WAO VIEW ON IMMUNOTHERAPY

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BILBAO SPAIN

quirónsalud

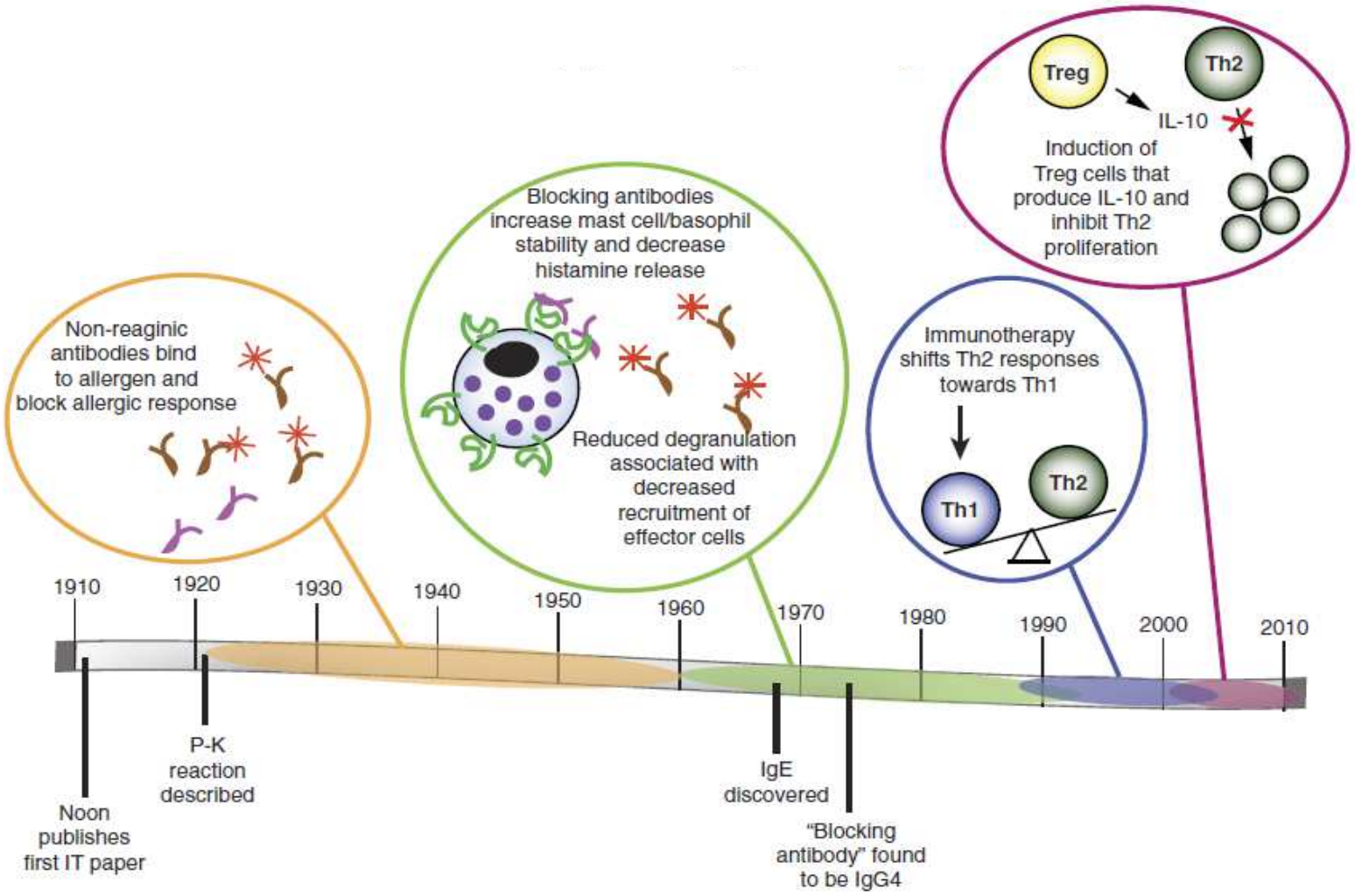
La salud persona a persona

AIT Definition

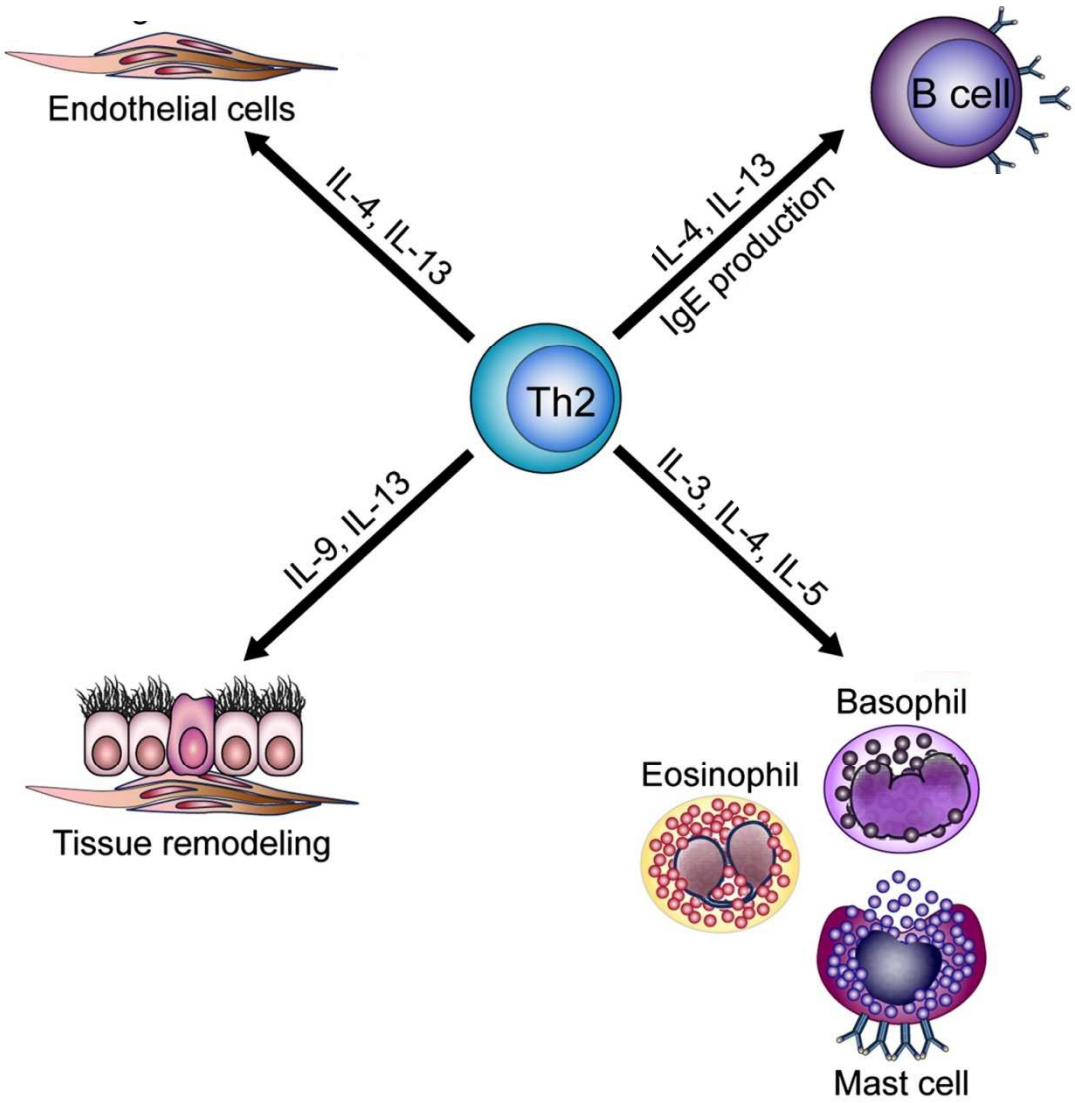
- Allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.

WHO Position Paper 1998

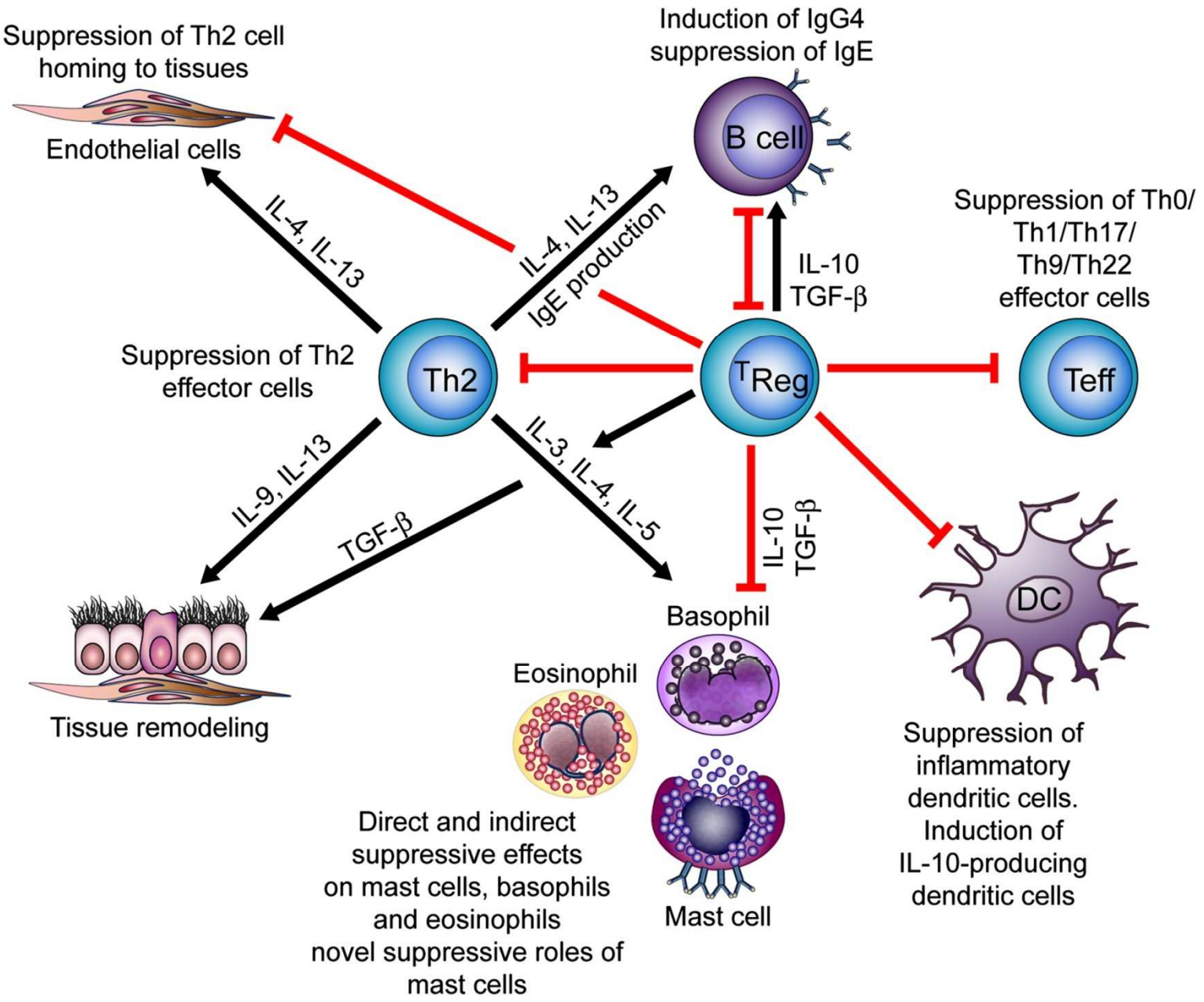
Mechanisms of action of AIT



Shakir EM et al. Ann Allergy Asthma Immunol. 2010 Nov;105(5):340-7

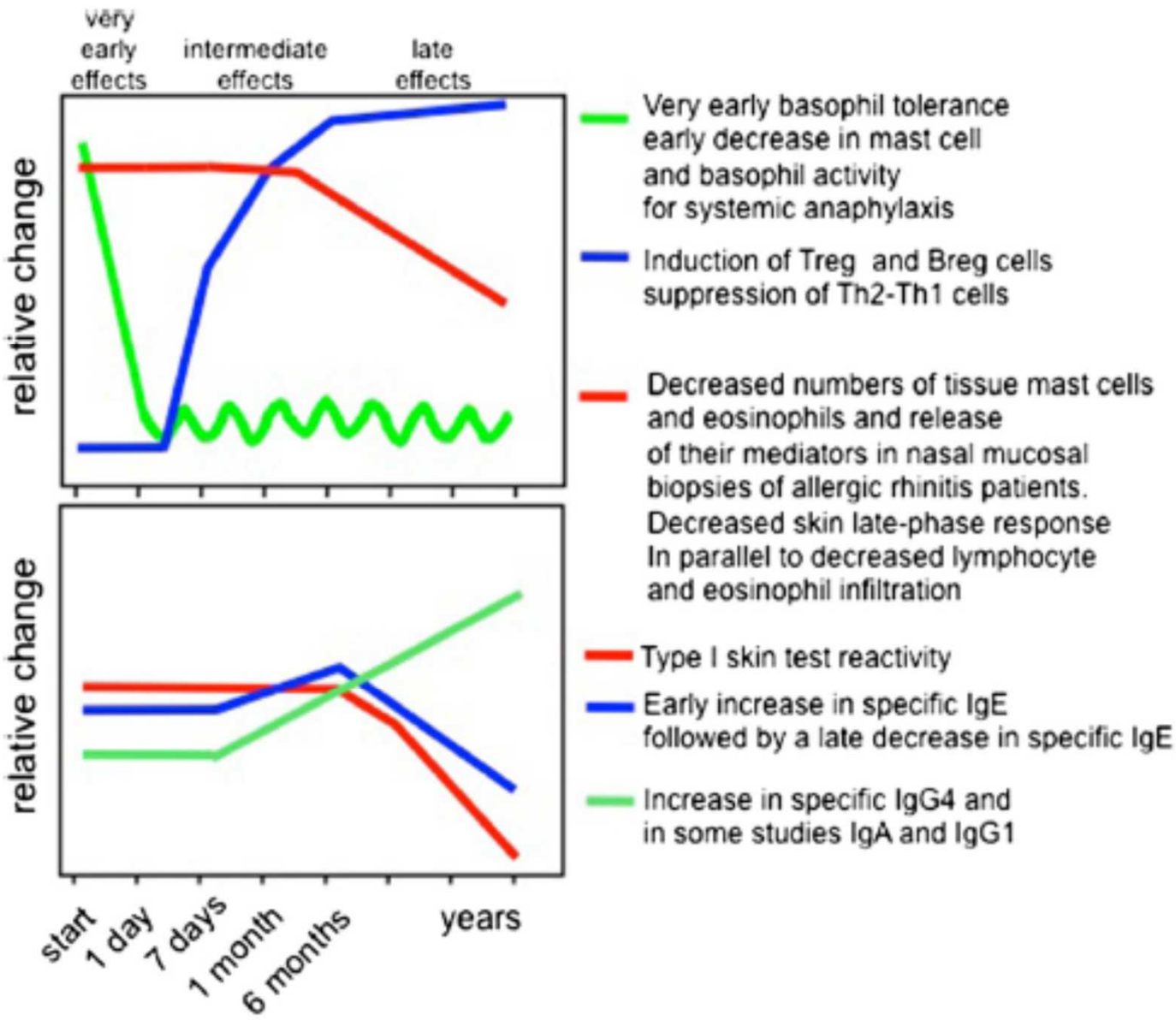


Akdis CA, Akdis M. J Allergy Clin Immunol. 2011 ;127(1):18-27
Akdis and Akdis World Allergy Organization Journal (2015) 8:17



Akdis CA, Akdis M. J Allergy Clin Immunol. 2011 ;127(1):18-27
Akdis and Akdis World Allergy Organization Journal (2015) 8:17

Immunologic changes during the course of AIT



Akdis and Akdis World Allergy Organization Journal (2015) 8:17

Future scenario in Allergy & Asthma treatment

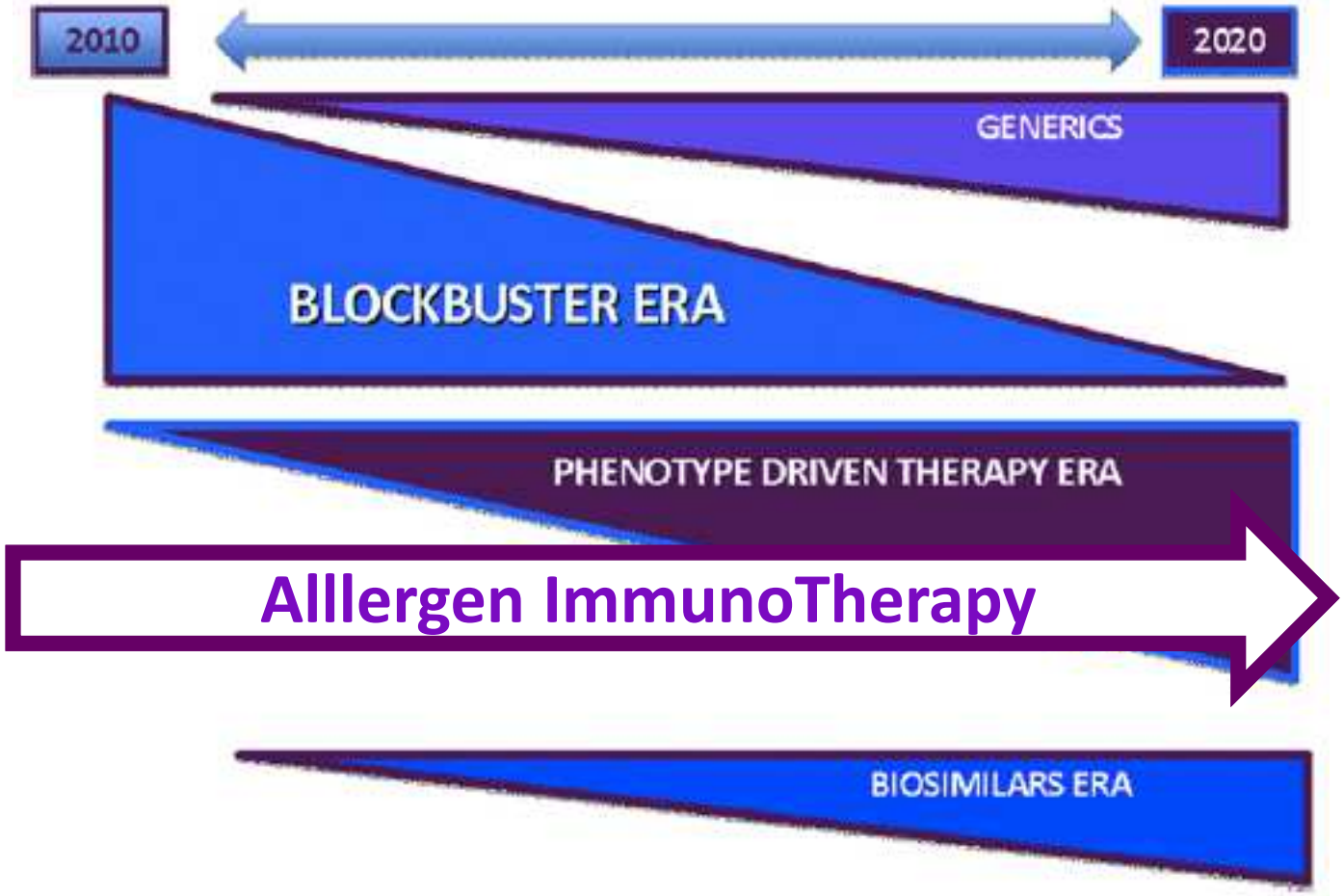


Fig. 1. Future scenario in allergy and asthma treatment.

