

giornata di studio sui  
**POLLINI**

approfondimenti di biologia molecolare,  
statistica, biodiversità e normativa

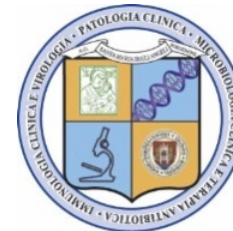
**24 febbraio 2017**

dalle 9.00 alle 16.00

ex Convento di San Francesco,  
piazza della Motta - Pordenone

# L'utilità del monitoraggio pollinico per l'allergologo

Danilo Villalta



**Allergologia e Immunologia Clinica  
Ospedale «S-Maria degli Angeli»  
Pordenone**



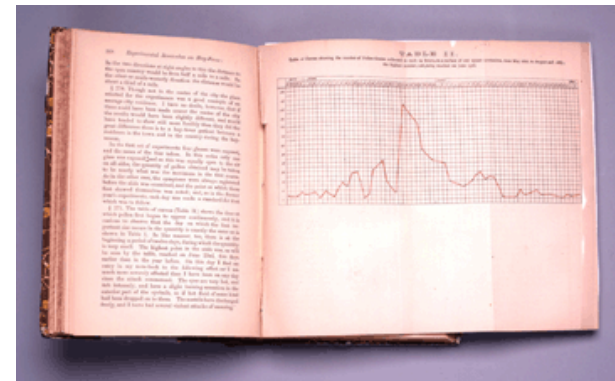
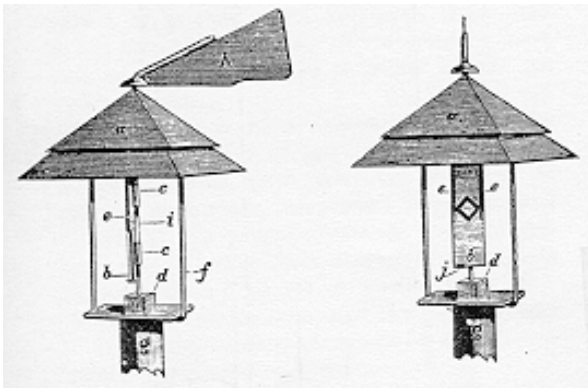
# La Preistoria dell'allergologia...



Charles Blackley (1820-1900)

**1873-80:** la “febbre da fieno riportata alla “Royal Medical Society” nel 1819 è causata dalle Graminaceae

1. Riprodusse i sintomi della malattia instillando nel naso un estratto pollinico (**1° test di scatenamento**)
2. Dimostrò che i pazienti con “febbre da fieno” sviluppavano un ponfo e un eritema, se nella cute precedentemente scarificata veniva posto un estratto pollinico (**1° prick test**)
3. Dimostrò la correlazione tra la presenza di pollini in atmosfera e la presenza dei sintomi (**nascita dell'aerobiologia**)



# Il monitoraggio pollinico e l'allergologo

- Correlare la presenza del polline con il periodo sintomatico del paziente
- Conoscenza dei pollini e periodo della loro presenza nel territorio in cui si opera
- Indicazioni su quanto prolungare la terapia sintomatica nel pollinosico
- Predizione di presenza o meno di sintomi se il paziente si sposta in zone diverse dalla sua abituale residenza



# Panallergeni in Pediatria



analisi trasversale (cross-sectional)  
sull'intera popolazione di pazienti  
reclutati per lo studio

