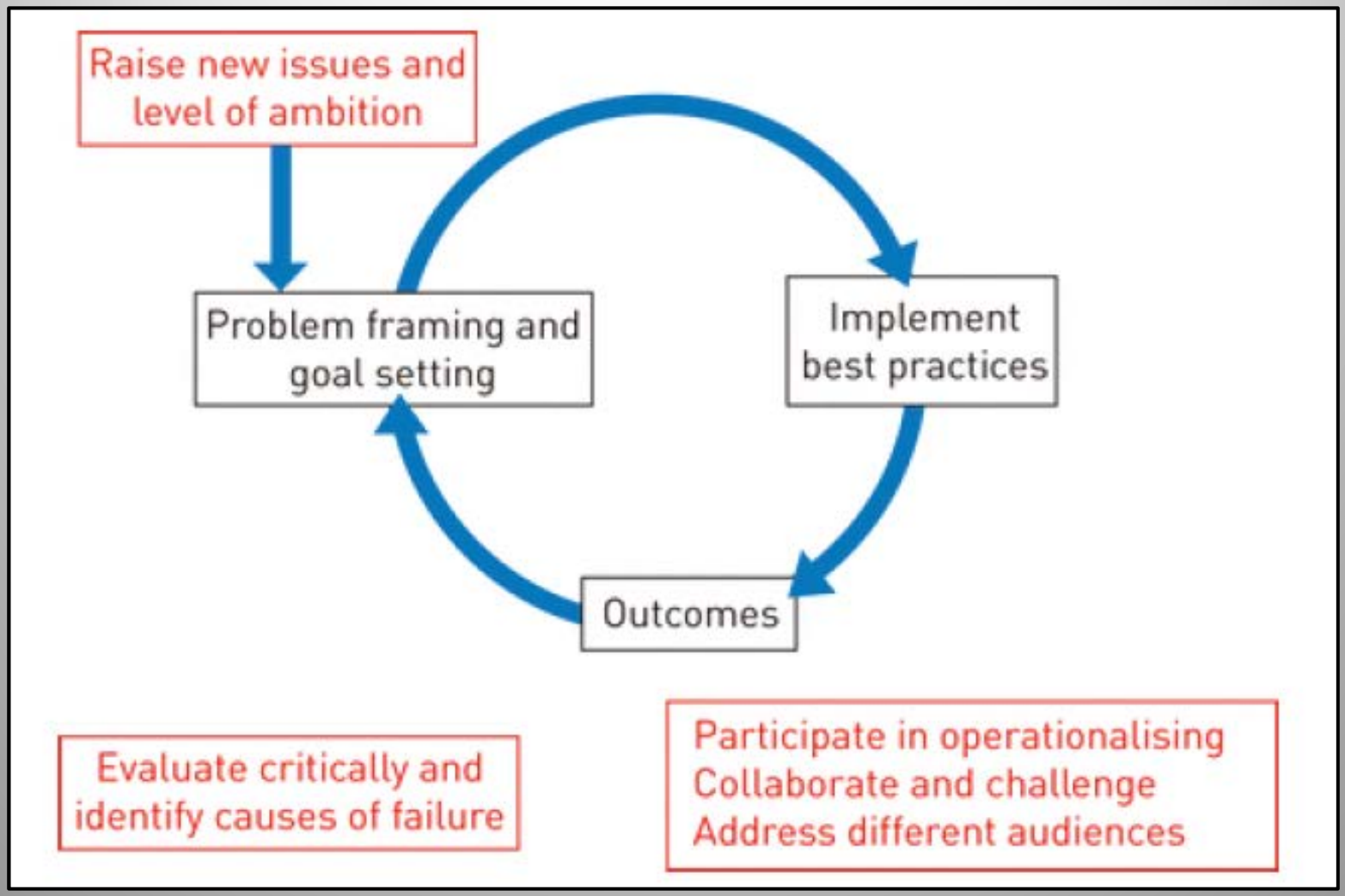
ARIA (allergic rhinitis and its impact on asthma) – 2008, 2010, 2016