Braido, Holgate, Canonica. Pulm.Pharm.Ther. 2012

Allergy Immunotherapy

1911	1960	1970	1986	1998	2000	2005	2006	2007	2008	2014
SCIT	First RCT SCIT	SLIT	First RCT SLIT	WHO	ARIA	First Meta SLIT	Large RCT SCIT	First Meta SCIT	Large RCT SLIT	EBM

Review

Allergy Asthma Immunol Res. 2016 Forthcoming.
Posted online 2016
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

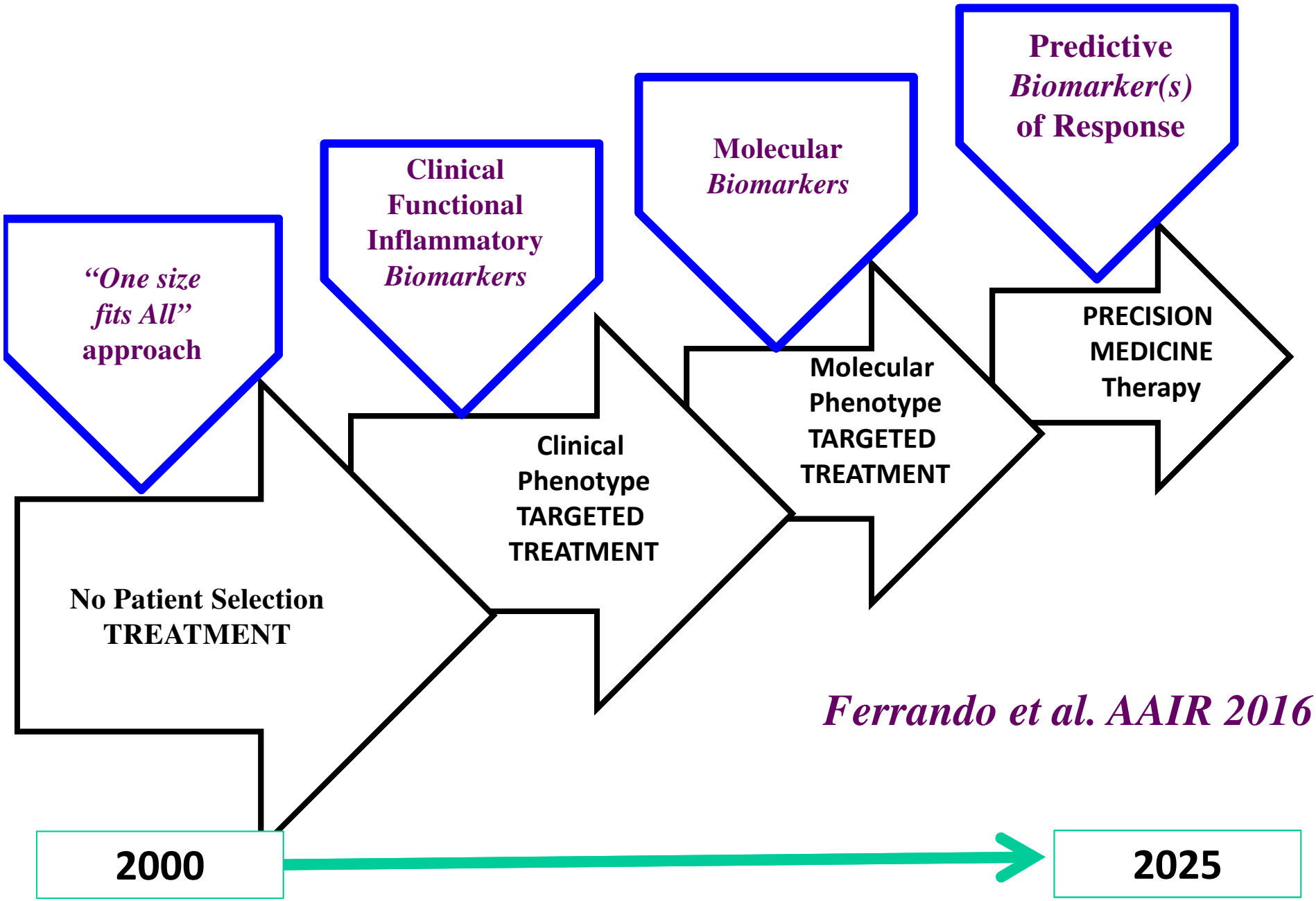
Personalized Medicine in Allergy

Matteo Ferrando,[1] Diego Bagnasco,[1] Gilda Varricchi,[2] Stefano Bernardi,[1] Alice Bragantini,[1] Giovanni Passalacqua,[1] Giorgio Walter Canonica[1*]

[1]*Allergy & Respiratory Diseases, DIMI Department of Internal Medicine, IRCCS AOU San Martino-IST, University of Genoa, Genoa, Italy*
[2]*Division of Clinical Immunology and Allergy, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy*

Ferrando et al. AAIR 2016

TREATMENT APPROACH EVOLUTION



Ferrando et al. AAIR 2016

Collins & Varmus NEJM 2015

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

— President Barack Obama, State of the Union Address, January 20, 2015

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

Perspective

The 21st Century Cures Act — A View from the NIH

Kathy L. Hudson, Ph.D., and Francis S. Collins, M.D., Ph.D.

NEJM 2017

PRECISION MEDICINE FUNDING

Funding for NIH Innovative Research Initiatives under the Cures Act.*				
Fiscal Year	BRAIN	PMI	Cancer Moonshot	Regenerative Medicine
		millions of $		
2017	10	40	300	2
2018	86	100	300	10
2019	115	186	400	10
2020	140	149	195	8
2021	100	109	195	
2022	152	150	194	
2023	450	419	216	
2024	172	235		
2025	91	36		
2026	195	31		
10-Yr total	1,511	1,455	1,800	30

* BRAIN denotes Brain Research through Advancing Innovative Neurotechnologies, and PMI Precision Medicine Initiative.

NEJM 2017

Canonica *et al. World Allergy Organization Journal* (2015) 8:31
DOI 10.1186/s40413-015-0079-7

WAO journal
WORLD ALLERGY ORGANIZATION

REVIEW Open Access

Allergen Immunotherapy (AIT): a prototype of Precision Medicine

GW Canonica[1*], C. Bachert[2], P. Hellings[3,4], D. Ryan[5], E. Valovirta[6], M. Wickman[7], O. De Beaumont[8] and J. Bousquet[9,10,11]

Canonica et al WAO J. 2015

AIT as PERSONALIZED THERAPY

Hamburg & Collins, NEJM 2010 [22]

Identification of Molecular Mechanism of disease

Diagnostic Tool for the Molecular Mechanism

Treatment Blocking the Molecular Mechanism

Canonica et al. WAO J.2015 [18]
Passalacqua & Canonica, CMA 2015 [23]

Molecular mechanism:
IgE, arming effector cells, binds allergen/component :mediator release & symptoms

Diagnostic Tool:
IgE to causal allergen/component detection

Treatment Blocking
the Molecular Mechanism
AIT- Allergen Immunotherapy (SCIT-SLIT)

Canonica et al. Curr..Opin.Pulm.Med. 2015

CLINICAL AND MOLECULAR ALLERGY

Passalacqua and Canonica *Clin Mol Allergy* (2015) 13:24
DOI 10.1186/s12948-015-0028-6

CLINICAL AND MOLECULAR ALLERGY

COMMENTARY Open Access

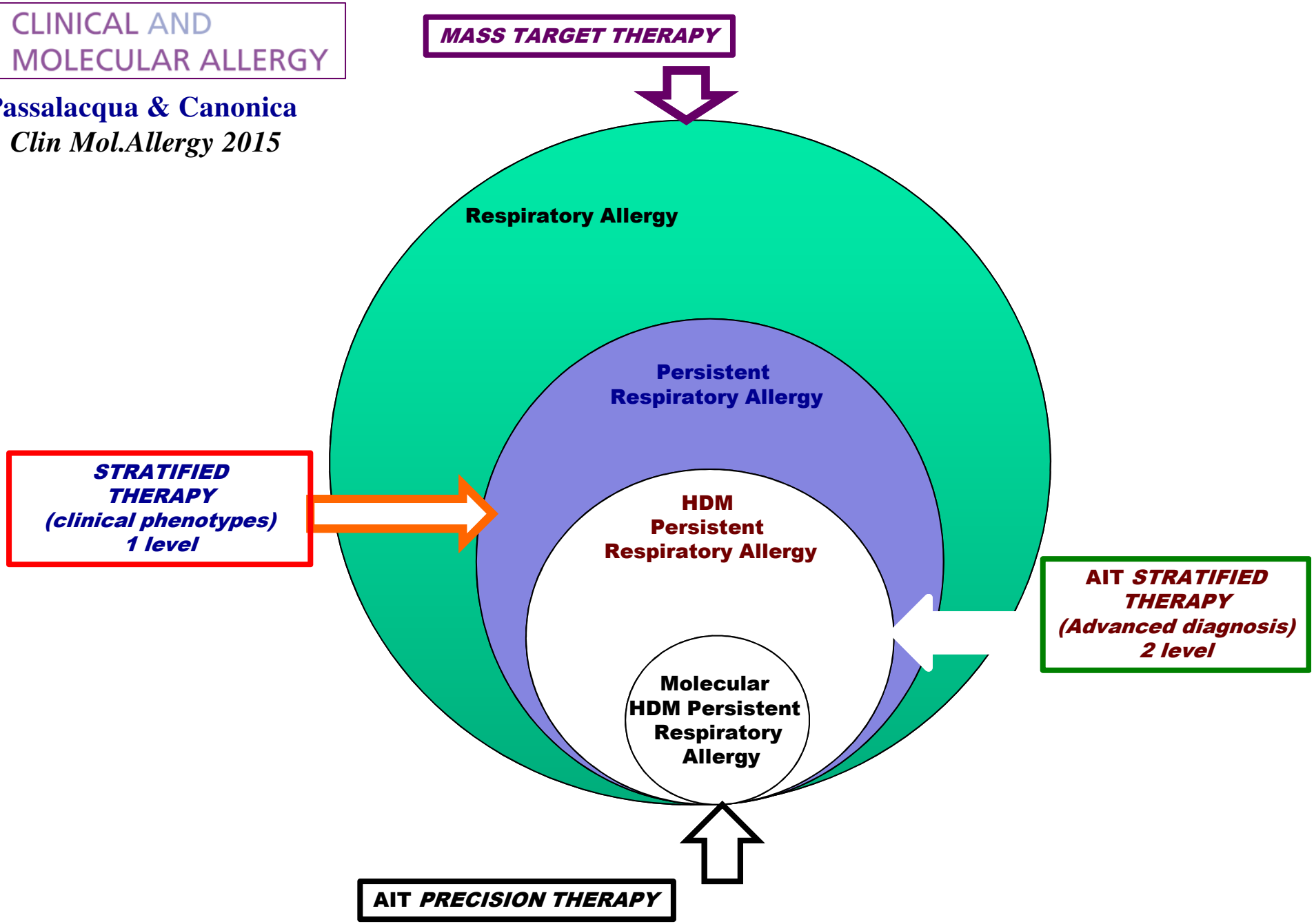
AIT (allergen immunotherapy): a model for the "precision medicine"

Giovanni Passalacqua* and Giorgio Walter Canonica

Passalacqua & Canonica CMA 2015

CLINICAL AND MOLECULAR ALLERGY

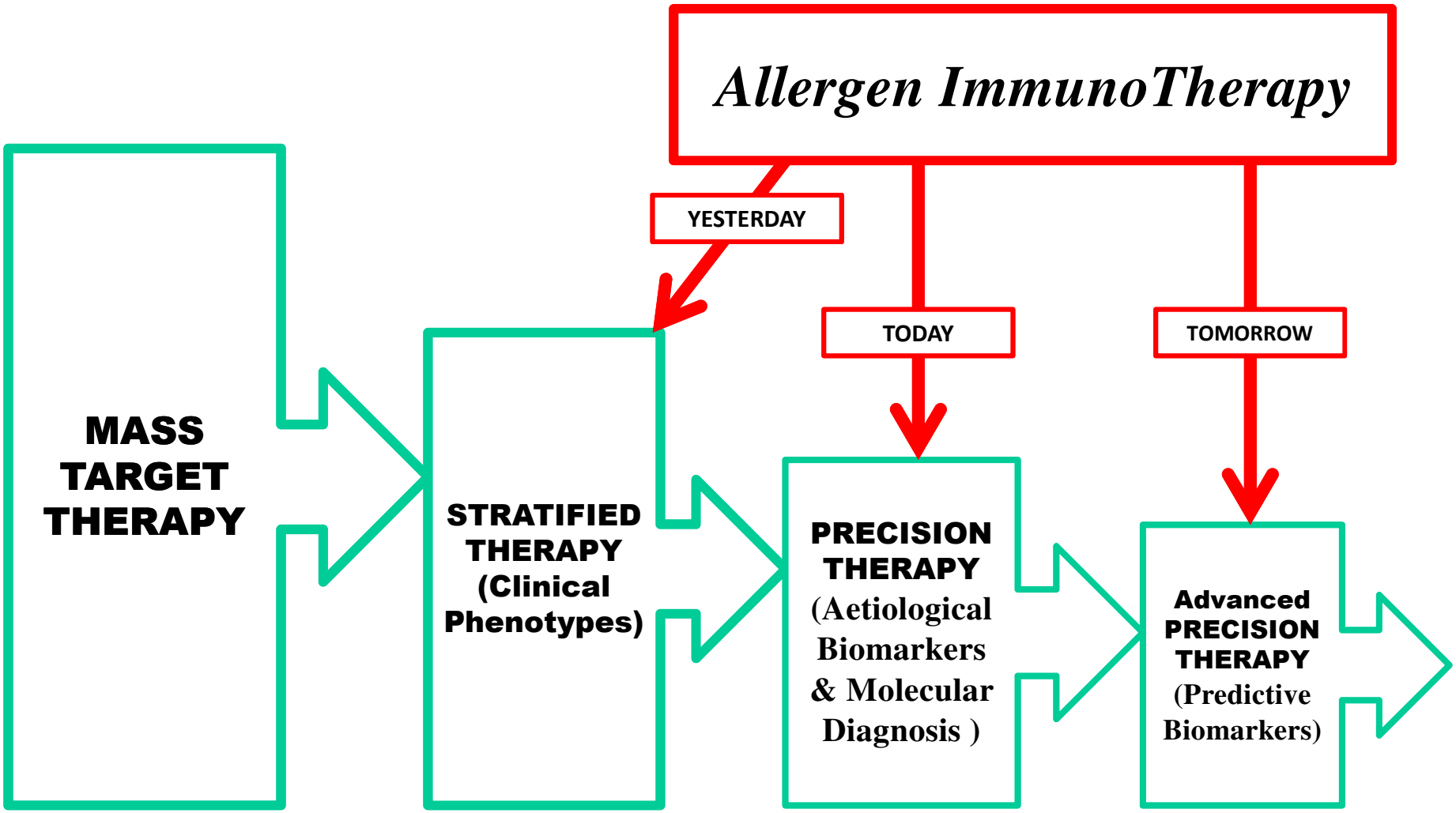
Passalacqua & Canonica
Clin Mol.Allergy 2015



CLINICAL AND MOLECULAR ALLERGY

Passalacqua & Canonica *Clin.Mol.Allergy*. 2015

Allergen ImmunoTherapy: The Path to Precision Medicine



Possibly, in the past, the concept of AIT as Precision Treatment was not properly considered or emphasized, but AIT was and still is upfront in this context

CLINICAL AND MOLECULAR ALLERGY

Passalacqua & Canonica C.M.A. 2015

CLINICAL AND MOLECULAR ALLERGY

Passalacqua & Canonica
Clin Mol.Allergy 2015

CONCLUSION

According to the current knowledge of mechanistic aspects, to the detailed identification of aetiological agents, and the not negligible longstanding experience,

AIT,

in the context of the other available therapies for respiratory allergy, is the most "personalized" treatment

Canonica et al. World Allergy Organization Journal _####################_
DOI 10.1186/s40413-015-0079-7

WAO journal
WORLD ALLERGY ORGANIZATION

REVIEW Open Access

Allergen Immunotherapy (AIT): a prototype of precision medicine

GW Canonica[1*], C. Bachert[2], P. Hellings[3,4], D. Ryan[5], E. Valovirta[6], M. Wickman[7], O. De Beaumont[8] and J. Bousquet[9,10,11]

Canonica et al WAO J. 2015

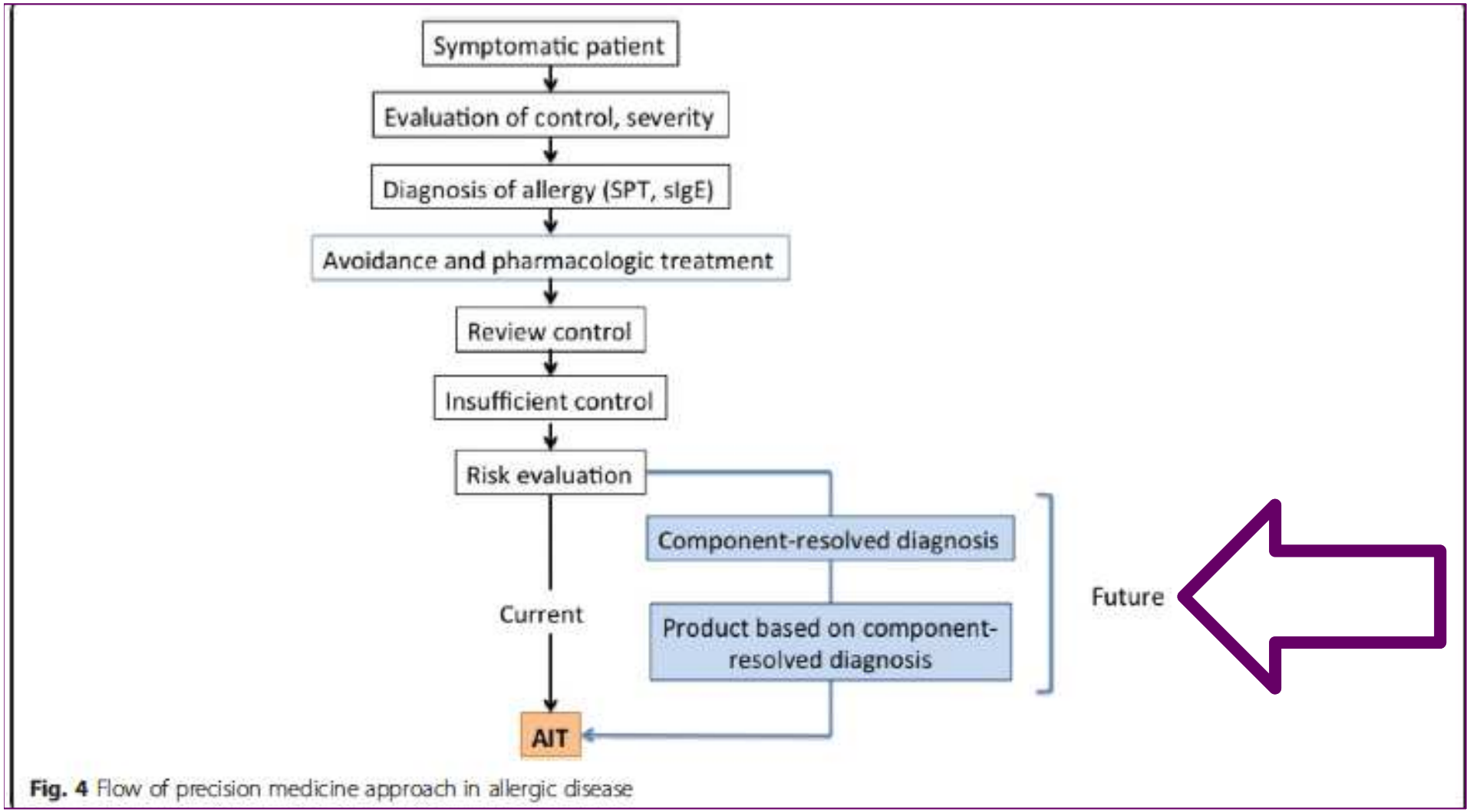
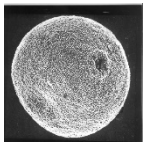


Fig. 4 Flow of precision medicine approach in allergic disease

Allergenic molecules of Phleum pratense



	Structure*	Molecular weight (kD)°	Biological Function^	IgE positivity among Europeans sensitized to grass pollen (%) ^
Phl p 1		33-36	Expansin	68 - 96
Phl p 4		55-60	Berberine Bridge Enzyme	70 - 88
Phl p 5		29-38	Ribonuclease	50 - 100
Phl p 2		11-12	Unknown	28 - 68
Phl p 6		13	Unknown	44 - 68
Phl p 11		20	Trypsin inhibitor	35 - 53
Phl p 12		14	Profilin	10 - 15,2
Phl p 7		6	Calcium binding protein	5 - 8