**grazie a Francesca Cipriani**

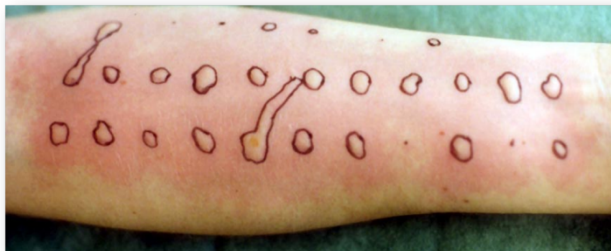
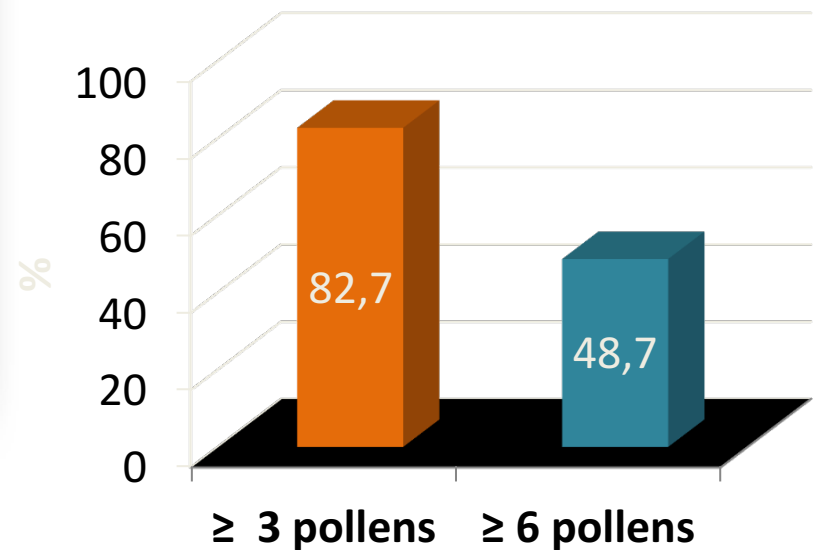
le prossime diapositive sono  
tratte dalla sua tesi di  
specializzazione

*dati preliminari in corso di pubblicazione*

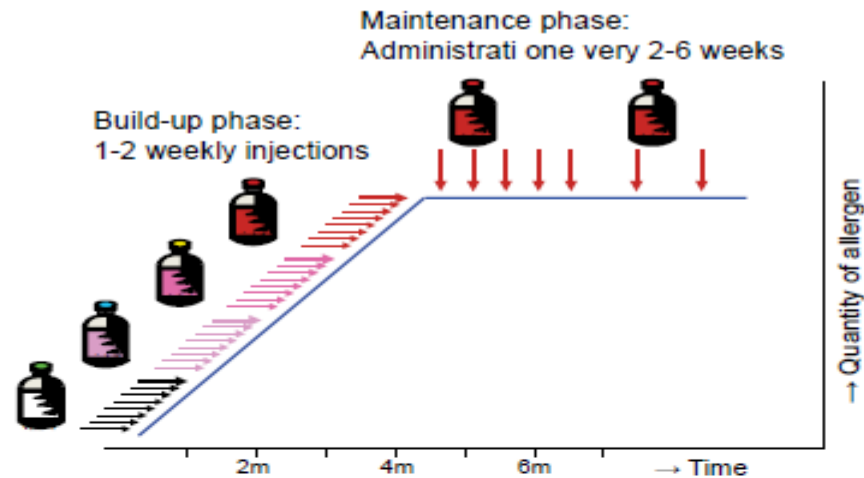
	Extract	N	%
Pollen	<i>P. pratense</i>	1259	89,3
	<i>C. dactylon</i>	982	69,6
	Olive tree	840	59,6
	<i>P. lanceolata</i>	815	57,8
	<i>C. album</i>	727	51,6
	Cypress	579	41,1
	Birch	518	36,7
	Plane	482	34,2
	Pellitory	479	34,0
	Hazel	467	33,1
	Absinthe	342	24,3
	Salsola	280	19,9
	Ambrosia	254	18,0
	Holm	83	5,9

Età media= 10,5 anni

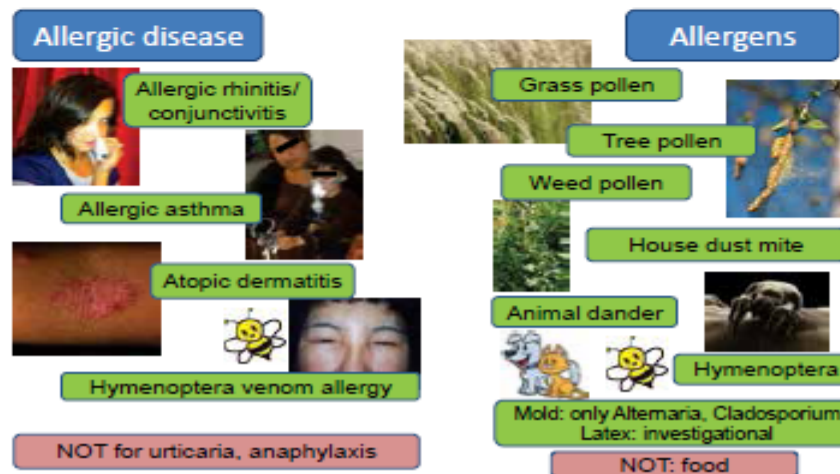
### Highly polisensitized



# Allergen Immunotherapy (AIT)



**Figure 1** General dosing schedule for SCIT. On average the build-up phase lasts 3-6 months, during which the allergy shots are given 1-2 times/week; in the maintenance phase injections are given every 2-6 weeks for at least 3 years.