EAACI Food Allergy and Anaphylaxis Guidelines 2014

EAACI Allergen Immunotherapy Guidelines 2017

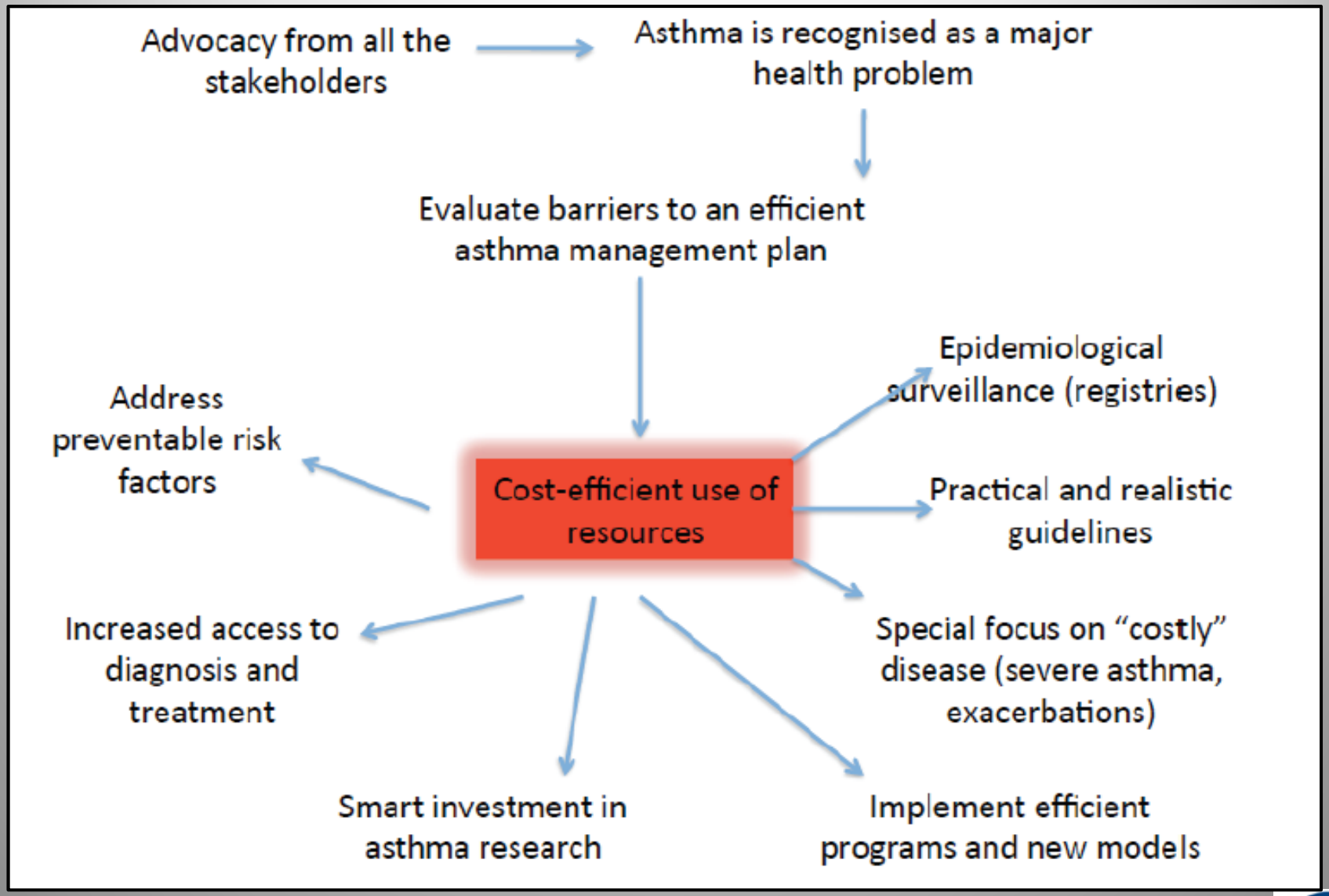
EAACI – AAAAI- ERS Asthma Guidelines 2019

New models of care – integrated care pathways



European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy, WP 10; Global Alliance against Chronic Respiratory Diseases,.
Eur Respir J. 2014;44(2):304-23