**www.proteinmodelportal.org (June 2012)*
°Andersson K, Lidholm J . IAAI 2003
^www.allergome.com (June 2012)

P Matricardi

APCS code	pt 8 0.35	rPhl p 1	rPhl p 2	rPhl p 4	rPhl p 5	rPhl p 6	rPhl p 7	rPhl p 11	rPhl p 12	n pos. mol.	n	%	cum. %
128	10000000	●								1	36	20,8	21
248	11111000	●	●	●	●	●				5	21	12,1	33
160	10100000	●		●						2	10	5,8	39
184	10111000	●		●	●	●				4	8	4,6	43
186	10111010	●		●	●	●		●		5	8	4,6	48
251	11111011	●	●	●	●	●		●	●	7	8	4,6	53
192	11000000	●	●							2	7	4,0	57
216	11011000	●	●		●	●				4	7	4,0	61
249	11111001	●	●	●	●	●			●	6	7	4,0	65
250	11111010	●	●	●	●	●		●		6	7	4,0	69
32	100000			●						1	5	2,9	72
224	11100000	●	●	●						3	5	2,9	75
152	10011000	●			●	●				3	4	2,3	77
185	10111001	●		●	●	●			●	5	4	2,3	79
208	11010000	●	●		●					3	3	1,7	81
218	11011010	●	●		●	●		●		5	3	1,7	83
48	110000			●	●					2	2	1,2	84
64	1000000		●							1	2	1,2	85
144	10010000	●			●					2	2	1,2	86
162	10100010	●		●				●		3	2	1,2	87
187	10111011	●		●	●	●		●	●	6	2	1,2	88
193	11000001	●	●						●	3	2	1,2	90
217	11011001	●	●		●	●			●	5	2	1,2	91
225	11100001	●	●	●					●	4	2	1,2	92
16	10000				●					1	1	0,6	92
34	100010			●				●		2	1	0,6	93
58	111010			●	●	●		●		4	1	0,6	94
96	1100000		●	●						2	1	0,6	94
129	10000001	●							●	2	1	0,6	95
130	10000010	●						●		2	1	0,6	95
132	10000100	●					●			2	1	0,6	96
156	10011100	●			●	●	●			4	1	0,6	97
188	10111100	●		●	●	●	●			5	1	0,6	97
194	11000010	●	●					●		3	1	0,6	98
232	11101000	●	●	●		●				4	1	0,6	98
240	11110000	●	●	●	●					4	1	0,6	99
254	11111110	●	●	●	●	●	●	●		7	1	0,6	99
255	11111111	●	●	●	●	●	●	●	●	8	1	0,6	100
0	0									0	3	1,7	

"APCS"
Allergen Profile Codification System

analysing profiles
at local level (Rome)
in «only» 176 children:

high heterogeneity
39 profiles

15 profiles to represent
80% of the population

+
co-sensitization
to other pollens!!
=
is each patient
«unique»

Pilot project on
patients in Rome

Tripodi et al. JACI 2012

doi: 10.1111/j.1365-2222.2008.03031.x

Clinical and Experimental Allergy, **38**, 1400–1408

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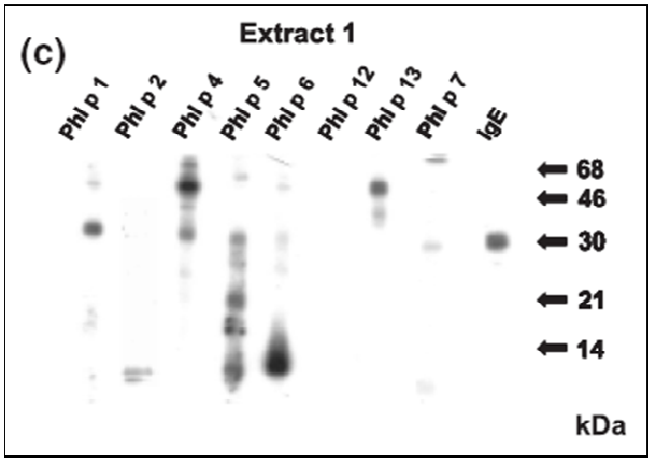
Journal compilation © 2008 Blackwell Publishing Ltd

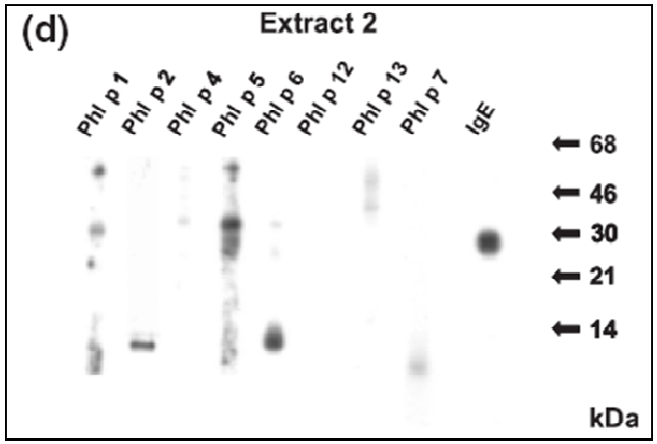
ORIGINAL PAPER Allergens

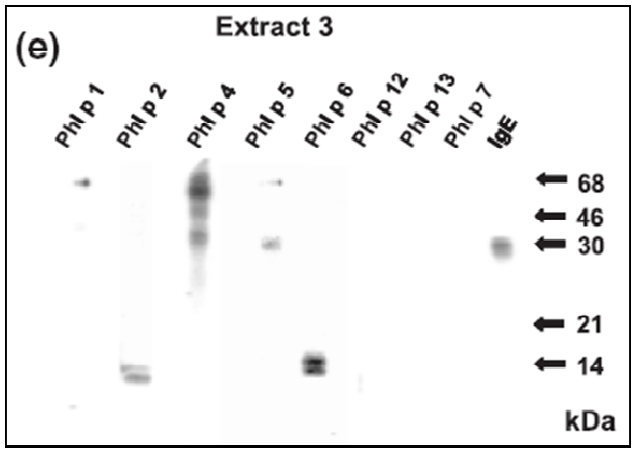
Heterogeneity of commercial timothy grass pollen extracts

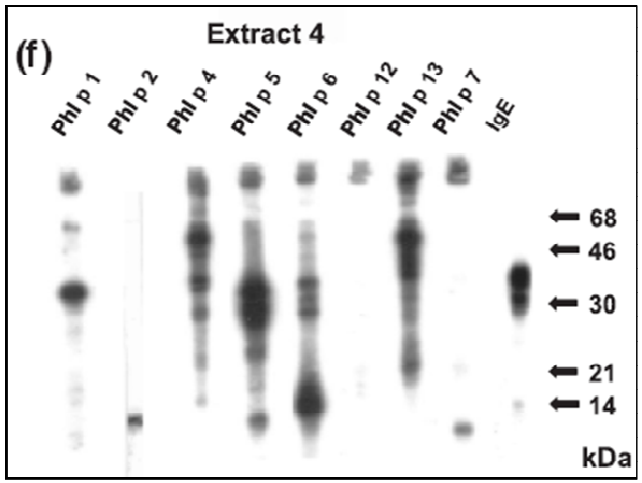
M. Focke*,†, K. Marth*,†, S. Flicker† and R. Valenta*,†

*Christian Doppler Laboratory for Allergy Research, and †Division of Immunopathology, Department of Pathophysiology, Center for Physiology and Pathophysiology, Vienna General Hospital, Medical University of Vienna, Austria









	ng/mL extract			Total protein	Percentage weight/ total protein		
	Phl p 1	Phl p 2	Phl p 5	(µg/mL)	Phl p 1	Phl p 2	Phl p 5
Extract 1	114.2	5618.3	40	77.9	0.15	7.21	0.05
Extract 2	97.9	2802.3	356	28.0	0.35	10.01	1.27
Extract 3	32.5	1128.3	391	24.1	0.13	4.68	1.62
Extract 4	384.4	6530.9	793	197.7	0.19	3.30	0.40

Table 2. Summary of skin prick test results mean weal areas in mm^2

Extract	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
1	14	96	80	13	52	156	25	26	78	184
2	26	20	92	70	30	86	22	14	68	110
3	32	40	62	36	46	143	17	13	56	90
4	27	89	175	40	15	191	26	39	75	130
Histamine	31	33	69	39	17	17	16	15	30	21

Characterization and comparison of commercially available mite extracts for *in vivo* diagnosis

B. Brunetto[1], R. Tinghino[1], M. C. Braschi[2], L. Antonicelli[2], C. Pini[1] & P. Iacovacci[1]

Allergy 2010; 65: 184–190

Table 2 Der p 1, Der f 1 and Mite group 2 analysis by ELISA in *Dermatophagoides pteronyssinus* and *D. farinae* extracts for *in vivo* diagnosis from various manufacturers

	Der p 1 *D. pteronyssinus*	Der f 1 *D. farinae*	Mite group 2 *D. pteronyssinus*	Mite group 2 *D. farinae*
Manufacturers	Mean* (±SD)	Mean* (±SD)	Mean* (±SD)	Mean* (±SD)
1	36.2 (±5.7)	122.9 (±17.3)	31.7 (±7.6)	3.3 (±0.7)
2	9.6 (±1.7)	36.5 (±3.8)	8.5 (±1.0)	3.6 (±0.2)
3	n.a.	196.1 (±7.7)	6.1 (±0.01)	1.3 (±0.2)
4	11.1 (±1.5)	115.7 (±26.9)	1.3 (±0.1)	2.4 (±0.5)
5	21.7 (±1.6)	190.4 (±26.5)	23.4 (±1.0)	10.4 (±2.1)
6	20.4 (±2.8)	59.1 (±1.7)	0.7 (±0.1)	1.5 (±0.2)
7	12.8 (±2.2)	114.0 (±11.1)	2.4 (±0.7)	2.0 (±0.06)
8	15.7 (±2.1)	26.5 (±6.8)	2.6 (±0.3)	4.0 (±0.4)

Update on immunotherapy for the treatment of asthma

Giorgio W. Canonica, Diego Bagnasco, Giovanna Ferrantino, Matteo Ferrando, and Giovanni Passalacqua

Canonica et al. Curr..Opin.Pulm.Med. 2015

ALLERGEN IMMUNOTHERAPY AND EVIDENCE-BASED MEDICINE: CRITICISM AND AUTOCRITICISM

PERSONAL

G.W.Canonica

AUTOCRITICISM about AIT

- *Metanalysis Studies*
- *Correct studies*
- *WRONG CONCLUSIONS*

Canonica et al. Curr..Opin.Pulm.Med. 2015

Canonica et al. Curr..Opin.Pulm.Med. 2015

ALLERGEN IMMUNOTHERAPY AND EVIDENCE-BASED MEDICINE: CRITICISM AND AUTOCRITICISM

The systematic reviews and meta-analyses invariably concluded that AIT is effective and well tolerated in allergic rhinitis, asthma, or both [4–11].

Table 1. EBM evidences for allergen immunotherapy in asthma

Efficacy EBM documented on a global basis (all allergens-class effect)
(Abramson *et al. Cochrane* 2010 [8] – Erekosima *et al. Laryngoscope* 2013 [9] – Calamita *et al. Allergy* 2006 [10] – Penagos *et al. Chest* 2008 [11])
Efficacy EBM documented for mites
(Compalati *et al. Allergy* 2009 [12] – Abramson *et al. Cochrane* 2010 [8])
Efficacy EBM documented for pollens
(Abramson *et al. Cochrane* 2010 [8])
SLIT efficacy documented by GRADE system
(Lin *et al. JAMA* 2013 [13])

SLIT, sublingual immunotherapy.

WHY Correct studies???

- All the published studies were included in the analysis……studies in which just ***Some Products*** were investigated.

Canonica et al. Curr..Opin.Pulm.Med. 2015

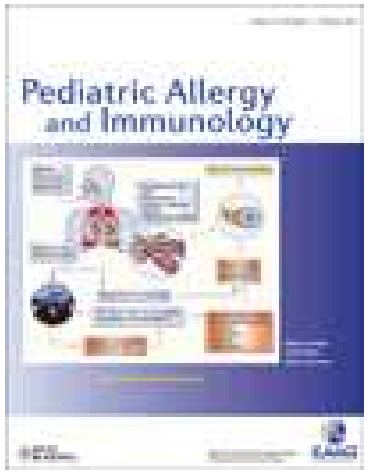
WHY WRONG CONCLUSIONS ???

- **The conclusion was AIT is Effective & Safe**

- **This conclusion offered the possibility of taking advantage also by Allergens/Products**

  <u>NEVER</u> tested in any study

Canonica et al. Curr..Opin.Pulm.Med. 2015



ORIGINAL ARTICLE

Sublingual immunotherapy not effective in house dust mite–allergic children in primary care

Cindy M. A. de Bot[1], Heleen Moed[1], Marjolein Y. Berger[1,2], Esther Röder[3], Wim C. J. Hop[4], Hans de Groot[5], Johan C. de Jongste[6], Roy Gerth van Wijk[3], Patrick J. E. Bindels[1] & Johannes C. van der Wouden[1]

[1]Department of General Practice, Erasmus MC-University Medical Center, Rotterdam, The Netherlands; [2]Department of General Practice, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Department of Allergology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands;[4]Department of Biostatistics, Erasmus MC-University Medical Center, Rotterdam, The Netherlands; [5]Department of Pediatric Allergology, Reinier de Graaf Groep, Delft, The Netherlands; [6]Department of Pediatric Respiratory Medicine, Erasmus MC-University Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands

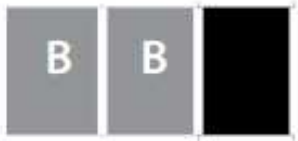
de Bot et al PAI 2011

SIGN 141 • British guideline on the management of asthma

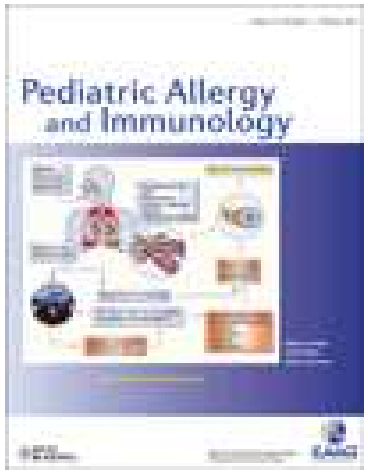
A national clinical guideline *October 2014*

Evidence

The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children.



Sublingual immunotherapy cannot currently be recommended for the treatment of asthma in routine practice in children or adults.



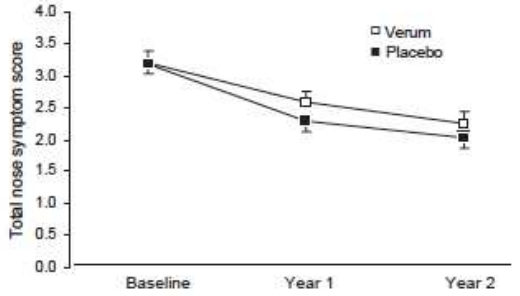


Figure 2 Mean daily total nose symptom score. Data shown are raw data. Error bars represent standard error of mean. The intensity of nose symptoms (rhinorrhea, blocked nose, sneezing, and itching) was subjectively assessed according to a grading scale: 0 = no complaints, 1 = minor complaints, 2 = moderate complaints, and 3 = serious complaints; the maximum score was 12.

In the currently marketed Oralgen® House Dust Mite (Oralgen Mijten®, Artu Biologicals, Lelystad, The Netherlands),

Conclusion

HDM-SLIT with a relatively low dosage was not effective in this primary care population of children with allergic rhinitis. SLIT was in general safe and well tolerated.

de Bot et al PAI 2011

Letter to the Editor
by
Bachert C., Canonica G.W., Bufe A.

2012

Pediatric Allergy and Immunology

CORRESPONDENCE

SIT: efficacy depends on product, not on route of application

Bachert C., Canonica G.W., Bufe A., PAI 2012

2012

Dear Editor,

We here refer to a recent publication 'Sublingual immunotherapy not effective in house dust mite-allergic children in primary care' by de Bot et al. (1); we believe that this title may be misleading for the following reasons:

1. The title suggests that sublingual immunotherapy for house dust mite 'in general' is not effective, but should clearly state that SLIT for HDM with a specific product is not effective.

2. The title also suggests that SLIT (eventually with this product) might be effective in the hands of specialists; to our knowledge, however, there is not a single published study to demonstrate efficacy of this product in any patient population.

2012

Bachert C., Canonica G.W., Bufe A., PAI 2012

Studies to demonstrate evidence for SIT are only available for some marketed products; however, because of a lack of differentiation between products, this evidence often is taken 'granted' for all SIT products in the general discussion, even including claims of long-term effects or efficacy and safety in children for SIT products that never have been studied adequately. On the other hand, studies with a noneffective product are misunderstood as representative for all products using a specific application route (SLIT vs. SCIT). These generalizations are not scientific and should therefore be avoided.

We therefore suggest to specify the SIT product in the title of the publication, and to avoid unjustified general statements on application routes or patient groups.

Yours faithfully,

Claus Bachert, G. Walter Canonica, Albrecht Bufe

Bachert et al. World Allergy Organization Journal (2015) 8:29
DOI 10.1186/s40413-015-0078-8

WAO journal
WORLD ALLERGY ORGANIZATION

POSITION ARTICLE AND GUIDELINES Open Access

Allergen immunotherapy on the way to product-based evaluation—a WAO statement

Claus Bachert[1*], Mark Larché[2], Sergio Bonini[3], Giorgio Walter Canonica[4], Thomas Kündig[5], Desiree Larenas-Linnemann[6], Dennis Ledford[7], Hugo Neffen[8], Ruby Pawankar[9] and Giovanni Passalacqua[4]

Bachert et al. WAO J 2015

Bachert et al.
WAO J 2015

Table 2 Criteria for a recommendable product for SIT

Minimum expectations for a SIT product to be used in adults:

At least one successful state-of-the-art DBPCR trial in adults for the first year of treatment, best preceded by a dose–response study (nasal provocation testing or allergen exposure chambers may be used for the dose finding)

Additional claims can be justified as follows:

Claims on sustained effects of a product should be based on a successful DBPCR study, based on appropriate sample size calculation, over 3 years of treatment

Claims on disease modifying effects: such studies need be followed up blindly for at least two consecutive years without treatment while maintaining monitoring symptoms

Claims for efficacy in asthmatics should be based on an appropriate successful DBPCR study in the appropriate patient group. For claims on tolerability in asthmatics only, the study can also be performed in allergic rhinitis subjects with comorbid asthma.