## Immunotherapy in polysensitized patients: new chances for the allergists?

The rationale of the POLISMAIL studies was based on several issues: (1) polysensitization usually starts from childhood, (2) polysensitization progresses with aging, (3) up to 80% of allergic adults are polysensitized, (4) polysensitization may depend on a T-regulatory cell defect, (5) polysensitization may significantly affect QoL, (6) polysensitization may be associated with more severe symptoms, and (7) polysensitization may discourage immunotherapy prescription. These studies were conducted in 11 allergy centers

multiple allergens, which have exposure overlap. In the Mediterranean area, characterized by a complex pollen pattern, molecular diagnosis can change SIT prescription.<sup>17</sup> In the United States, this is

### Table 1

The possible added values provided by molecular diagnosis for a correct immunotherapy in polysensitized patients

- Quick and thorough information on sensitization profile
- Explanation for symptoms or diagnostic results due to cross-reactivity
- Intelligibility of complex results (ie, pan-allergens)
- More precise identification of candidate to immunotherapy
- Potential reduction of specific immunotherapy costs

**Polysensitization should be no longer represent an ostacle in prescribing SLIT because a treatment limited to 1 to 2 allergen extracts might be effective in improving the clinical symptoms and QoL of patients, while maintaining the well-known safety of this therapy**



REVIEW

Open Access

# Allergen Immunotherapy (AIT): a prototype of Precision Medicine



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

Precise information and biomarkers provided by systems medicine and network medicine will address the discovery of Allergen immunotherapy biomarkers for (i) identification of the causes, (ii) stratification of eligible patients for AIT and (iii) the assessment of AIT efficacy.

⋮



# THE PRECISION MEDICINE INITIATIVE



*“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals...”*

*President Obama, January 30, 2015*



*Allergen source*



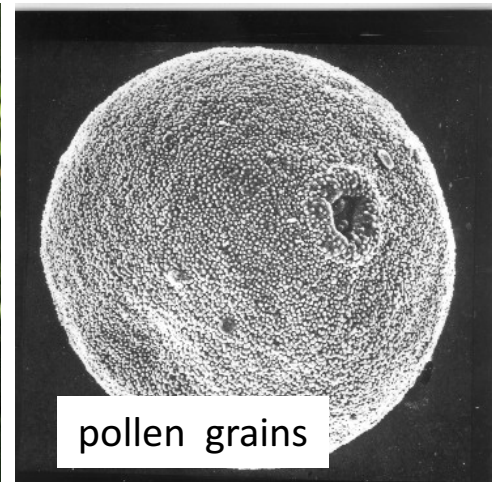
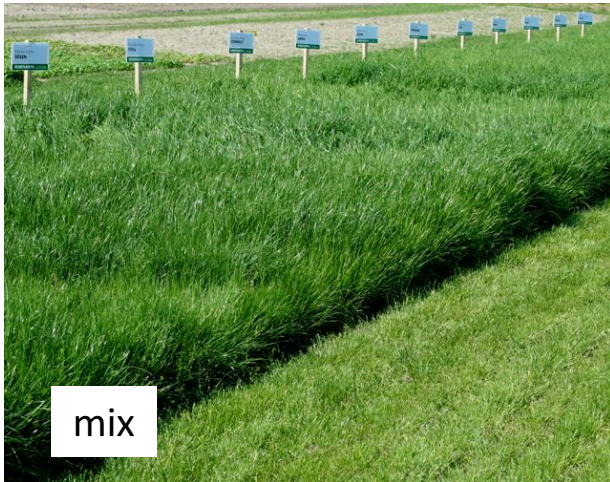
*Allergen extract*