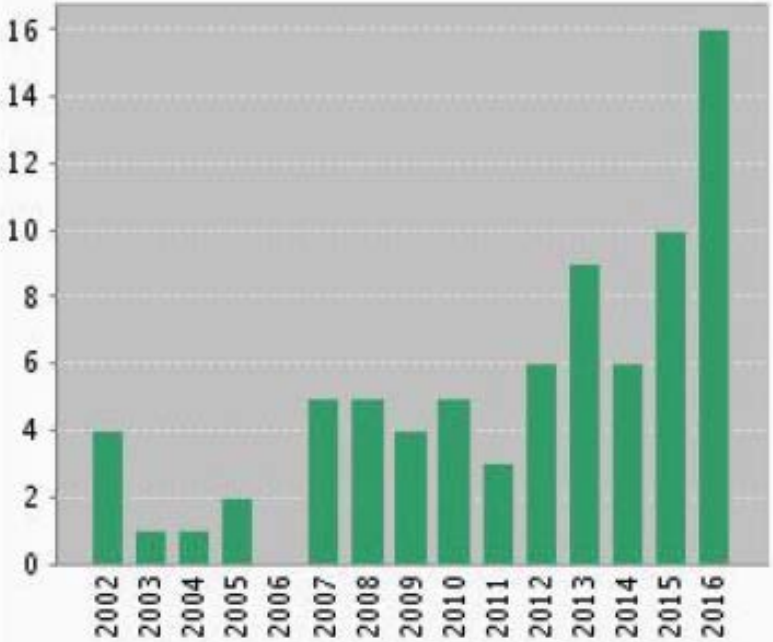
Asthma "best-buys" management plan



Agache I. Global Atlas of Asthma, 2013

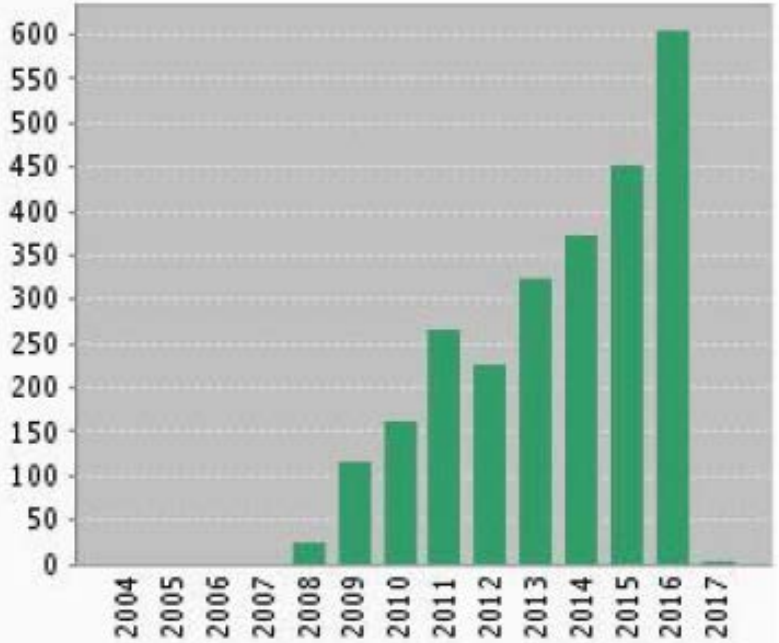
2. Evolution and development plans for career development

Published Items in Each Year



The latest 20 years are displayed.

Citations in Each Year

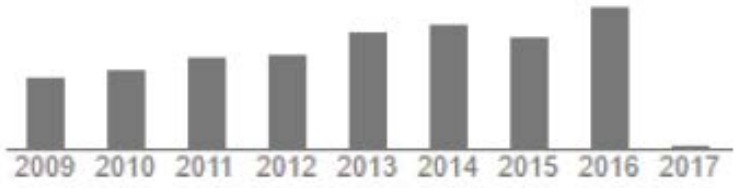


The latest 20 years are displayed.

Results found:	77
Sum of the Times Cited [?] :	2567
Sum of Times Cited without self-citations [?] :	2500
Citing Articles [?] :	2296
Citing Articles without self-citations [?] :	2265
Average Citations per Item [?] :	33.34
h-index [?] :	18

Google Scholar

Citation indices	All	Since 2012
Citations	8590	4644
h-index	20	20
i10-index	32	32



Academic development

1996-2000	Junior Assistant Professor
2000-2006	Assistant Professor
2003-today	Head of Immunology Discipline
2006-2007	Lecturer
2007-today	Associate Professor
2010-today	Physiology Discipline

Key achievements

- Interactive teaching and creative scientific research

- New curriculum for immunology, physiology for MD and allied health – undergraduate and master programmes

- Practical reference guides for students: immunology and pneumology

Scientific development future plans

Asthma endotypes

- PN-II-RUTE-2014-4-2303 project, Endotypes of Non-Eosinophilic Asthma (ENDANA)
- Type 2 asthma subendotypes
- Pediatric asthma endotypes
- The role of exposome in asthma – consensus document EAACI-AAAAI

Precision medicine

- **Biomarkers and endotypes for allergen immunotherapy – in collaboration with Swiss Institute for Allergy and Asthma Research (SIAF)**

- **Mobile health/Allergy 2.0 and 3.0**

- **Development of protocols for educational intervention in the community for asthma management – in collaboration with Pharmaceutical Group of the EU**

Professional development future plans

- **2017-2019: President of the European Academy of Allergy and Clinical Immunology**

- **facilitate the cooperation between international and national societies as a scaffold for**

1. local adaptation and implementation

- **guidelines**
- **cutting-edge research**
- **best practices**
- **efficient health policies**

2. advocacy for promoting asthma as a major health problem.

Academic activity future plans

New educational portfolio for students and HCPs - purposeful education

Facilitate both professional and career development

Key concepts: work-experience and social service

New tools facilitating interactive learning

- **tutorials for the faculty master programmes and for the doctoral school,**
- **multidisciplinary learner programmes,**
- **interactive brainstorming, buzz-sessions,**

Think-Pair share, incident process

Building the community feeling for students and teachers

Increased engagement in shaping the academic landscape and the organizational culture

Close working relationship between the student and faculty research mentor

Support for early career researches through national and international cooperative projects.

PhD coordination and full professorship