Minimum expectations for a SIT product to be used in children:

At least one state-of-the-art DBPCR confirmatory trial in children for the first year of treatment

Additional claims can be justified as follows:

Claims on sustained effects of a product should be based on a successful DBPCR study, based on appropriate sample size calculation, over 3 years of treatment

Claims on disease modifying effects: such studies have to be followed up at least two consecutive years without treatment while maintaining monitoring symptoms

The AIM is to declare:

PRODUCT X……

…….due to its features, meets the international requirements

EMA regulation

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 20 November 2008
Doc. Ref. CHMP/EWP/18504/2006

COMMITTEE FOR MEDICINAL PI
(CHMP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GUIDELINE ON THE CLINICAL DEVELOP
IMMUNOTHERAPY FOR THE TREAT

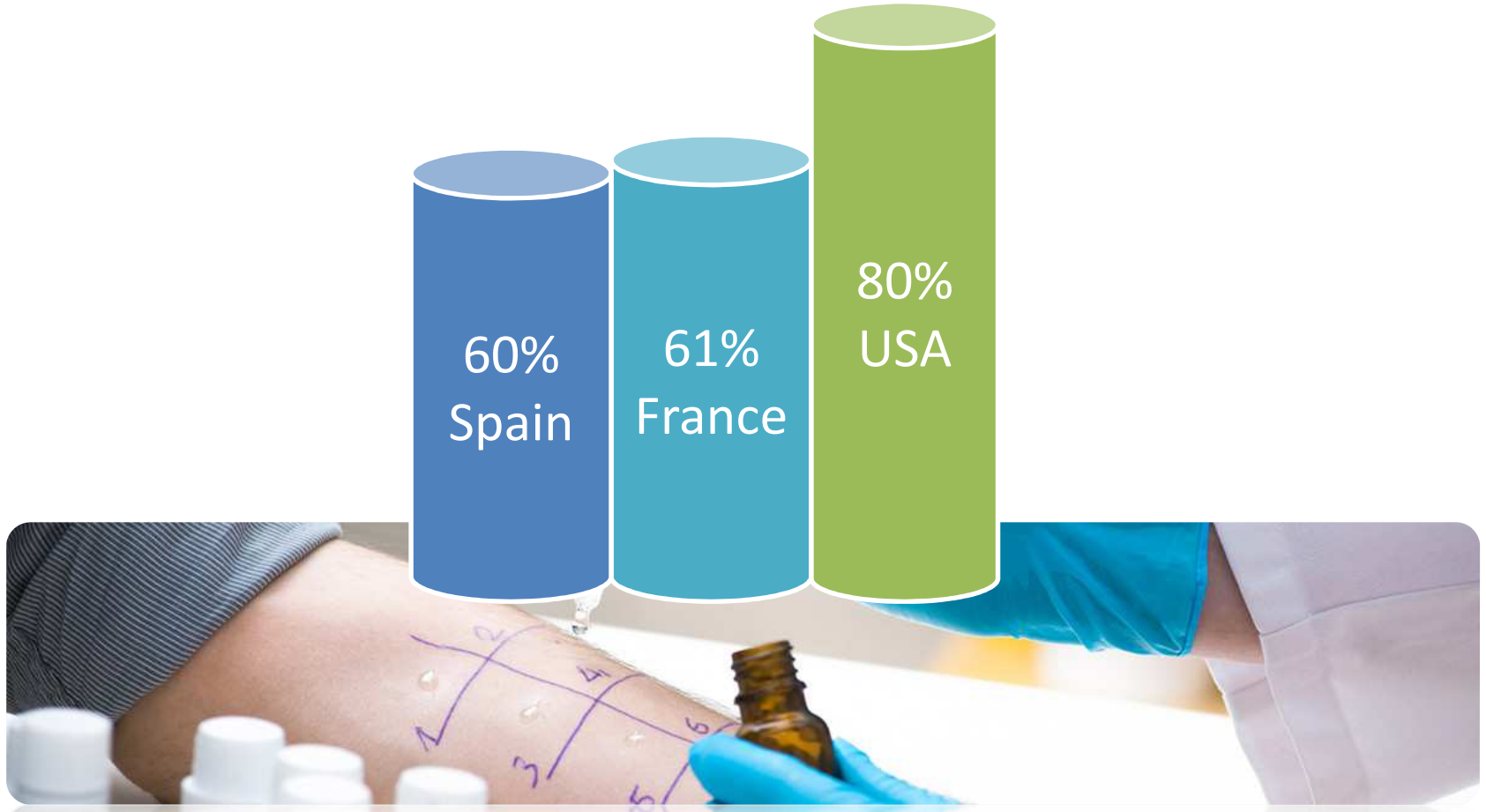
16 February 2015
EMA/PDCO/737605/2009
Human Medicines Development and Evaluation

EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy

Revision 4*

Polysensitization, a reality

Among patients consulting for allergy…



1. Orovitg et al. JIACI 2011
2. Didier et al.Rev. Fr. Allergol 2010
3. Craig et al. JACI 2008

Polysensitization, a reality

- polysensitization is more commonly associated with asthma and rhinitis comorbidity
- prevalence of diagnosed asthma increases with increasing numbers of positive SPT
- rhinitis is usually associated with mono- or polysensitization, whereas asthma is more often associated with polysensitization and multimorbidities

Boulet LP et al. Clin Exp Allergy 1997
Sears MR et al. Clin Exp Allergy 1993
Simpson A, et al. AJRCCM 2010

Bousquet J, et al. Allergy 1982
Burte E et al. PLoS One. 2015
Bousquet J, et al. Allergy. 2015

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

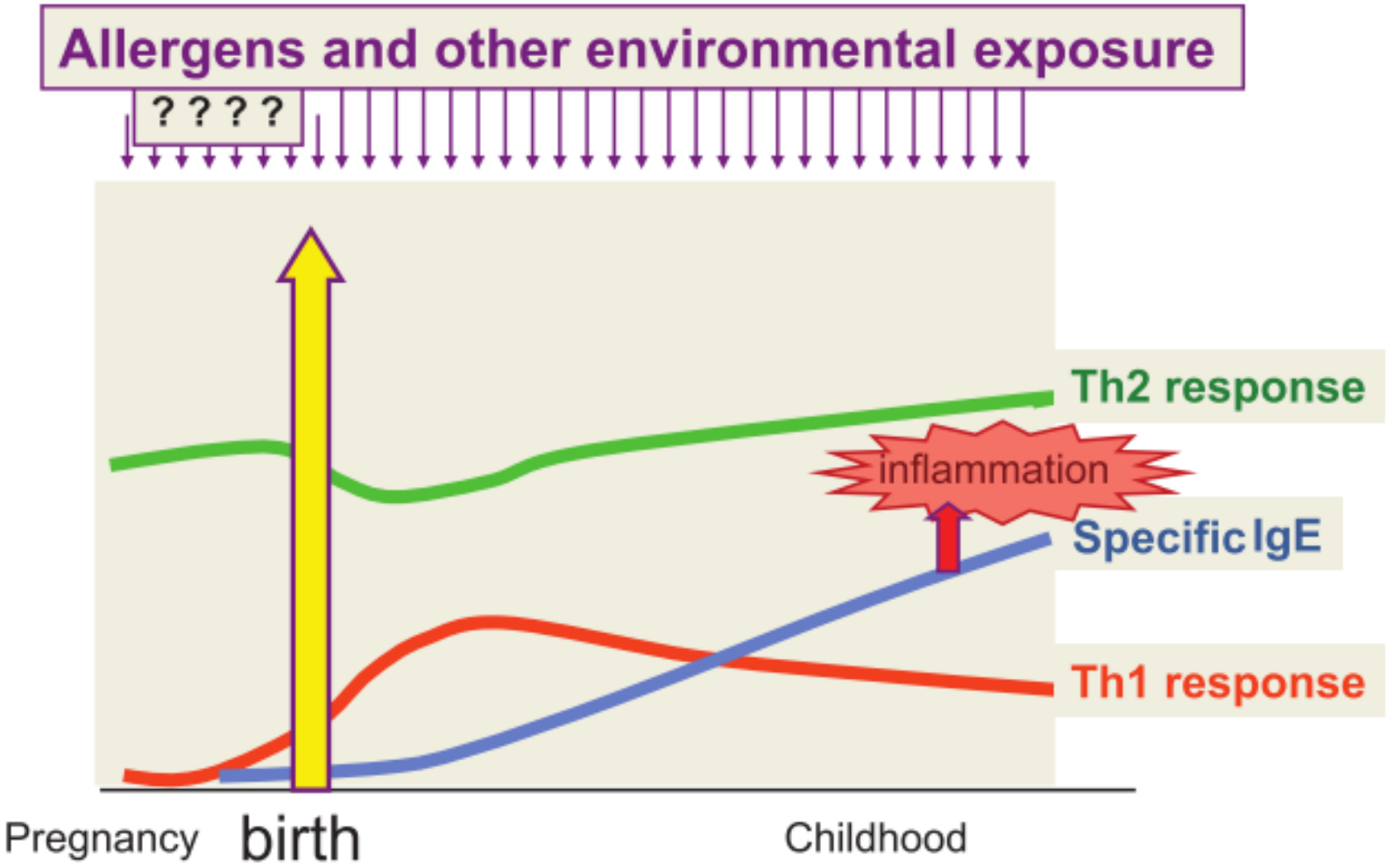
Allergy

POSITION PAPER

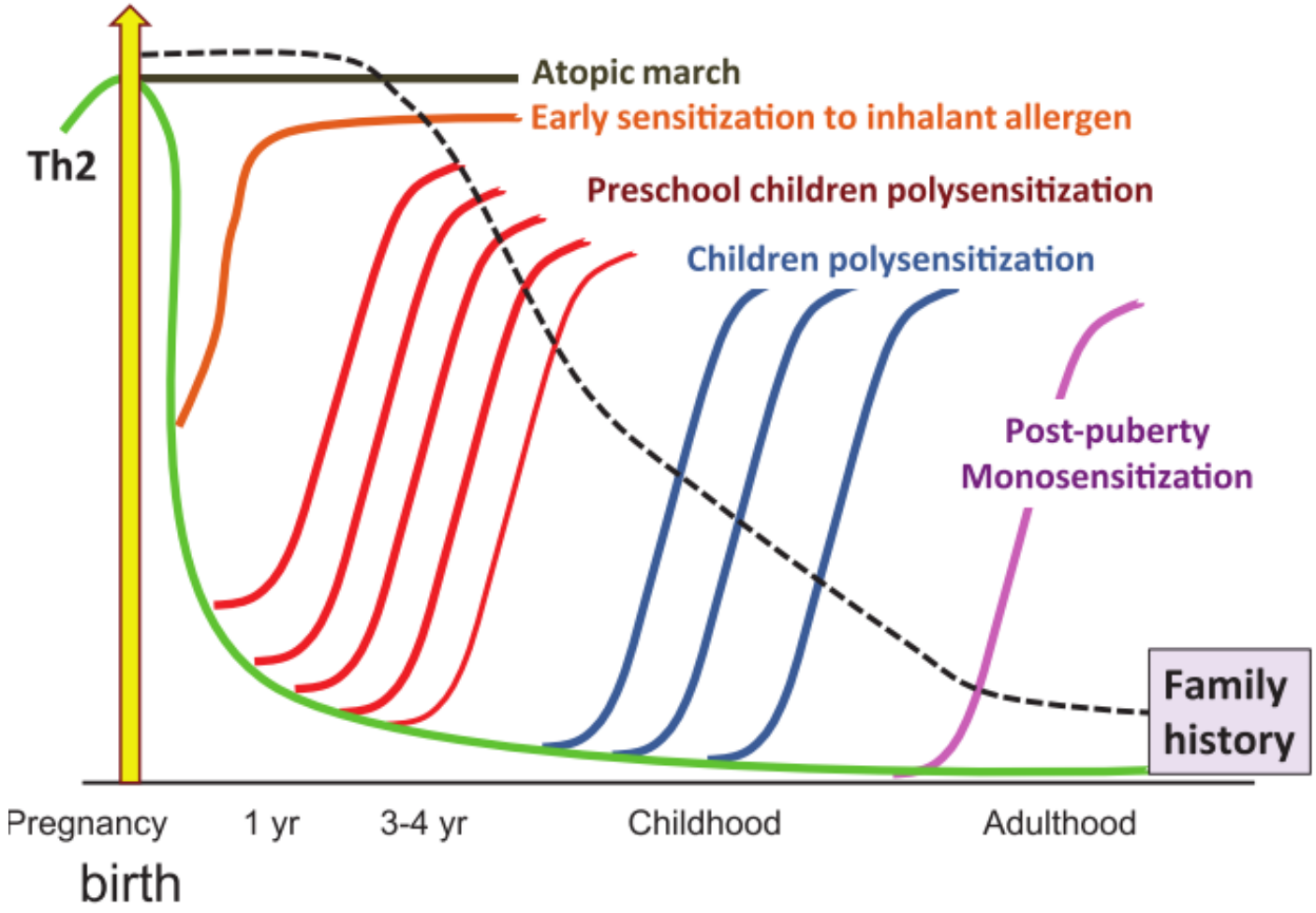
Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis

J. Bousquet[1,2,3,4,*], J. M. Anto[5,6,7,8], M. Wickman[9,10], T. Keil[11,12], R. Valenta[13], T. Haahtela[14], K. Lodrup Carlsen[15,16], M. van Hage[17], C. Akdis[18], C. Bachert[19], M. Akdis[18], C. Auffray[20], I. Annesi-Maesano[21,22], C. Bindslev-Jensen[23], A. Cambon-Thomsen[24], K. H. Carlsen[15,25], L. Chatzi[26], F. Forastiere[27], J. Garcia-Aymerich[5,6,7,8], U. Gehrig[28], S. Guerra[5], J. Heinrich[29], G. H. Koppelman[30], M. L. Kowalski[31], B. Lambrecht[32], C. Lupinek[13], D. Maier[33], E. Melén[10], I. Momas[34,35], S. Palkonen[36], M. Pinart[5], D. Postma[37], V. Siroux[38], H. A. Smit[28], J. Sunyer[5,6,7,8], J. Wright[39], T. Zuberbier[40,41], S. H. Arshad[42], R. Nadif[3,4], C. Thijs[43], N. Andersson[9,10], A. Asarnoj[9,10], N. Ballardini[9,10], S. Ballereau[20], A. Bedbrook[2], M. Benet[5], A. Bergstrom[9,10], B. Brunekreef[28], E. Burte[3,4], M. Calderon[44], G. De Carlo[36], P. Demoly[45], E. Eller[23], M. P. Fantini[46], H. Hammad[32], C. Hohman[11], J. Just[50,51], M. Kerkhof[37], M. Kogevinas[5,6,7,8], J. Kull[9,10]