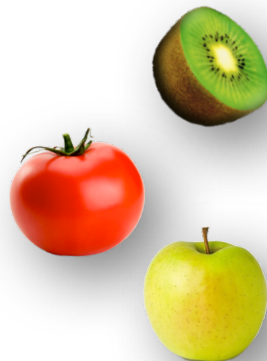
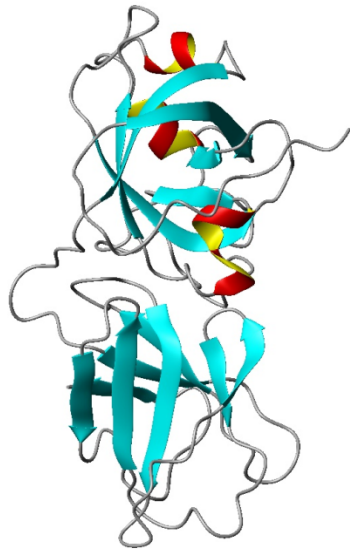
*Specific allergen components*



*Cross-reactive allergen components*



Phl p 1



- Phl p 1
- Phl p 2
- Phl p 3
- Phl p 4
- Phl p 5
- Phl p 6
- Phl p 7 **Polcalcina**
- Phl p 11
- Phl p 12 **Profilina**



Mauro 39 aa: **Prick test:**

- Mix Graminaceae 4+
- Assenzio 4+
- Plantago l 4+
- Cipresso 2+
- Betulaceae 3+
- Parietaria 3+
- Ambrosia 3+
- Olivo 3+

# Eseguita diagnostica molecolare

## ImmunoCAP Specific IgE 0-100

Test name	Test long name	Conc
g205	rPhl p 1 (ricombinante)	46,8 kUA/l
g215	rPhl p 5b	17,5 kUA/l
t215	rBet v 1 (ricombinante)	0,01 kUA/l
t216	rBet v 2 profilin (ricomb.)	0,02 kUA/l
t220	rBet v 4 (ricombinante)	23,7 kUA/l
w231	nArt v 1	0,02 kUA/l
w211	rPar j 2 (ricombinante)	0,02 kUA/l
t226	nCup a 1 Cipresso	0,18 kUA/l
t224	rOle e 1 Olive	0,01 kUA/l
w230	nAmb a 1	0,07 kUA/l
w9	Lanciuola	18,5 kUA/l

Are patients „allergic to grass pollens“  
all the same  
from an immunological point-of-view?



i.e. is one grass pollen preparation good for everybody?

**Molecular profiles of IgE to *Phleum pratense* in children with grass pollen allergy: Implications for specific immunotherapy**

**39 profili diversi di IgE**  
specifiche (> 0,35 kU/L) per  
le 8 molecole del Phleum:

- Phl p 1
- Phl p 2
- Phl p 4
- Phl p 5
- Phl p 6
- Phl p 7
- Phl p 11
- Phl p 12

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.
128	10000000	●								1
248	11111000	●	●	●	●	●				5
160	10100000	●		●						2
184	10111000	●		●	●	●				4
186	10111010	●		●	●	●		●		5
251	11111011	●	●	●	●	●		●	●	7
192	11000000	●	●							2
216	11011000	●	●		●	●				4
249	11111001	●	●	●	●	●			●	6
250	11111010	●	●	●	●	●		●		6
32	100000			●						1
224	11100000	●	●	●						3
152	10011000	●			●	●				3
185	10111001	●		●	●	●			●	5
208	11010000	●	●		●					3
218	11011010	●	●		●	●		●		5
48	110000			●	●					2
64	1000000		●							1
144	10010000	●			●					2
162	10100010	●		●				●		3
187	10111011	●		●	●	●		●	●	6
193	11000001	●	●						●	3
217	11011001	●	●		●	●			●	5
225	11100001	●	●	●					●	4
16	10000				●					1
34	100010			●				●		2
58	111010			●	●	●		●		4
96	1100000		●	●						2
129	10000001	●							●	2
130	10000010	●						●		2
132	10000100	●					●			2
156	10011100	●			●	●	●			4
188	10111100	●		●	●	●	●			5
194	11000010	●	●					●		3
232	11101000	●	●	●		●				4
240	11110000	●	●	●	●					4
254	11111110	●	●	●	●	●	●	●		7
255	11111111	●	●	●	●	●	●	●	●	8
0	0									0