Bousquet J et al. Allergy. 2015 Sep;70(9):1062-78

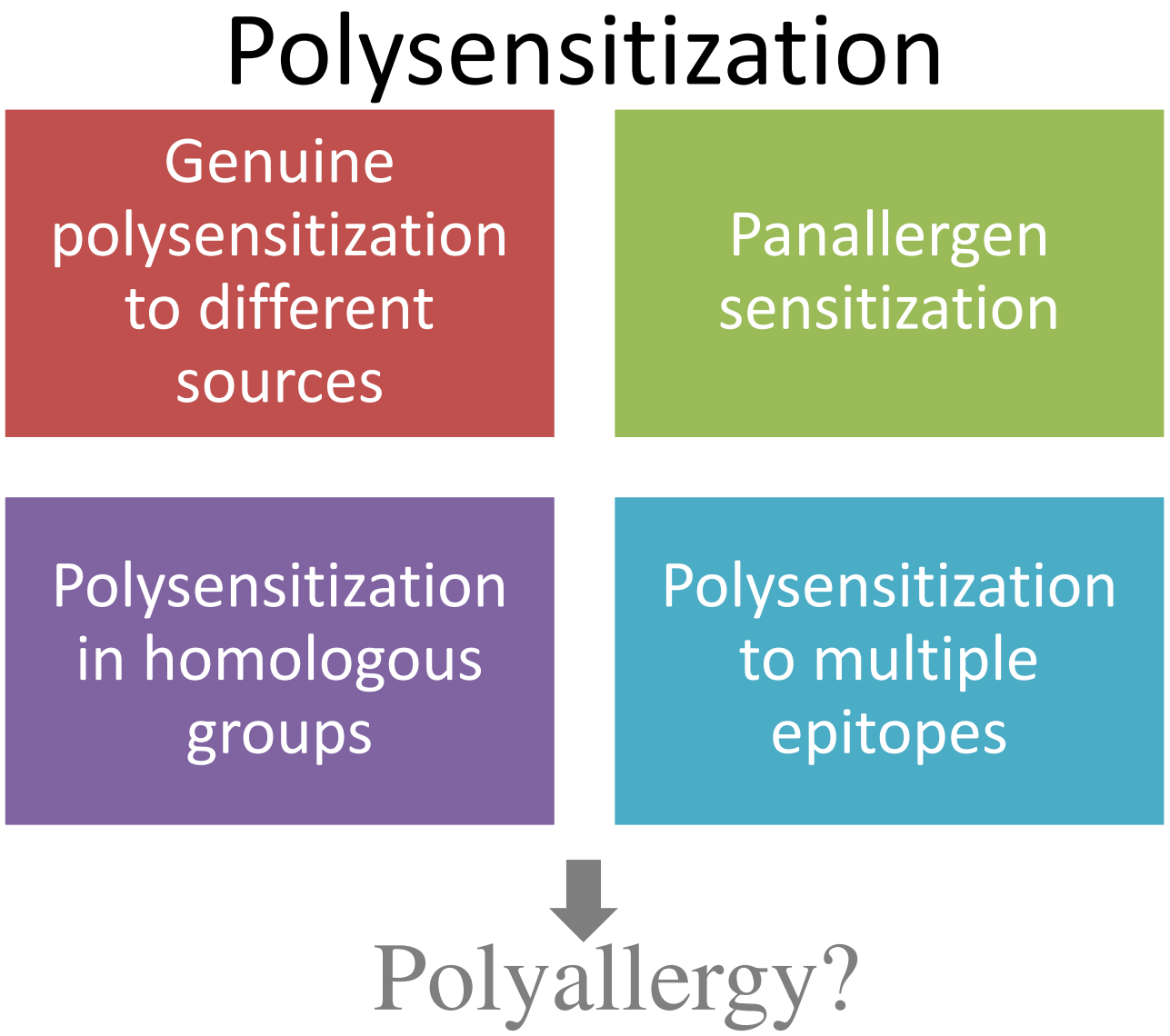


Bousquet J et al. Allergy. 2015 Sep;70(9):1062-78

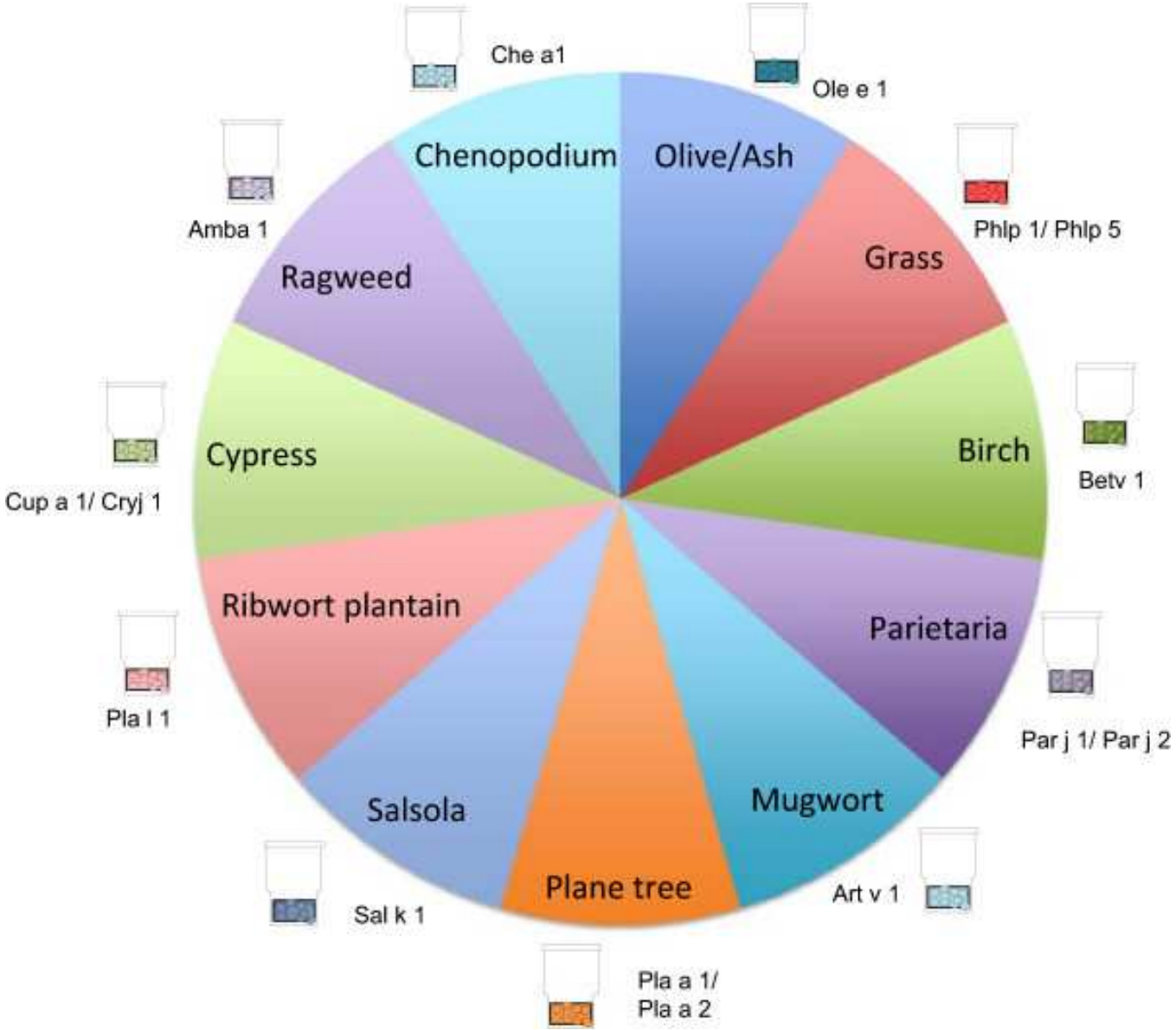


Bousquet J et al. Allergy. 2015 Sep;70(9):1062-78

Polysensitization is different from polyallergy

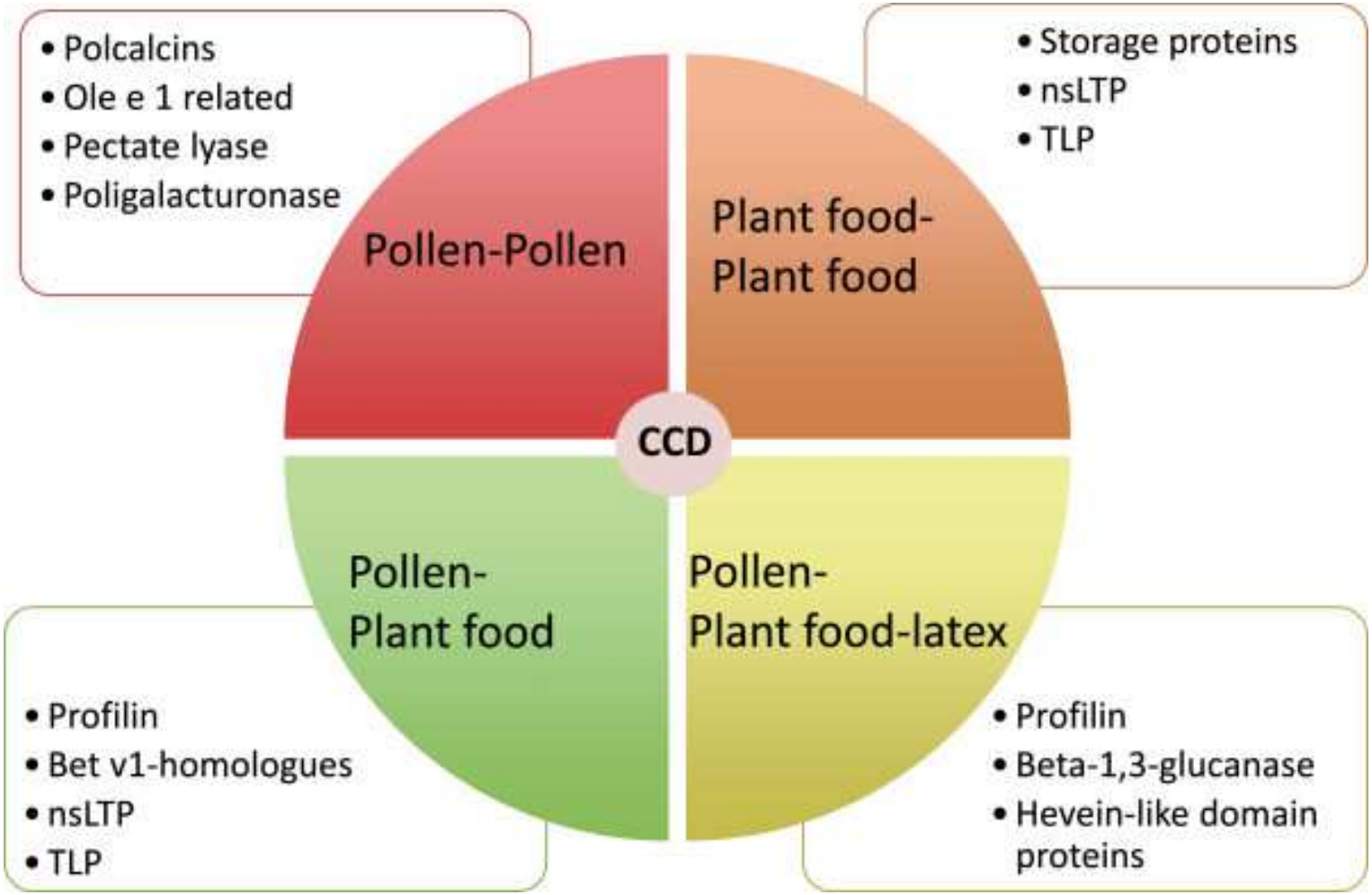


Pollen species-specific allergens



Luengo and Cardona Clinical and Translational Allergy 2014 ***4****:28*

Cross-reactive allergens

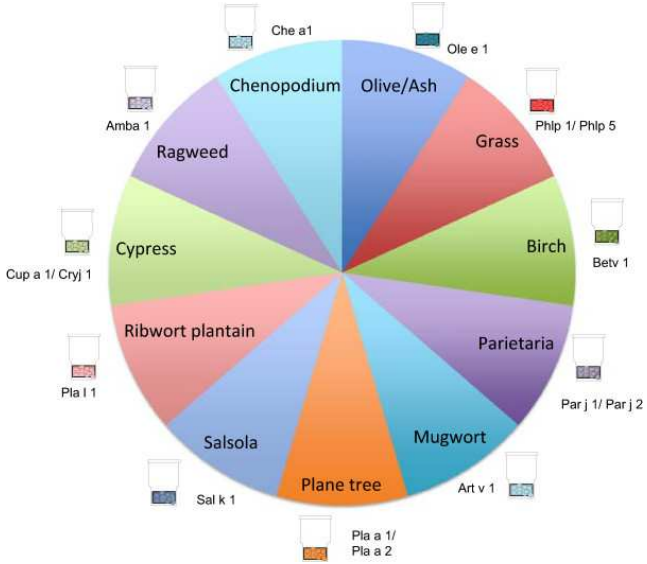


CCD: Cross-reactive carbohydrate determinants; nsLTP: Non-specific lipid transfer proteins; TLP: thaumatin-like proteins.

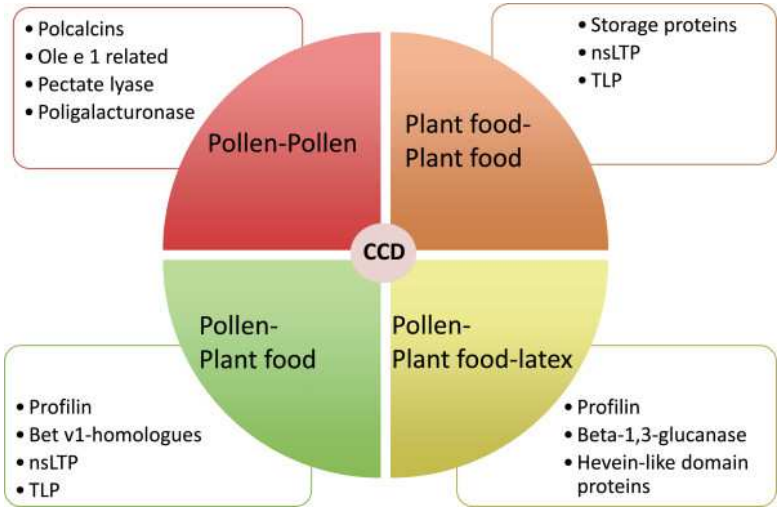
Indication of specific immunotherapy

• The first premise for the prescription of immunotherapy based on CRD is the assessment of IgE positivity to genuine versus cross-reactive allergens

Pollen species-specific allergens



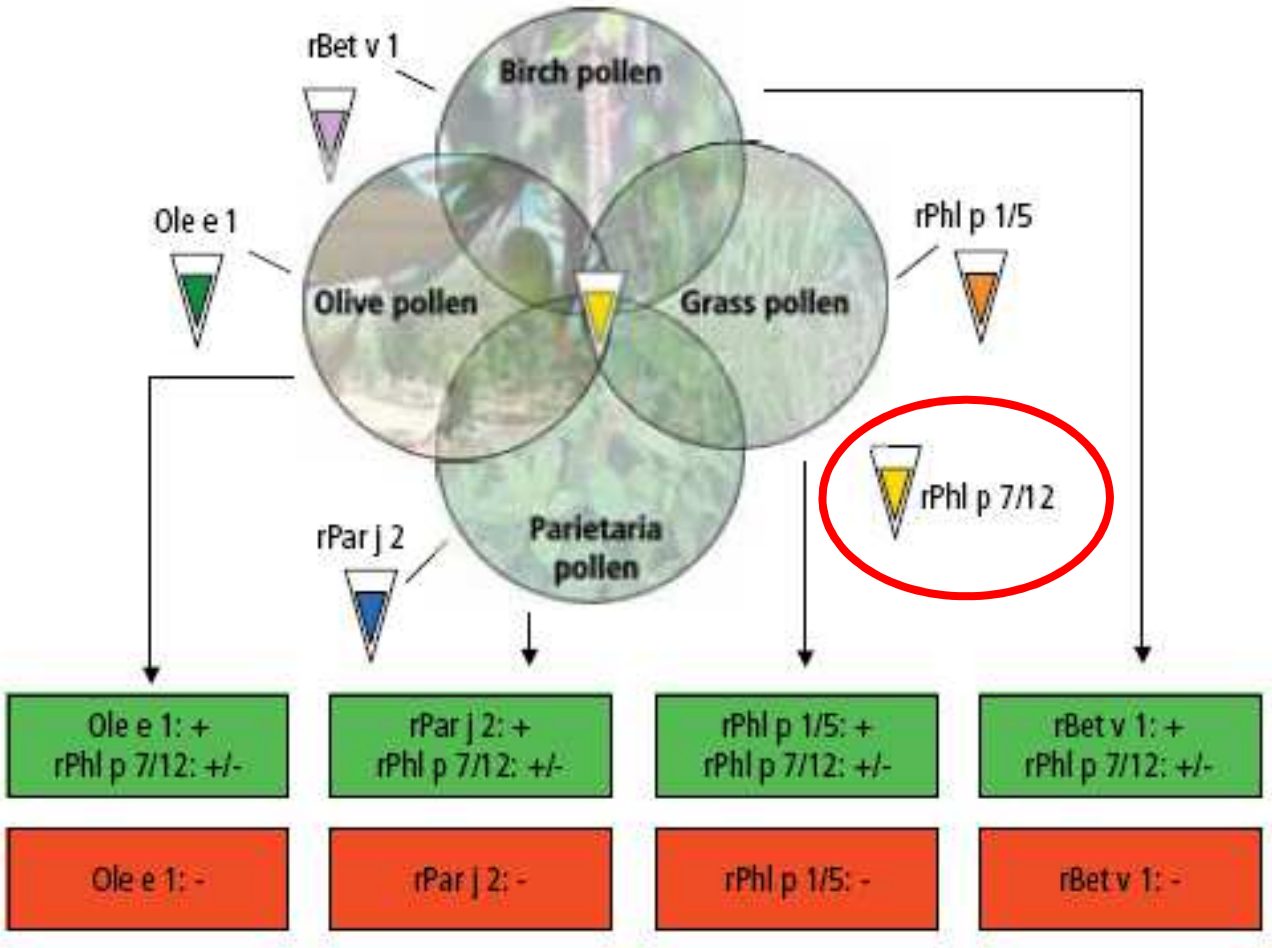
Cross-reactive allergens



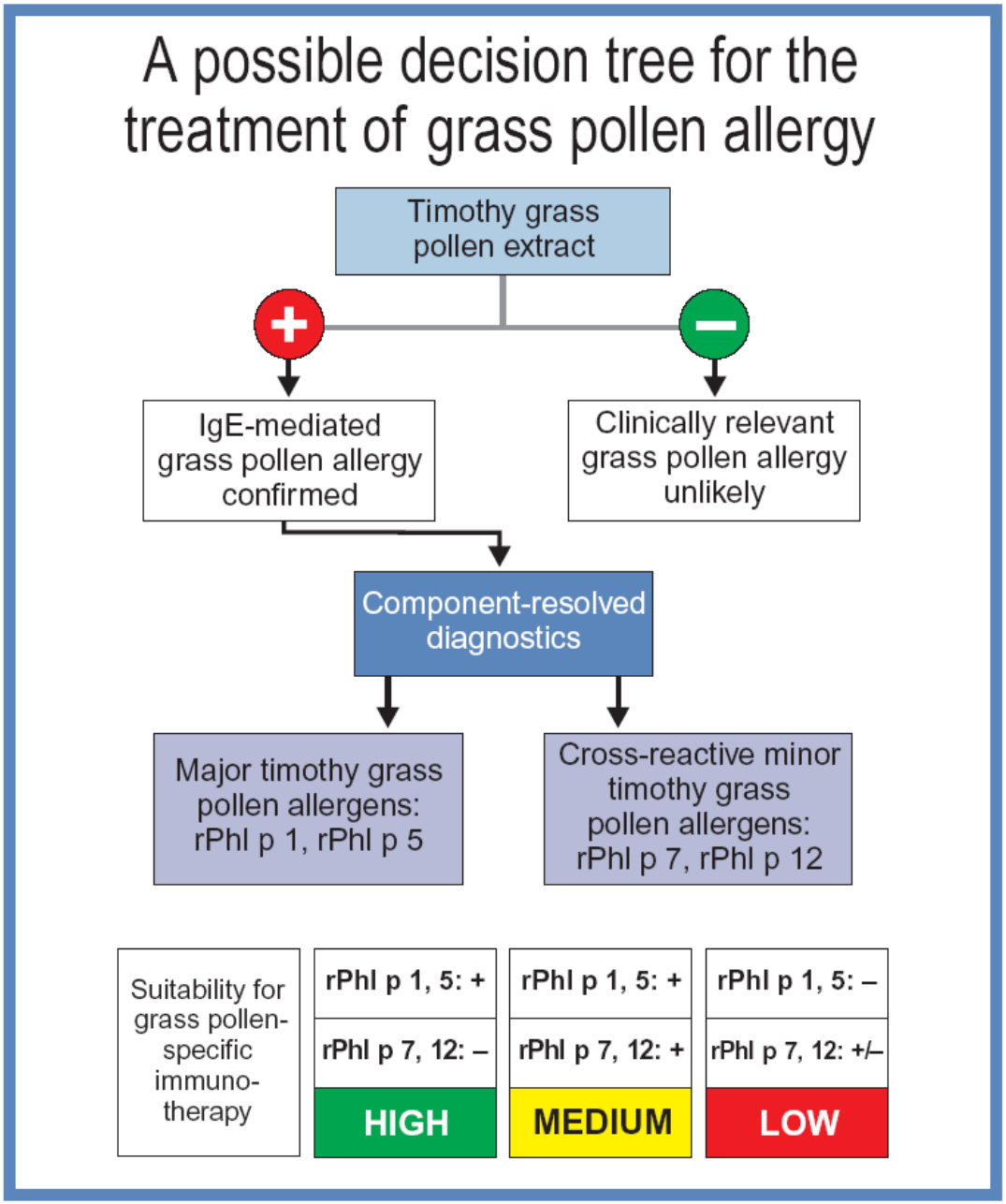
*Luengo and Cardona Clinical and Translational Allergy 2014 **4**:28*

CRT: component resolved therapy

Immunotherapy



Valenta R, et al. JIACI. 2007; 17: 88-92



Valenta R. The future of antigen-specific immunotherapy of allergy.
Nat Rev Immunol. 2002;2:446-53.

Inhalant oligo/monosensitization

Single-allergen immunotherapy with grass pollen extract has proved to be as safe and effective for that specific allergy both in polysensitized as in monosensitized patients, provided that the allergen extract administered matches the patient's most relevant sensitization.

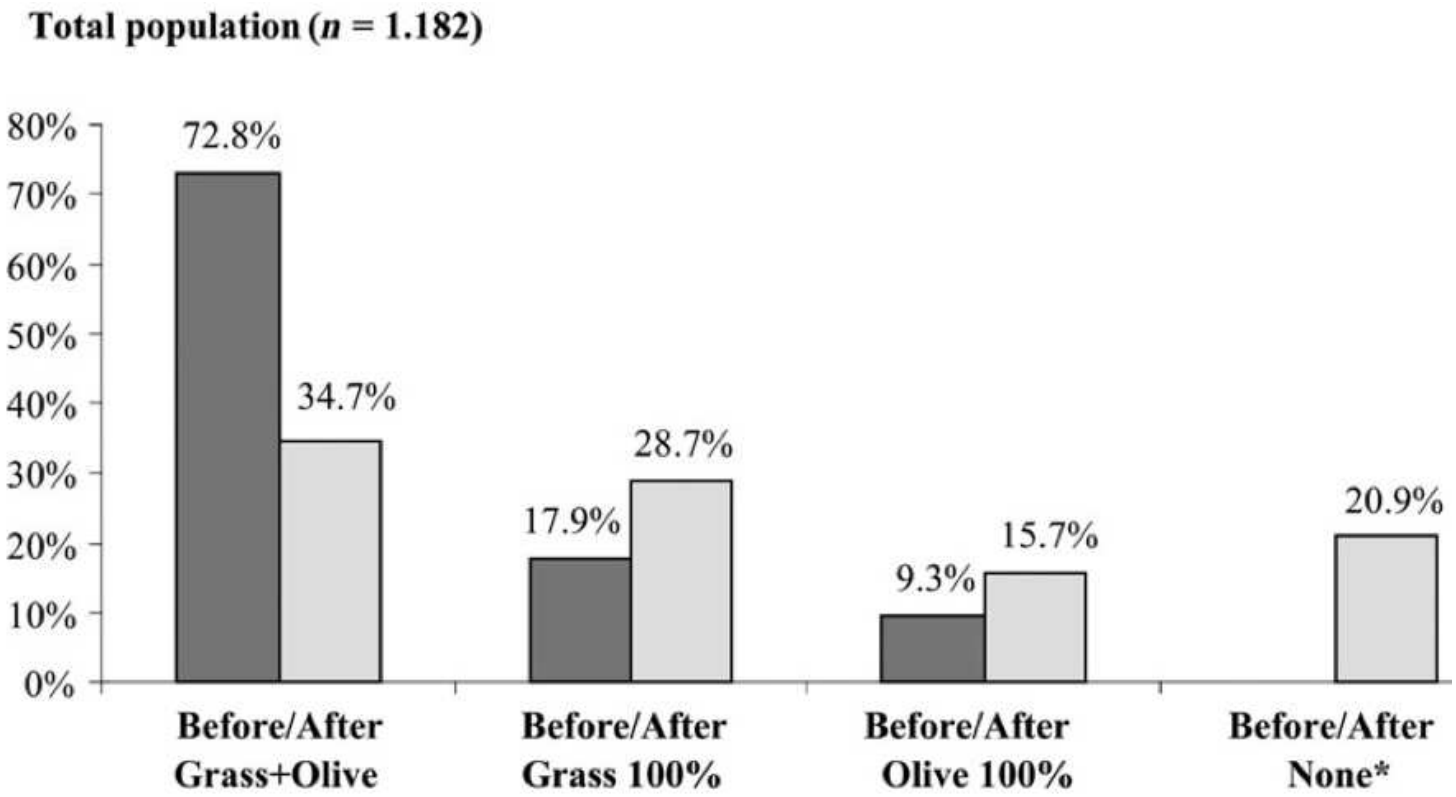
Passalacqua G. Curr Opin Allergy Clin Immunol 2014, 14:20–24.

There is a need to adequately evaluate in prospective studies if CRD-guided patient selection results in improved efficacy of immunotherapy.

Luengo O & Cardona V. Clinical and Translational Allergy 2014 **4**:28

Olive, grass or both? Molecular diagnosis for the allergen immunotherapy selection in polysensitized pollinic patients

C. Moreno[1], J. L. Justicia[2], J. Quiralte[3], Á. Moreno-Ancillo[4], A. Iglesias-Cadarso[5], M. Torrecillas[6], N. Labarta[7], M. A. García[2] & I. Dávila[8]



Moreno C et al. Allergy. 2014 Oct;69(10):1357-63

BRIEF COMMUNICATION

How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area

J. Sastre[1,2], M. E. Landivar[1], M. Ruiz-García[1], M. V. Andregnette-Rosigno[1] & I. Mahillo[3]

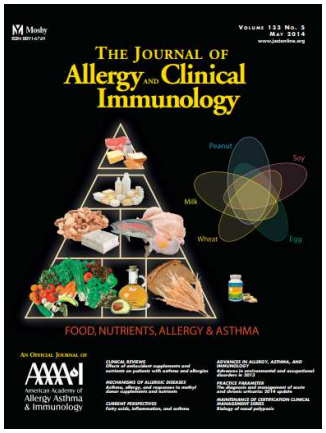
N= 141. RC y/o AB sensibilizados a pólenes ± alergia alimentos

Extract for SIT	Indication of SIT based on SPT	Indication of SIT based on MD	Number of patients with agreement of SIT (%)	Number of patients with disagreement of SIT	Kappa agreement for SIT based on SPT or MD
Grass	17	10	97 (68)	44 (32)	0.117 ± 0.0825 *P* = 0.0781
Olive	1	1	132 (93)	9 (7)	0.1624 ± 0.0639 *P* = 0.0055
Grass + olive	4	1	101 (71)	40 (29)	0.0505 ± 0.0548 *P* = 0.1782
Grass + cypress	0	1	132 (93)	9 (7)	0.1711 ± 0.0471 *P* = 0.0001
Grass + plane	0	1	133 (94)	8 (6)	0.1897 ± 0.0493 *P* = 0.0001
Olive + cypress	0	2	141 (100)	0 (0)	1 ± 0.0842 *P* < 0.0001
Other extracts	3	4	129 (91)	12 (9)	0.3586 ± 0.0798 *P* < 0.0001
Total	25	20	62 (46)	79 (54)	0.1057 ± 0.0413

Allergy. 2012; 67: 709-711

The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever

Giovanna Stringari, MD,[a,b*] Salvatore Tripodi, MD,[c*] Carlo Caffarelli, MD,[b*] Arianna Dondi, MD,[d,e] Riccardo Asero, MD,[f] Andrea Di Rienzo Businco, MD,[c] Annamaria Bianchi, MD,[g] Paolo Candelotti, MD,[g] Giampaolo Ricci, MD,[e] Federica Bellini, MD,[e] Nunzia Maiello, MD,[h] Michele Miraglia del Giudice, MD,[h] Tullio Frediani, MD,[i] Simona Sodano, MD,[i] Iride Dello Iacono, MD,[j] Francesco Macrì, MD,[i] Ilaria Peparini, MD,[i] Carlotta Povesi Dascola, MD,[b] Maria Francesca Patria, MD,[k] Elena Varin, MD,[l] Diego Peroni, MD,[m] Pasquale Comberiati, MD,[m] Loredana Chini, MD,[n] Viviana Moschese, MD,[n] Sandra Lucarelli, MD,[i] Roberto Bernardini, MD,[o] Giuseppe Pingitore, MD,[p] Umberto Pelosi, MD, PhD,[q] Mariangela Tosca, MD,[r] Anastasia Cirisano, MD,[s] Diego Faggian, Biol Sci,[t] Alessandro Travaglini, MSc,[u] Mario Plebani, MD,[t] and Paolo Maria Matricardi, MD[a*]: The Italian Pediatric Allergy Network (I-PAN) *Berlin, Germany, and Parma, Carpi, Rome, Bologna, Milan, Ascoli Piceno, Naples, Benevento, Verona, Empoli, Iglesias, Genoa, Crotone, and Padua, Italy*



Stringari G, Tripodi S, Caffarelli C. et al. J Allergy Clin Immunol. 2014 Jul;134(1):75-81

Fig 4 – Discordance rate between SIT prescription based on SPT or on SPT and CRD in 651children with AR, according to doctors' decision

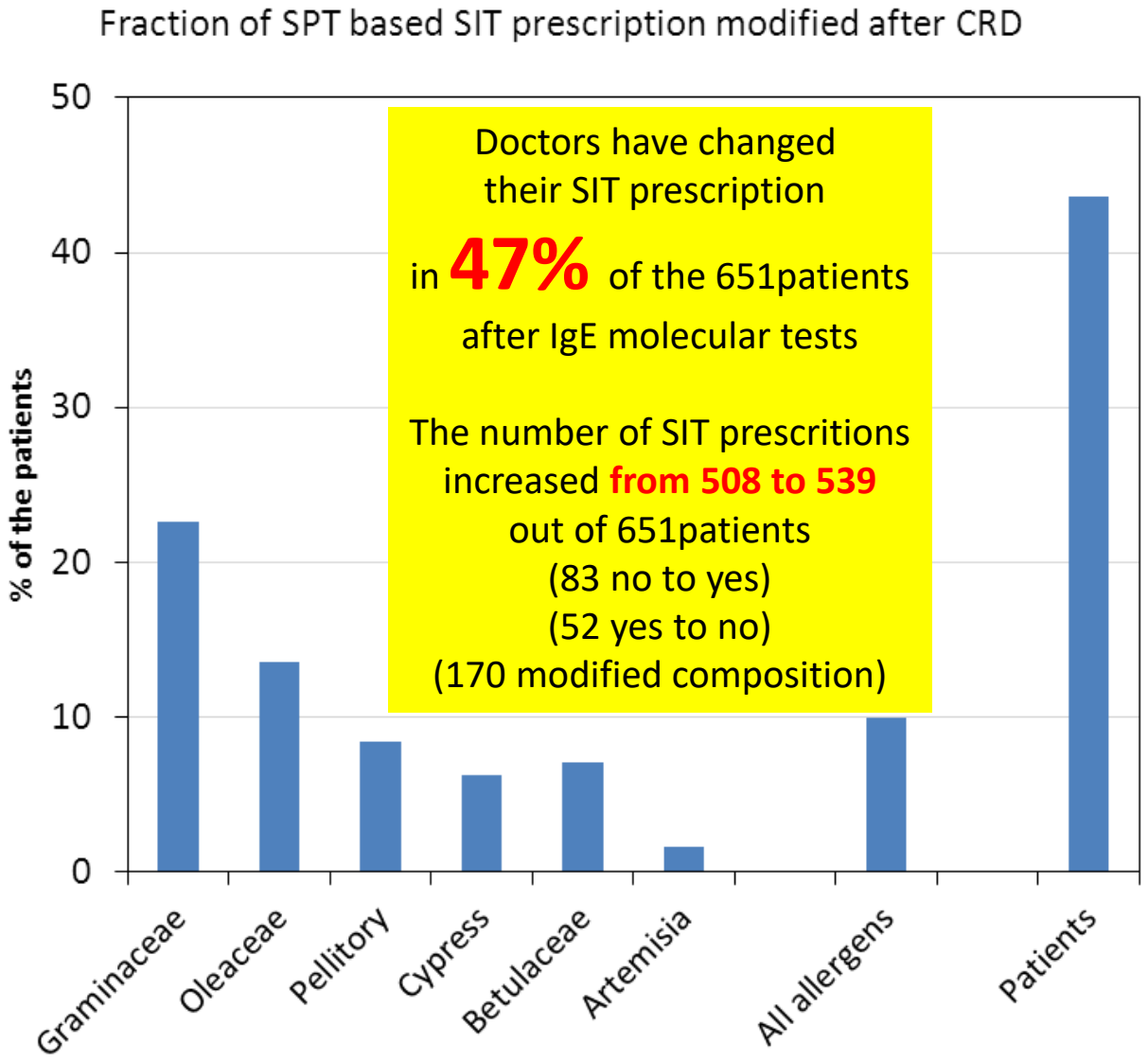
CLINICIANS

14 allergists

about 90 patients each

Randomly assigned

by climatic area



Stringari G, Tripodi S, Caffarelli C. et al. J Allergy Clin Immunol. 2014 Jul;134(1):75-81

P Matricardi

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Benvenuto in ALLERGYMonitor

Inserisci il tuo cognome:

pertini

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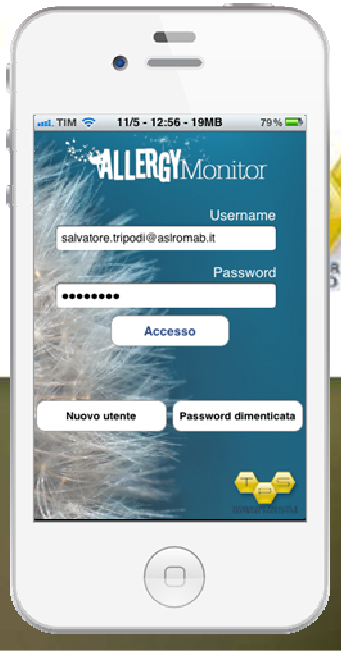
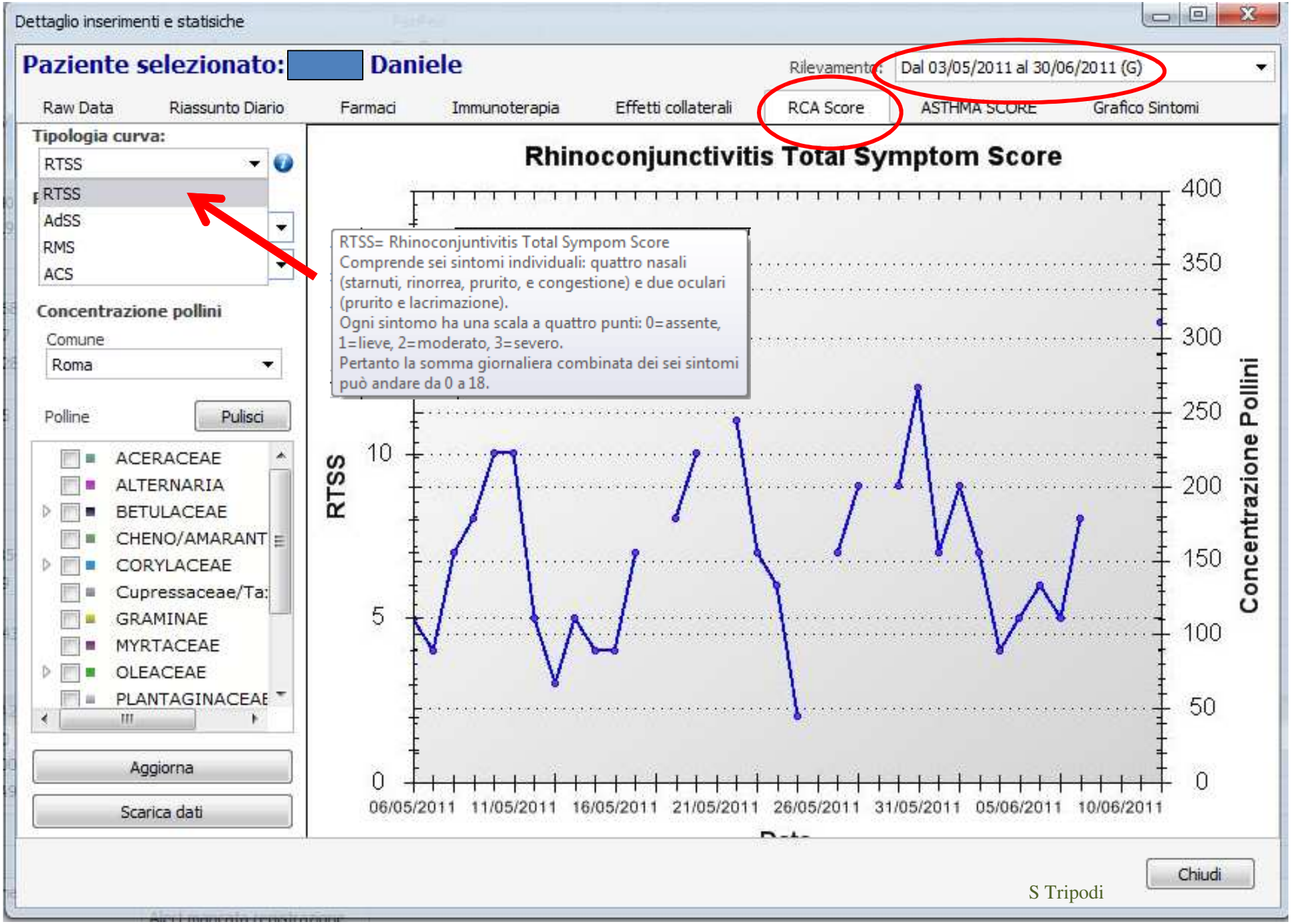
genoaxxx

Accedi



S Tripod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Raw Data
Riassunto Diario
Farmaci
Immunoterapia
Effetti collaterali
RCA Score
ASTHMA SCORE
Grafico Sintomi
Tipologia curva:
RTSS
RTSS
AdSS
RMS
ACS
Concentrazione pollini
Comune
Roma
Polline
Pulisci
ACERACEAE
ALTERNARIA
BETULACEAE
CHENO/AMARANT
CORYLACEAE
Cupressaceae/Ta:
GRAMINAE
MYRTACEAE
OLEACEAE
PLANTAGINACEAE
Aggiorna
Scarica dati
Rhinoconjunctivitis Total Symptom Score
RTSS= Rhinoconjuntivitis Total Sympom Score
Comprende sei sintomi individuali: quattro nasali (starnuti, rinorrea, prurito, e congestione) e due oculari (prurito e lacrimazione).
Ogni sintomo ha una scala a quattro punti: 0=assente, 1=lieve, 2=moderato, 3=severo.
Pertanto la somma giornaliera combinata dei sei sintomi può andare da 0 a 18.
RTSS
Concentrazione Pollini
0
5
10
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50
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16/05/2011
21/05/2011
26/05/2011
31/05/2011
05/06/2011
10/06/2011
Chiudi

S Tripodi

Clinical case

Simone, 13 aa., Tivoli
Seasonal allergic rhinoconjunctivitis during last four years

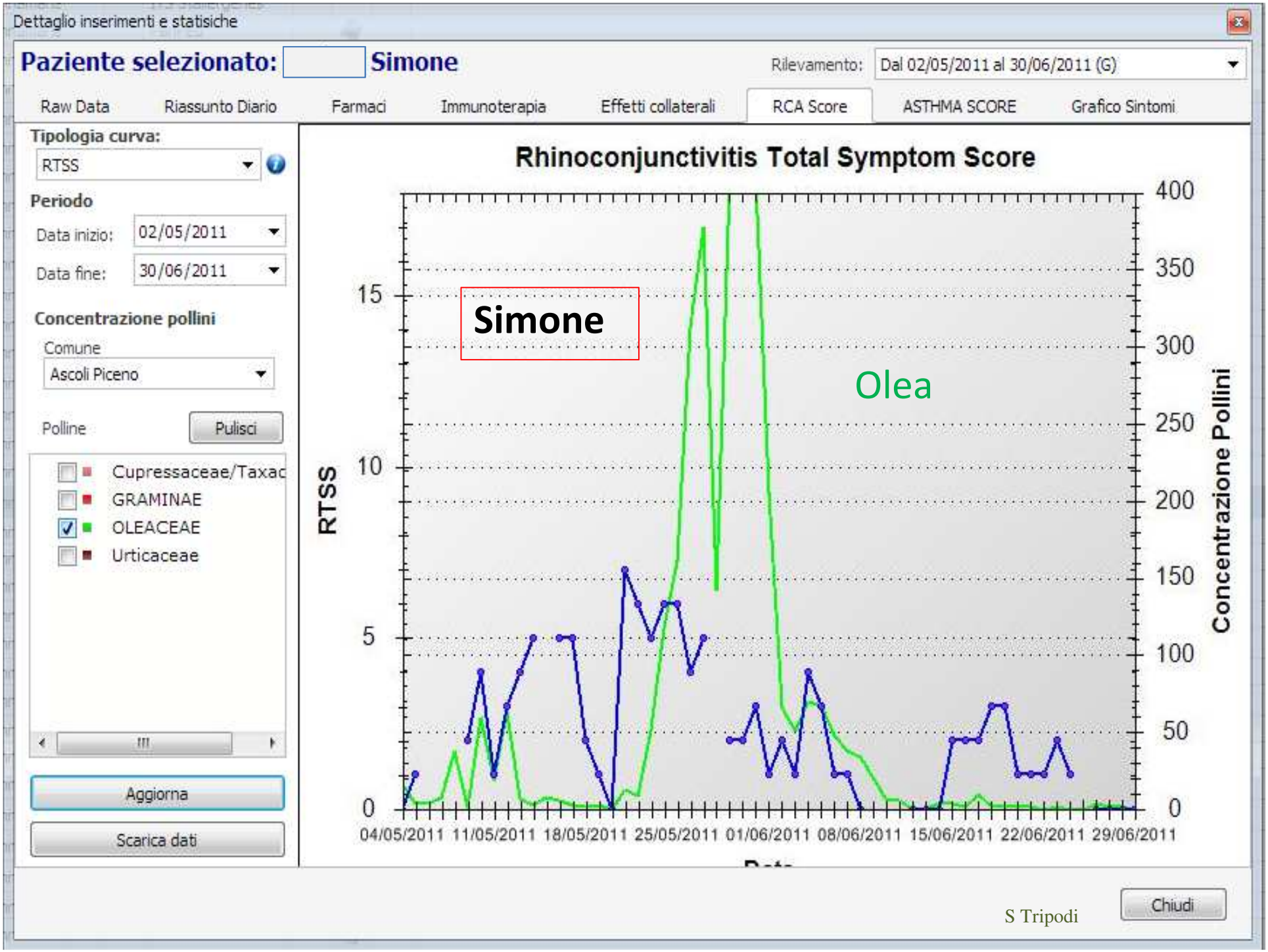
Symptoms in April, May and June

SPT positive for Olive tree and grass

Positive specific IgE to Phl p 1, Phl p 5 and Ole e 1

Which specific Immunotherapy?

= Grass and Olive tree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Farmaci
Immunoterapia
Effetti collaterali
RCA Score
ASTHMA SCORE
Grafico Sintomi
Tipologia curva:
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Periodo
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Data fine: 30/06/2011
Concentrazione pollini
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Polline
Pulisci
Cupressaceae/Taxac
GRAMINAE
OLEACEAE
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Rhinoconjunctivitis Total Symptom Score
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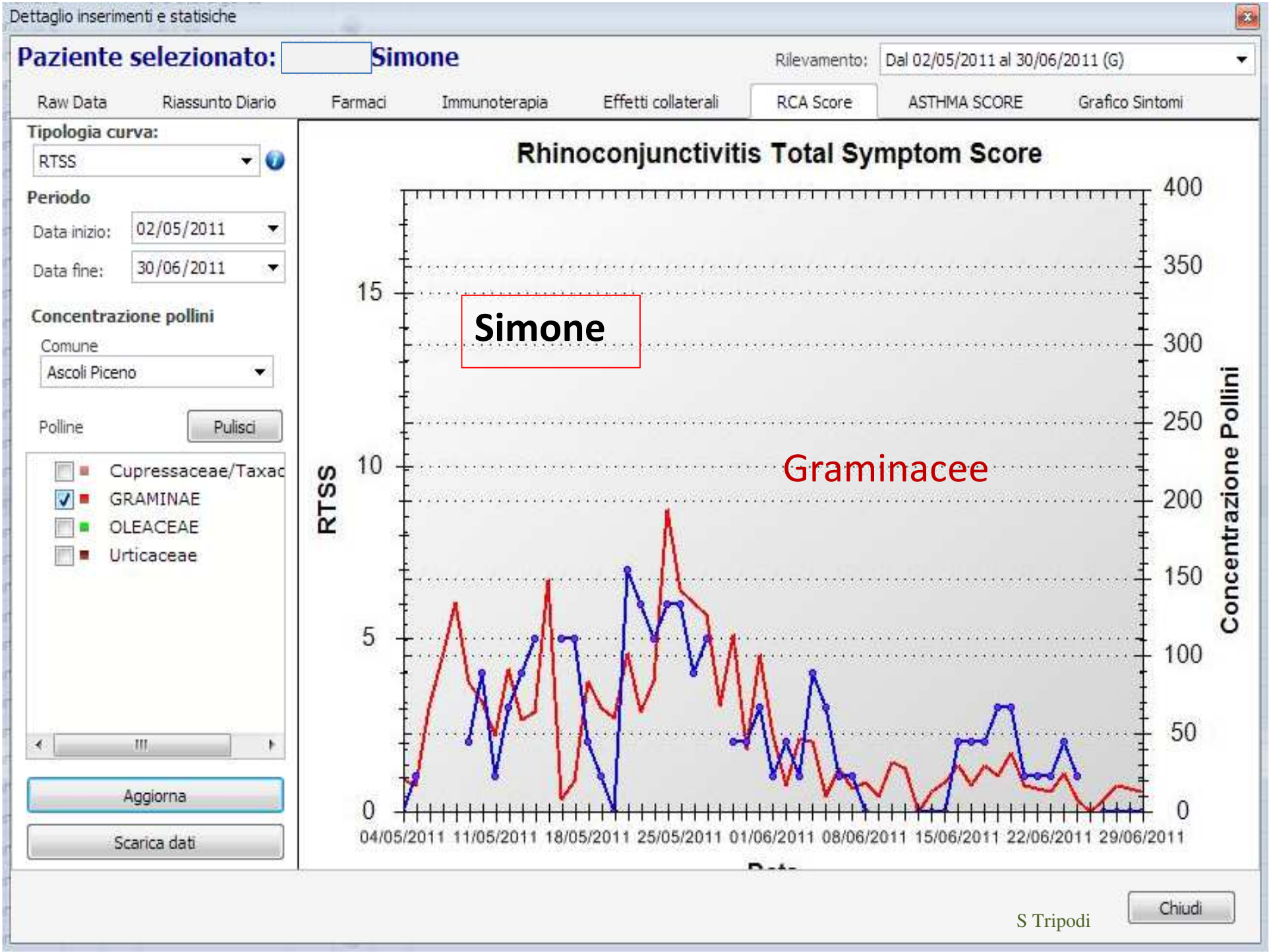
Chiudi

S Tripodi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29/06/2011
Chiudi

S Tripodi

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Symptoms in April, May and June

SPT positive for Olive tree and grass

Positive specific IgE to Phl p 1, Phl p 5 and Ole e 1

Which specific Immunotherapy?