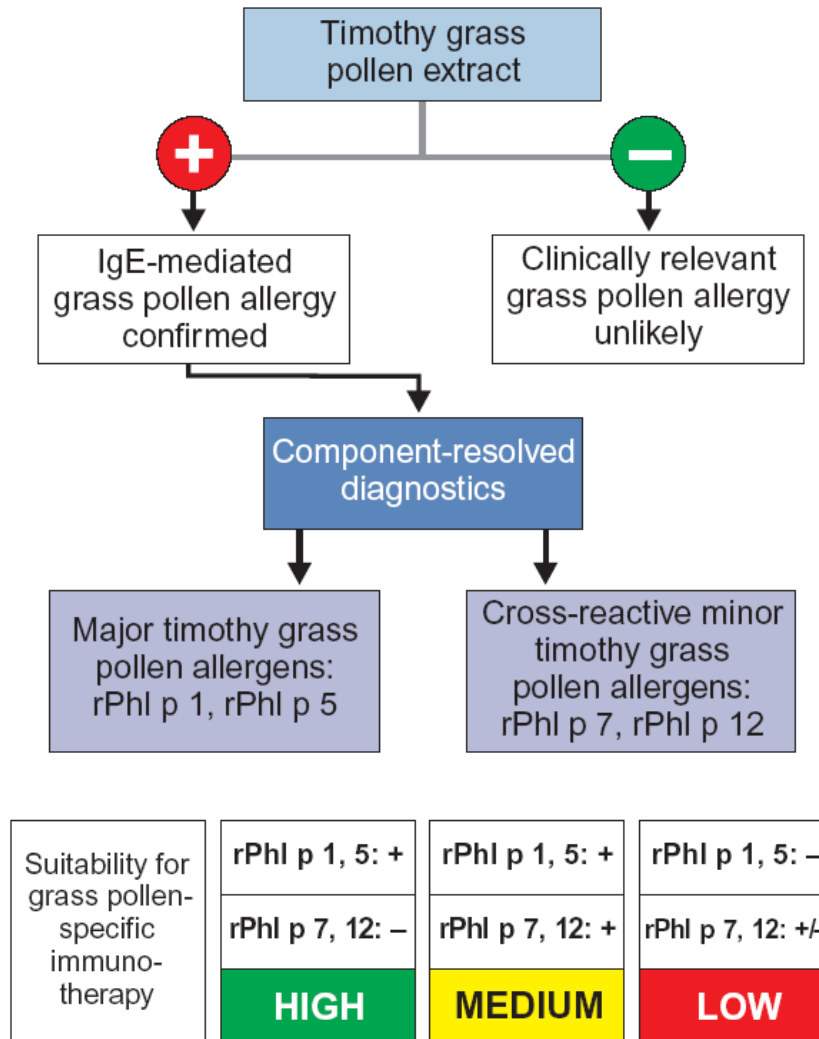
# Molecular profile clustering of IgE responses and potential implications for specific immunotherapy

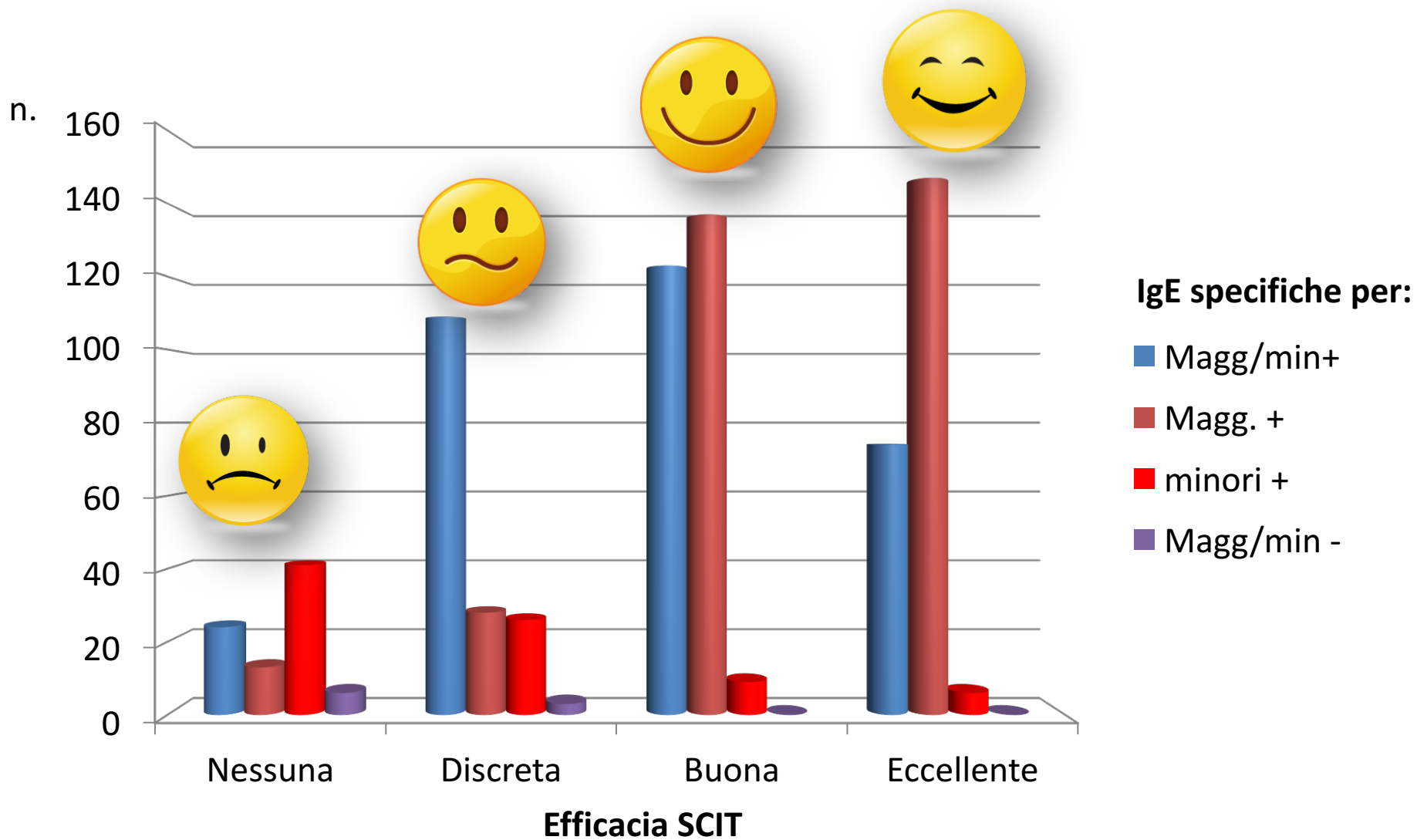
Paolo M. Matricardi

Patient's profiles <sup>o</sup>	Example patient's profiles <sup>o</sup>	Molecular SIT profile	Example molecular overlapping <sup>o</sup>	Patient's immunization category	Frequency by category n (%)
216		+	=	Matching	7/176 (4%)
217, 218, <i>248</i> , 249, 250, 251, 254, 255		+	=	Mis-match type 1 underpowered	50/176 (28%)
16, 48, 64, <i>128</i> , 144, 152, 192, 208		+	=	Mis-match type 2 overpowered	57/176 (32%)
58, <i>96</i> , 129, 130, 132, 156, 160, 162, 184, 185, 186, 187, 188, 193, 194, 224, 225, 232, 240		+	=	Mis-match type 3 mixed	53/176 (30%)
0, 32, <i>34</i>		+	=	Mis-match type 4 unrelated	9/176 (5%)

<sup>o</sup>the pattern chosen as an example is marked in italic red

# A possible decision tree for the treatment of grass pollen allergy





# A WAO - ARIA - GA<sup>2</sup>LEN consensus document on molecular-based allergy diagnostics

Giorgio Walter Canonica<sup>1\*</sup>, Ignacio J Ansotegui<sup>2</sup>, Ruby Pawankar<sup>3</sup>, Peter Schmid-Grendelmeier<sup>4</sup>, Marianne van Hage<sup>5</sup>, Carlos E Baena-Cagnani<sup>6</sup>, Giovanni Melioli<sup>7</sup>, Carlos Nunes<sup>8</sup>, Giovanni Passalacqua<sup>9</sup>, Lanny Rosenwasser<sup>10</sup>, Hugh Sampson<sup>11</sup>, Joaquin Sastre<sup>12</sup>, Jean Bousquet<sup>13</sup>, Torsten Zuberbier<sup>14</sup> and WAO-ARIA-GA<sup>2</sup>LEN Task Force: Katrina Allen, Riccardo Asero, Barbara Bohle, Linda Cox, Frederic de Blay, Motohiro Ebisawa, Rene Maximiliano-Gomez, Sandra Gonzalez-Diaz, Tari Haahtela, Stephen Holgate, Thilo Jakob, Mark Larche, Paolo Maria Matricardi, John Oppenheimer, Lars K Poulsen, Harald E Renz, Nelson Rosario, Marc Rothenberg, Mario Sanchez-Borges, Enrico Scala, Rudolf Valenta