= Grass and ~~Olive tree~~

Polysensitization

Genuine polysensitization to different sources

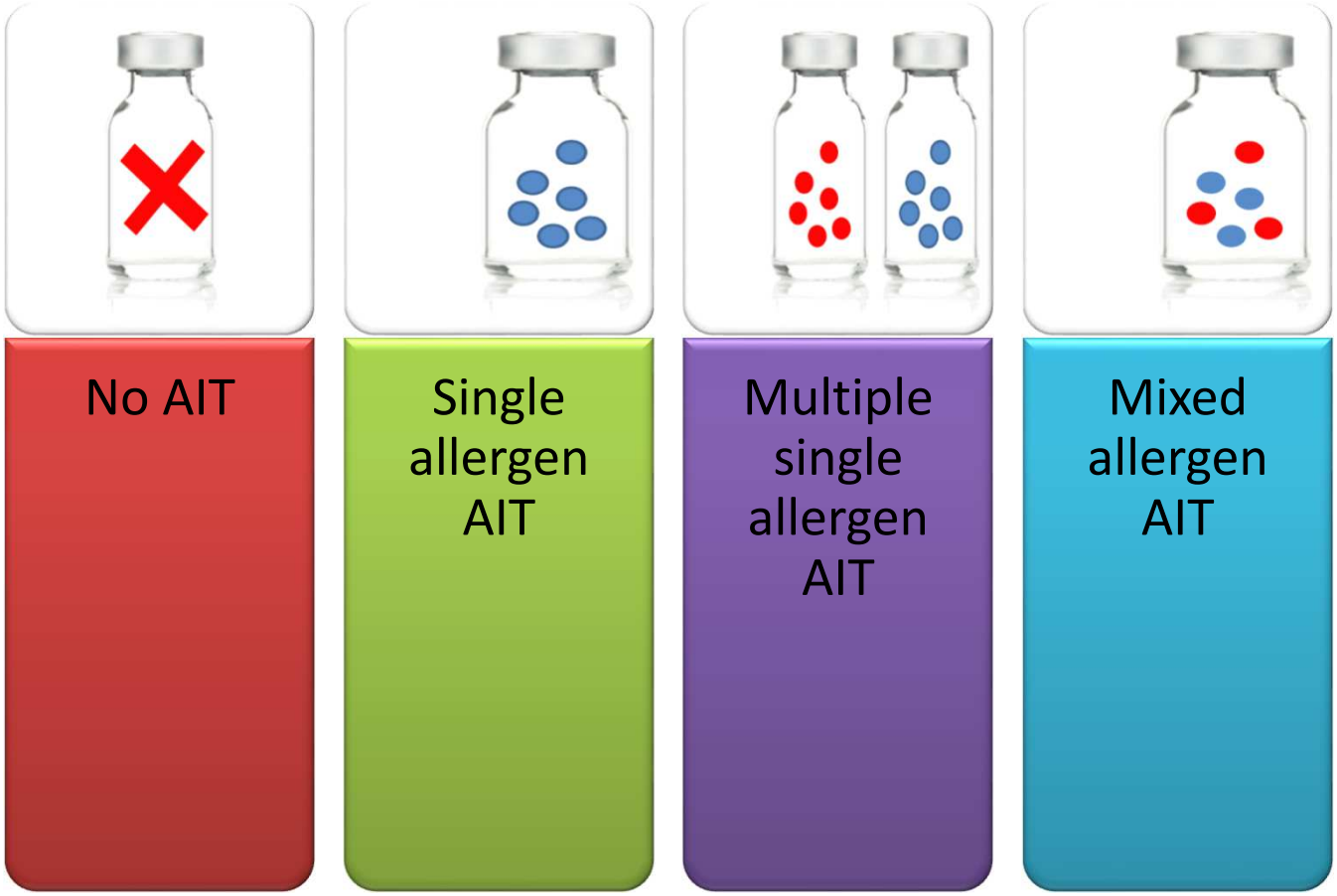
Panallergen sensitization

Polysensitization in homologous groups

Polysensitization to multiple epitopes

Polyallergy?

Which strategies do we have to treat polysensitized patients?



CME review article

This educational activity is supported by an educational grant from GlaxoSmithKline

Comparison of allergen immunotherapy practice patterns in the United States and Europe

Linda Cox, MD,* and Lars Jacobsen, MSc†

Table 1. Comparison of the Differences Between US and European Allergen Extracts and Specific Immunotherapy Practice Patterns

Variable	United States	Europe
Regulatory agency	FDA	EMEA
Standardization		
Method	$ID_{50}EAL$	Nordic
Test technique	Intradermal	Percutaneous
End point	Extract dilution that produces sum of erythema of 50 mm	Extract dilution that produces a wheal equal to the histamine control
Potency determination	Comparison with CBER reference control	Compared with in-house reference
Future focus	Overall allergenicity	Major allergen content
Potency units	BAU, wt/vol, PNU, milligrams of major allergen for ragweed and cat	Varies; each company essentially has its own potency units, some provide milligrams of major allergen
Extract formulation		
Location	Prepared in physicians offices	Prepared at extract manufacturer site
No. of allergens	Multiple	Generally 1
Allergen extract types	Aqueous and glycerinated unmodified extracts, alum-precipitated depot extracts	Approximately 100% depot extract, 20% allergoid, <5% adjuvants
SLIT	Approximately 5.9% of allergists, no FDA-approved formulation	Approximately 45% of prescribed SIT, solution and tablets available, some are registered
Reimbursement	Covered as a medical service by government and private insurers, prices can be negotiated but private insurers often use government schedule	Varies, extract companies negotiate coverage with each country

Abbreviations: BAU, bioequivalent allergy units; CBER, Center for Biologics Evaluation and Research; EMEA, European Medicinal Agency; FDA, Food and Drug Administration; PNU, protein nitrogen units; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

AIT

Allergen Immunotherapy

USA

Allergen Bar 2016

Courtesy of
Prof C.Bachert

Which strategies do we have to treat polysensitized patients?

Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: Looking at the published evidence

Moisés A. Calderón, MD, PhD,[a] Linda Cox, MD,[b] Thomas B. Casale, MD,[c] Philippe Moingeon, PhD,[d] and Pascal Demoly, MD, PhD[e] *London, United Kingdom, Davie, Fla, Omaha, Neb, and Antony and Montpellier, France*

In allergen immunotherapy there is debate as to whether polysensitized patients are best treated with many allergens simultaneously (chosen according to the sensitization profile, a predominantly North American approach) or a single allergen (chosen according to the most clinically problematic allergy, a predominantly European approach). In patients seeking treatment for moderate-to-severe respiratory allergies, polysensitization is more prevalent (range, 50% to 80%) than monosensitization in both the United States and Europe. Safe, effective, single-allergen preparations will most likely have been immunotherapy protocols elicit distinct immune responses in monosensitized and polysensitized patients. Sublingual and subcutaneous multiallergen immunotherapy in polysensitized patients requires more supporting data to validate its efficacy in practice. (J Allergy Clin Immunol 2012;129:929-34.)

Key words: *Allergy, allergen immunotherapy, polysensitization, monosensitization, polyallergic, subcutaneous immunotherapy, sublingual immunotherapy, safety, efficacy*

Single allergen SCIT

- Frew AJ et al. J Allergy Clin Immunol. 2006;117:31
  - **SCIT SQ-U grass (ALK)**
  - **276**/347 **polysensitized**
  - **Similar degree of improvement**
- Kim SH et al. Allergy Asthma Immunol Res. 2014; 6: 535-40
  - **HDM SCIT 2 years (Hollister-Stier Laboratories**, Spokane, WA, USA)
  - **30 HDM-polysensitized** (A), 30 HDM-polysensitized (B)
  - **Similar degree of improvement**
- Soyyigit S et al. Ann Allergy Asthma Immunol. 2016; 116:244-251
  - **D pteronyssinus (ALK)**
  - 22 monosensytized, **24 polysensitized**
  - **Significant improvement in polysensitized, immunologic changes**

Good

Single allergen SLIT

Good

- Malling HJ et al. Clin Exp Allergy. 2009; 39: 387-93
  - SLIT IR grass tablet
  - 559 patients: 51.5–57.4% polysensitized
  - Similar clinical outcomes
- Nelson H. Allergy. 2013; 68:252-5
  - SLIT SQ grass tablet
  - Post hoc analysis of pooled data from six randomized DBPC trials (N = 1871)
  - Similar clinical outcomes

Mixed allergen AIT

neutral

- Nelson HS. J Allergy Clin Immunol. 2009; 123: 763-9
  - 13 studies
  - **Few were well-designed, well-powered DBPC trials**. Head-to-head comparative data with single-allergen regimens were rarely provided.
  - Simultaneous delivery of multiple unrelated allergens can be clinically effective but that there was a **need for additional investigation** (particularly in SLIT).

Mixed allergen SLIT

Bad

- Amar SM et al. J Allergy Clin Immunol. 2009; 124: 150-156
  - **54 patients**: placebo vs single-allergen SLIT (19 mcg of Phl p 5 daily) vs multiallergen SLIT (the same dose of timothy extract plus 9 additional pollen extracts)
  - There were **no significant** symptom or medication score differences versus placebo in either treatment group
  - Changes in various **immune parameters** for the single-allergen group

Mixed allergen SCIT

- Bousquet J et al. J Allergy Clin Immunol. 1991; 88:43-53
  - Patients monosensitized to ***Cynodon*** **vs polysensitized** (Cynodon + other allergens)
  - SCIT: Cynodon vs Cynodon+other vs placebo
  - **Only monosensitized** patients showed a significant clinical effect
- Kim KW et al. J Korean Med Sci. 2006; 21:1012-6
  - Patients monosensitized to **HDM vs polysensitized** (HDM +other)
  - SCIT: HDM vs mixtures
  - **Positive clinical outcome**
  - However, the reduction was significantly ($P < 0.05$) **less intense in the polysensitized group**

neutral Bad

Mixed allergen SCIT

Good

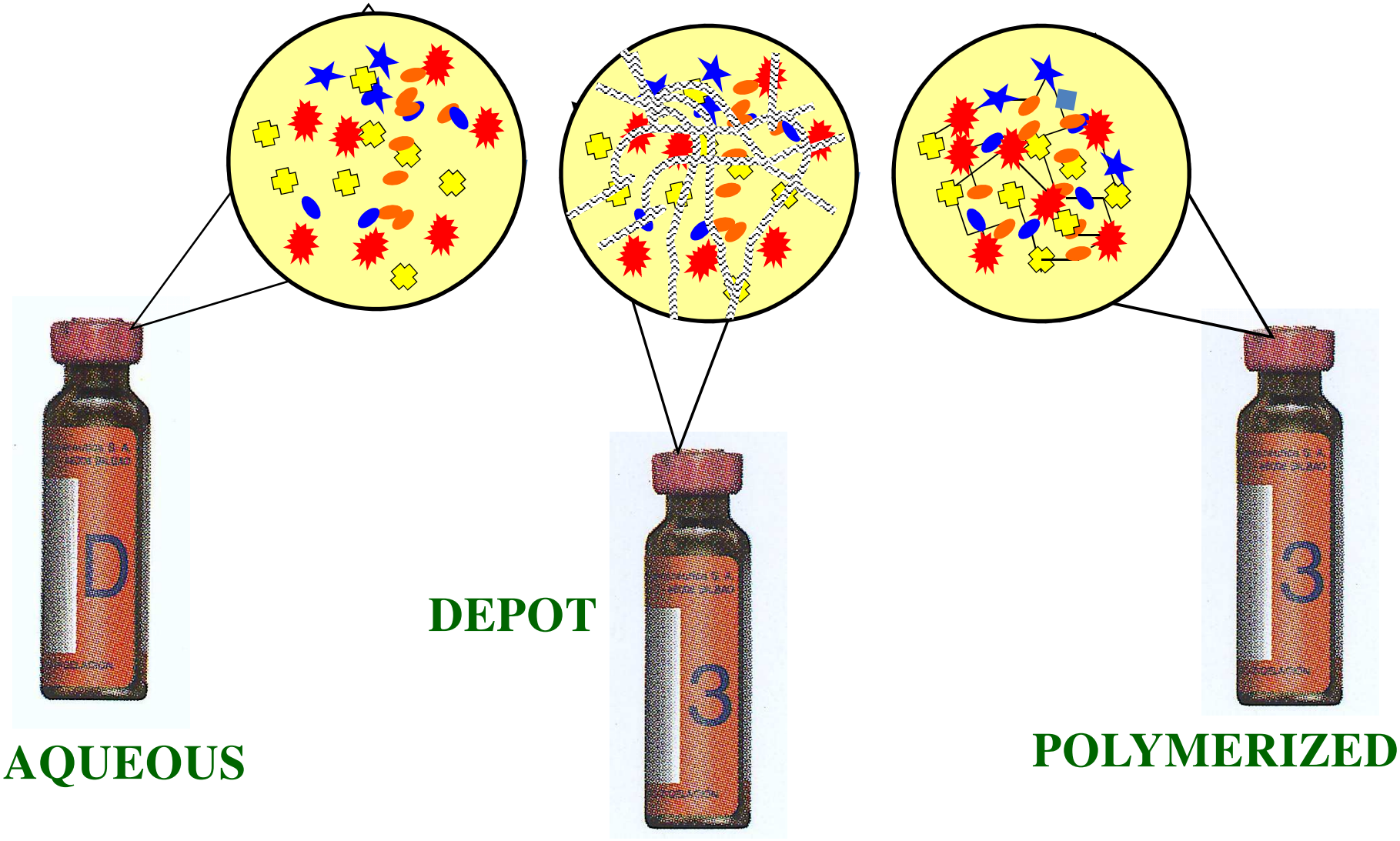
- Pfaar O et al. Allergy 2013;68:1306-13
  - DBPC trial
  - depigmented-polymerized birch and grass pollen extract (LETI)
  - 285 patients
  - **Positive clinical efficacy, immunologic changes, safety**

Grasses/Birch mix

- Its **safety** profile is comparable to that of grasses or birch alone.
- It has demonstrated **efficacy** against both grasses and birch seasons.

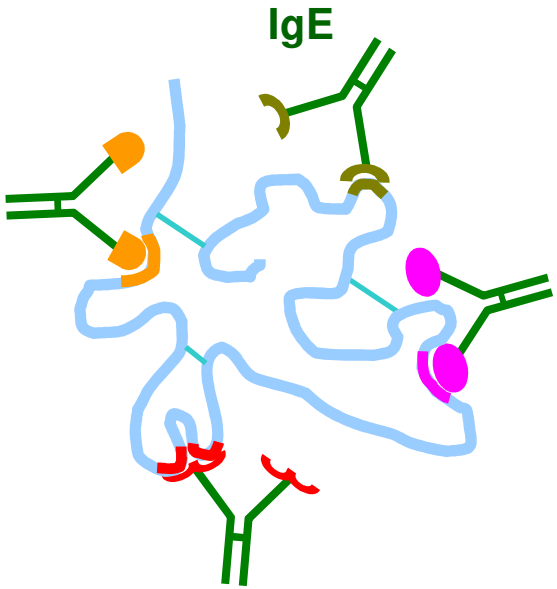
Pfaar et al. Allergy 2013
Pfaar et al. Pediatr Allergy Immunol 2015

ALLERGEN EXTRACTS



POLYMERIZATION

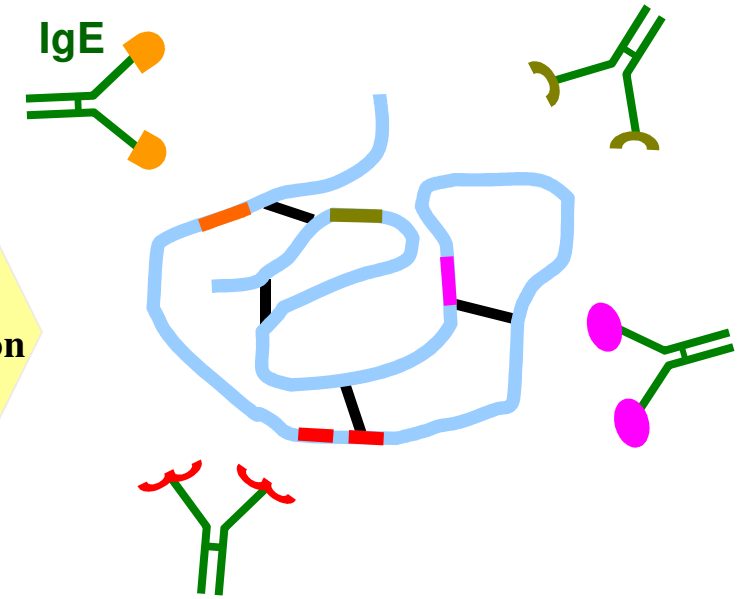
NATIVE ALLERGEN



HIGH allergenicity

Chemical polymerization

POLYMERIZED ALLERGEN



LOW allergenicity

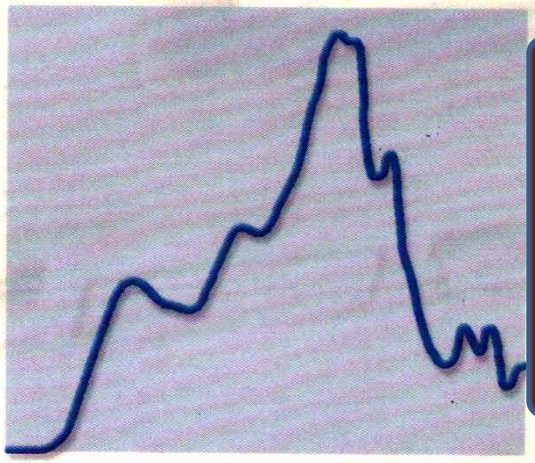
QUALITY CONTROL
Degree of extract polymerization

- **Chromatography and electrophoresis to monitor the degree of extract polymerization**

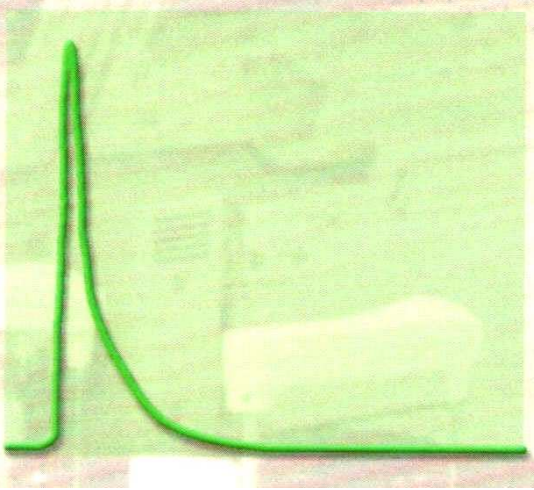
Olea europaea extract

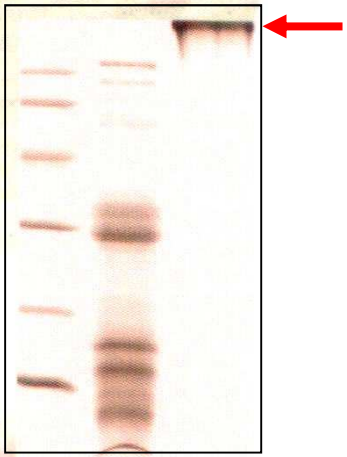
Olea europaea Polymerized extract

Marker
Extract
Polymrized extract



Polymerization





Efficacy of IT on AR & Asthma using polymerized extracts

-symptoms score:	-1,25 (-2,10 to -0.40)
-medication score:	-1,07 (-1,66 to -0,48)
-symptom+medication score:	-1,84 (-2,85 to -0,84)
-quality of life:	-0,87 (-1,14 to -0,61)
-specific bronchial challenge test:	-0,73 (-1,12 to -0,34)
-prick test reduction:	-0,61 (-0,90 to -0,31).

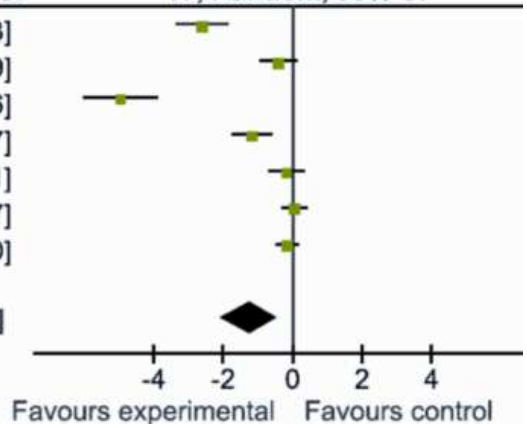
A Nieto Allergy 2012

Simptoms score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alvarez-Cuesta	1,43	0,47	25	3	0,68	28	13,8%	-2,6192 [-3,3672, -1,8713]
Ameal 2005	1,15	1,79	29	2,39	3,76	26	14,6%	-0,4227 [-0,9584, 0,1129]
Colas	4,32	0,52	41	7,97	1,05	19	12,4%	-4,9549 [-6,0212, -3,8886]
García-Robaina	9,7	10,01	27	29,41	21,16	27	14,4%	-1,1735 [-1,7544, -0,5927]
Hoiby 2010	0,59	0,43	31	0,66	0,33	30	14,7%	-0,1799 [-0,6830, 0,3231]
Pfaar 2010	6,55	4,52	117	6,38	3,91	40	15,0%	0,0387 [-0,3203, 0,3977]
Pfaar 2012	0,594	0,431	137	0,655	0,3338	47	15,1%	-0,1487 [-0,4803, 0,1830]
Total (95% CI)			**407**			**217**	**100,0%**	**-1,2514 [-2,1026, -0,4001]**

Heterogeneity: Tau² = 1,22; Chi² = 117,57, df = 6 (P < 0.00001); I² = 95%

Test for overall effect: Z = 2,88 (P = 0,004)



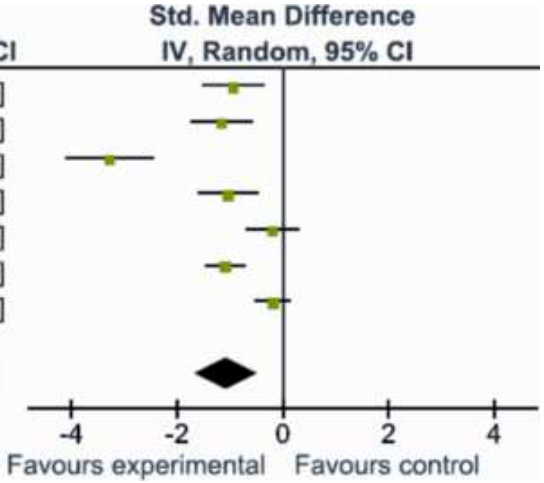
A Nieto Allergy 2012

Medication score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alvarez-Cuesta	0,22	0,11	25	0,76	0,77	28	14,1%	-0,9411 [-1,5117, -0,3706]
Ameal 2005	1,53	2,27	29	4,71	3,13	26	14,1%	-1,1568 [-1,7317, -0,5819]
Colas	0,78	0,08	41	1,12	0,14	19	12,4%	-3,2755 [-4,0900, -2,4610]
García-Robaina	8,76	8,76	27	23,69	18,23	27	14,1%	-1,0288 [-1,5990, -0,4586]
Hoiby 2010	2,26	2,65	31	2,76	2,53	30	14,5%	-0,1905 [-0,6936, 0,3127]
Pfaar 2010	2,66	2,59	117	7,98	8,64	40	15,3%	-1,0851 [-1,4641, -0,7061]
Pfaar 2012	2,256	2,6468	137	2,758	2,5292	47	15,5%	-0,1910 [-0,5229, 0,1409]
Total (95% CI)			**407**			**217**	**100,0%**	**-1,0699 [-1,6562, -0,4835]**

Heterogeneity: $Tau^2 = 0,55$; $Chi^2 = 58,56$, df = 6 ($P < 0.00001$); $I^2 = 90\%$

Test for overall effect: Z = 3,58 (P = 0,0003)



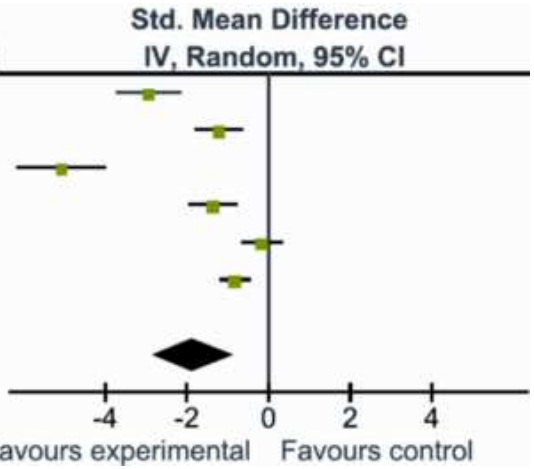
A Nieto Allergy 2012

Symptoms + medication score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alvarez-Cuesta	1,64	0,54	25	3,76	0,83	28	16,2%	-2,95 [-3,74, -2,15]
Ameal 2005	2,62	2,97	29	7,11	4,32	26	17,0%	-1,21 [-1,79, -0,63]
Colas	5,11	0,54	41	9,08	1,13	19	14,9%	-5,07 [-6,15, -3,99]
García-Robaina	18,45	15,49	27	53,1	31,95	27	17,0%	-1,36 [-1,96, -0,76]
Hoiby 2010	2,91	2,77	31	3,37	2,7	30	17,3%	-0,17 [-0,67, 0,34]
Pfaar 2010	9,03	4,8	117	13,78	7,78	40	17,6%	-0,83 [-1,20, -0,46]
Total (95% CI)			**270**			**170**	**100,0%**	**-1,84 [-2,85, -0,84]**

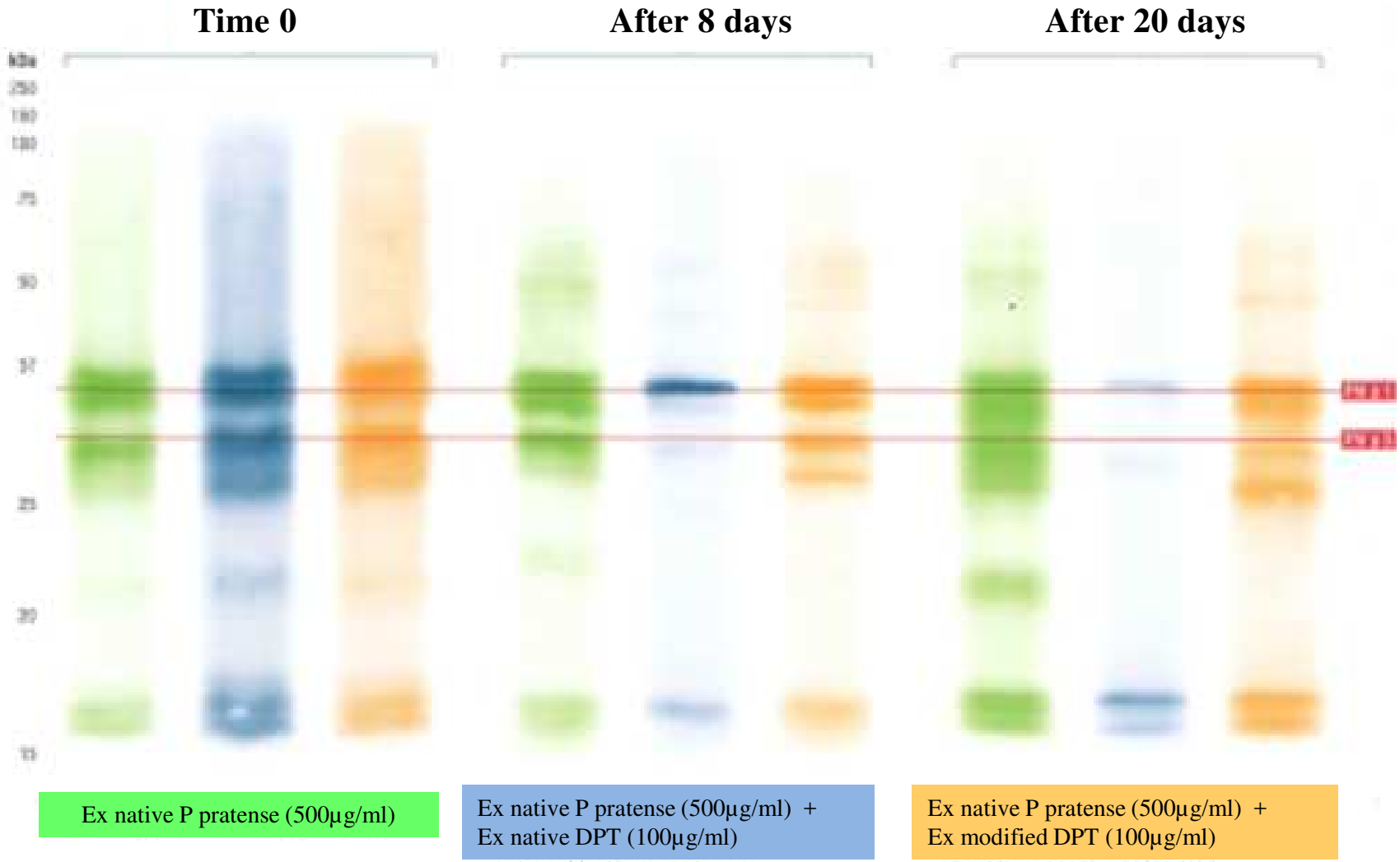
Heterogeneity: Tau² = 1,45; Chi² = 87,84, df = 5 (P < 0.00001); I² = 94%

Test for overall effect: Z = 3,61 (P = 0,0003)



A Nieto Allergy 2012

Proteolytic activity of DPT on Phleum pratense



E. Fernández-Caldas et al. Grass and mite mixtures: how does the proteolytic activity of Dermatophagoides pteronyssinus affect Phleum pratense extracts?

Allergen immunotherapy: A practice parameter third update

J ALLERGY CLIN IMMUNOL
JANUARY 2011

Chief Editors: **Linda Cox, MD, Harold Nelson, MD, and Richard Lockey, MD**

Workgroup Contributors: **Christopher Calabria, MD, Thomas Chacko, MD, Ira Finegold, MD, Michael Nelson, MD, PhD, and Richard Weber, MD**

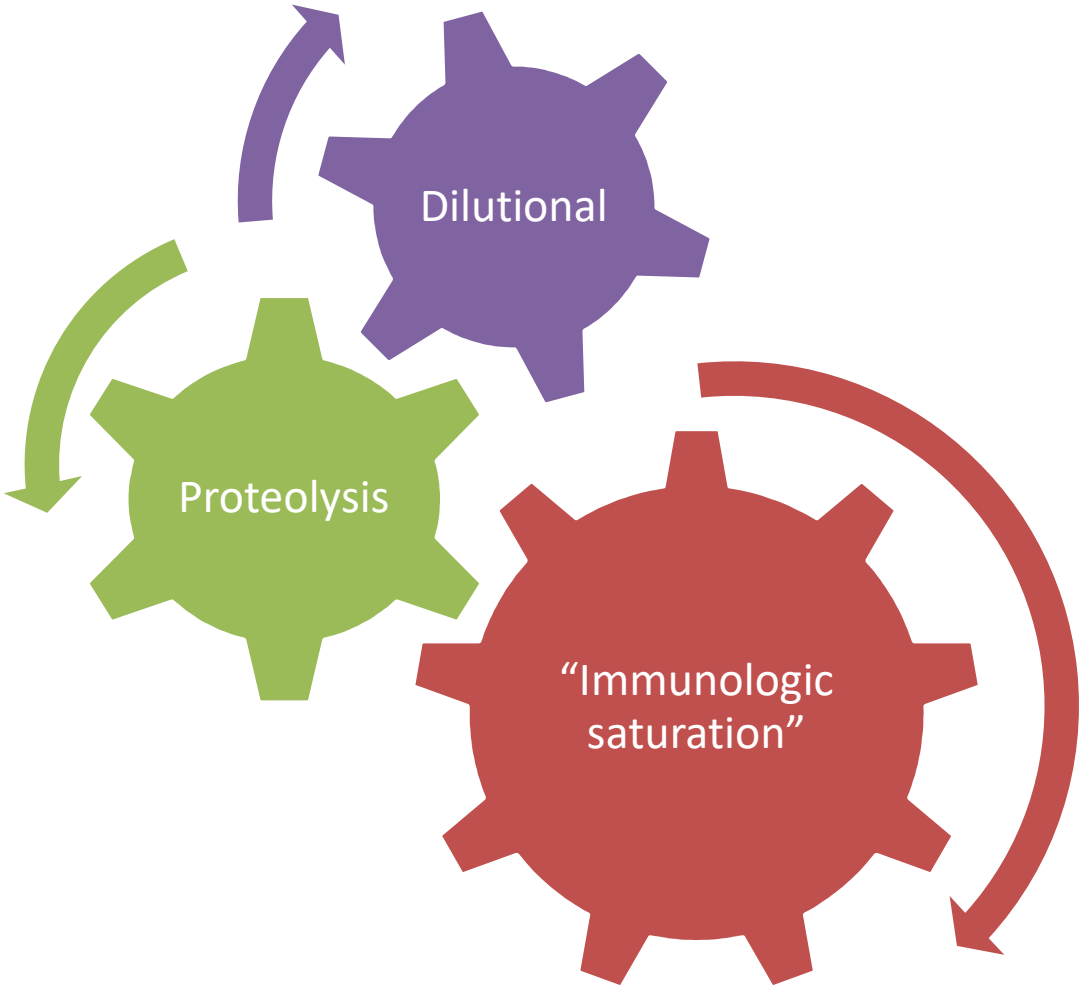
Task Force Reviewers: **David I. Bernstein, MD, Joann Blessing-Moore, MD, David A. Khan, MD, David M. Lang, MD,**

Summary Statement 72:

"*The **limited** number of studies investigating the efficacy of **multiallergen immunotherapy** have produced conflicting results. In general, multiallergen trials have demonstrated efficacy, although some failed to provide results specific to the multiallergens*"

"*It is important to treat the patients **only with relevant allergens***"

Risks of allergen mixing



Passalacqua & Canonica

Imm Allergy Clin North Am 2015

Allergen Immunotherapy

History and Future Developments

Giovanni Passalacqua, MD*, Giorgio Walter Canonica, MD

Canonica et al. Curr..Opin.Pulm.Med. 2015

KEY POINTS

- According to the latest scientific evidence, we have evaluated the correct approach to the use of AIT in asthmatic patients.
- One of our purposes was to dispel the doubts on the use of AIT in asthmatic patients, using the correct AIT in a specific phenotype of patients.
- Personalized Medicine as a promising therapeutic approach applied to a specific phenotype of patients studied using biomarkers.
- Diatribe SCIT versus SLIT: two different tools in the allergist's therapeutic armamentarium.

Which Patients for Immunotherapy?

Appropriate clinical manifestations.

Demonstrated IgE-mediated sensitivity to relevant allergen(s)

Significant exposure to the relevant allergen(s)

Availability of high quality extract for the relevant allergen(s).

Asthma, if present, adequately controlled.

Requirements for Physician Competencies in Allergy: Key Clinical Competencies Appropriate for the Care of Patients With Allergic or Immunologic Diseases

A Position Statement of the World Allergy Organization

Michael A. Kaliner, Sergio Del Giacco, Carlos D. Crisci, Anthony J. Frew, Guanghui Liu, Jorge Maspero, Hee-Bom Moon, Takemasa Nakagawa, Paul C. Potter, Lanny J. Rosenwasser, Anand B. Singh, Erkka Valovirta, Paul Van Cauwenberge, John O. Warner, and WAO Specialty and Training Council

A. The immunotherapy has been prescribed by a specialist.
B. The first-level physician and other professionals have had adequate training in allergy and the recognition
and management of anaphylaxis to provide this service safely.
C. The location where immunotherapy is performed fulfills all the conditions for patient safety. The site where immunotherapy is performed should be equipped to treat severe allergic reactions

WAO Grading System for SLIT Local Reactions

Symptom/sign	Grade 1 – Mild	Grade 2 – Moderate	Grade 3 - Severe	Unknown severity
Abdominal pain, Diarrhea Ear itching Pruritus/swelling of mouth, tongue or lip Nausea Throat irritation Uvular oedema Vomiting	● Not troublesome **AND** ● No symptomatic treatment required **AND** ● No discontinuation of SLIT because of local side effects	● Troublesome **OR** ● Requires symptomatic treatment **AND** ●No discontinuation of SLIT because of local side effects	Grade 2 AND SLIT discontinued because of local side effects	The treatment is discontinued but there is no subjective and/or objective description of the severity from the patient/physician
Each local adverse event can be early (<30 minutes) or delayed				

Passalacqua et al, Grading side effects of sublingual immunotherapy speaking the same language. 2011

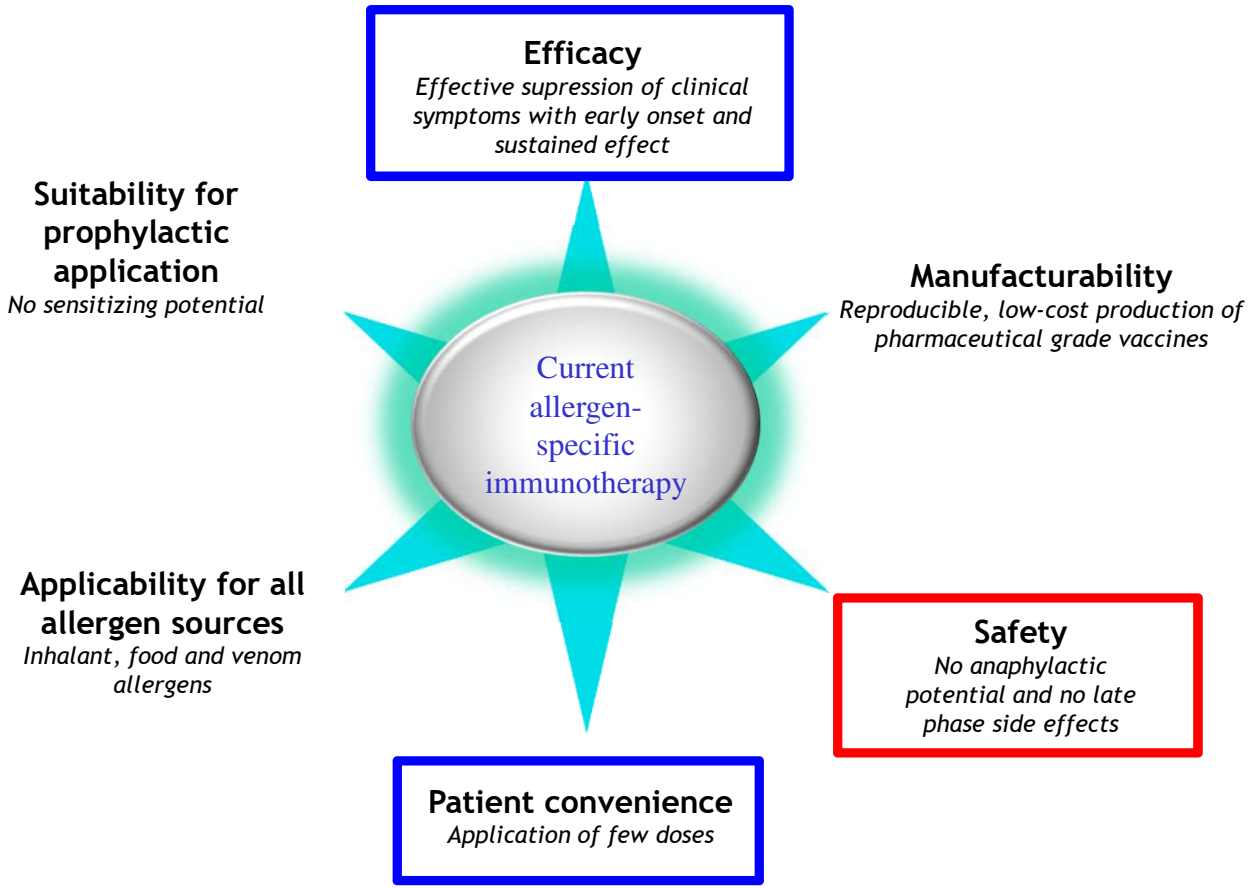
WAO Grading System for Severe Allergic Reactions

TABLE I. Proposed modification of the 2010 WAO grading system

Grading system for SARs				
			Grade 4	Grade 5
Grade 1	**Grade 2**	**Grade 3**	**Anaphylaxis**	
Symptom(s)/sign(s) from 1 organ system present Cutaneous • Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site And/or • Tingling, or itching of the lips* or • Angioedema (not laryngeal)* Or Upper respiratory • Nasal symptoms (eg, sneezing, rhinorrea, nasal pruritus, and/or nasal congestion) And/or • Throat-clearing (itchy throat)* And/or • Cough not related to bronchospasm Or Conjunctival • Erythema, pruritus, or tearing Or Other • Nausea • Metallic taste	Symptom(s)/sign(s) from ≥2 organ symptoms listed in grade 1	Lower airway • Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment And/or Gastrointestinal • Abdominal cramps* and/or vomiting/diarrhea Other • Uterine cramps • Any symptom(s)/sign(s) from grade 1 would be included	Lower airway • Severe bronchospasm, eg, not responding or worsening in spite of treatment And/or Upper airway • Laryngeal edema with stridor • Any symptom(s)/sign(s) from grades 1 or 3 would be included	Lower or upper airway • Respiratory failure and/or Cardiovascular • Collapse/hypotension† And/or Loss of consciousness (vasovagal excluded) • Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

Cox L, Sanchez-Borges M & Lockey RF. J Allergy Clin Immunol Pract 2017;5:58-62

Requirements for improved allergy vaccines



R. Valenta *et al. J. Allergy Clin Immunol* 2016; 137: 351-7.

WAO Symposium

ROME/VATICAN CITY

27-29 April, 2017 - Rome, Italy/Vatican City