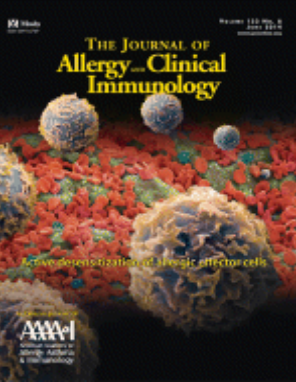
- 1. Resolving genuine versus cross-reactive sensitization in poly-sensitized patients**
- 2. Assessing the risk of severe, systemic versus mild local reactions in food allergy, thereby reducing unnecessary anxiety for the patient and the need for food challenge testing**
- 3. Identifying patients and triggering allergens for specific immunotherapy (SIT)**

## BRIEF COMMUNICATION

**How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area**J. Sastre<sup>1,2</sup>, M. E. Landivar<sup>1</sup>, M. Ruiz-García<sup>1</sup>, M. V. Andregnette-Rosigno<sup>1</sup> & I. Mahillo<sup>3</sup><sup>1</sup>Fundacion Jiménez Díaz, Allergy Department, Fundación Jiménez Díaz, Madrid, Spain; <sup>2</sup>CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain; <sup>3</sup>Department of Epidemiology, ISS Fundación Jiménez Díaz, Madrid, Spain**Table 1** Agreement and disagreement in indication of immunotherapy based on skin prick test only and molecular diagnosis

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 <i>P</i> = 0.0781
Olive	1	1	132 (93)	9 (7)	0.1624 ± 0.0639 <i>P</i> = 0.0055
Grass + olive	4	1	101 (71)	40 (29)	0.0505 ± 0.0548 <i>P</i> = 0.1782
Grass + cypress	0	1	132 (93)	9 (7)	0.1711 ± 0.0471 <i>P</i> = 0.0001
Grass + plane	0	1	133 (94)	8 (6)	0.1897 ± 0.0493 <i>P</i> = 0.0001
Olive + cypress	0	2	141 (100)	0 (0)	1 ± 0.0842 <i>P</i> < 0.0001
Other extracts	3	4	129 (91)	12 (9)	0.3586 ± 0.0798 <i>P</i> < 0.0001
Total	25	20	62 (46) <b>46%</b>	79 (54) <b>54%</b>	0.1057 ± 0.0413

SIT, specific immunotherapy; MD, molecular diagnosis.



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

Stringari G et al 2014 Jul 134(1):75-81

TABLE VI. Effect of CRD\* on SIT prescription made on the basis of SPT responses by doctors in 651 Italian children affected by hay fever

SIT after SPT	Not prescribed						Prescribed						All			
	All (n = 651)		No SIT		SIT		All (n = 651)		No SIT		Changed SIT composition		Unchanged SIT composition		Changed SIT (n = 651)	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Grass pollen	215	33	135	63	80	37	436	67	74	17	NA	NA	362	83	154	24
Olive	538	83	484	90	54	10	113	17	58	51	NA	NA	55	49	112	17
Pellitory	542	83	498	92	44	8	109	17	21	19	NA	NA	88	81	65	10
Cypress	618	95	578	94	40	6	33	5	8	24	NA	NA	25	76	48	7
Betulaceae	612	94	591	97	21	3	39	6	15	38	NA	NA	24	62	36	6
Mugwort	636	98	632	99	4	1	15	2	6	40	NA	NA	9	60	10	2
All allergens	3161	100	2918	92	243	8	745	100	182	24	NA	NA	563	76	425	11
Patients	143	22	60	42	83	58	508	78	52	10	170	33	286	56	305	47

**Conclusion: 47% of SIT prescriptions changed**

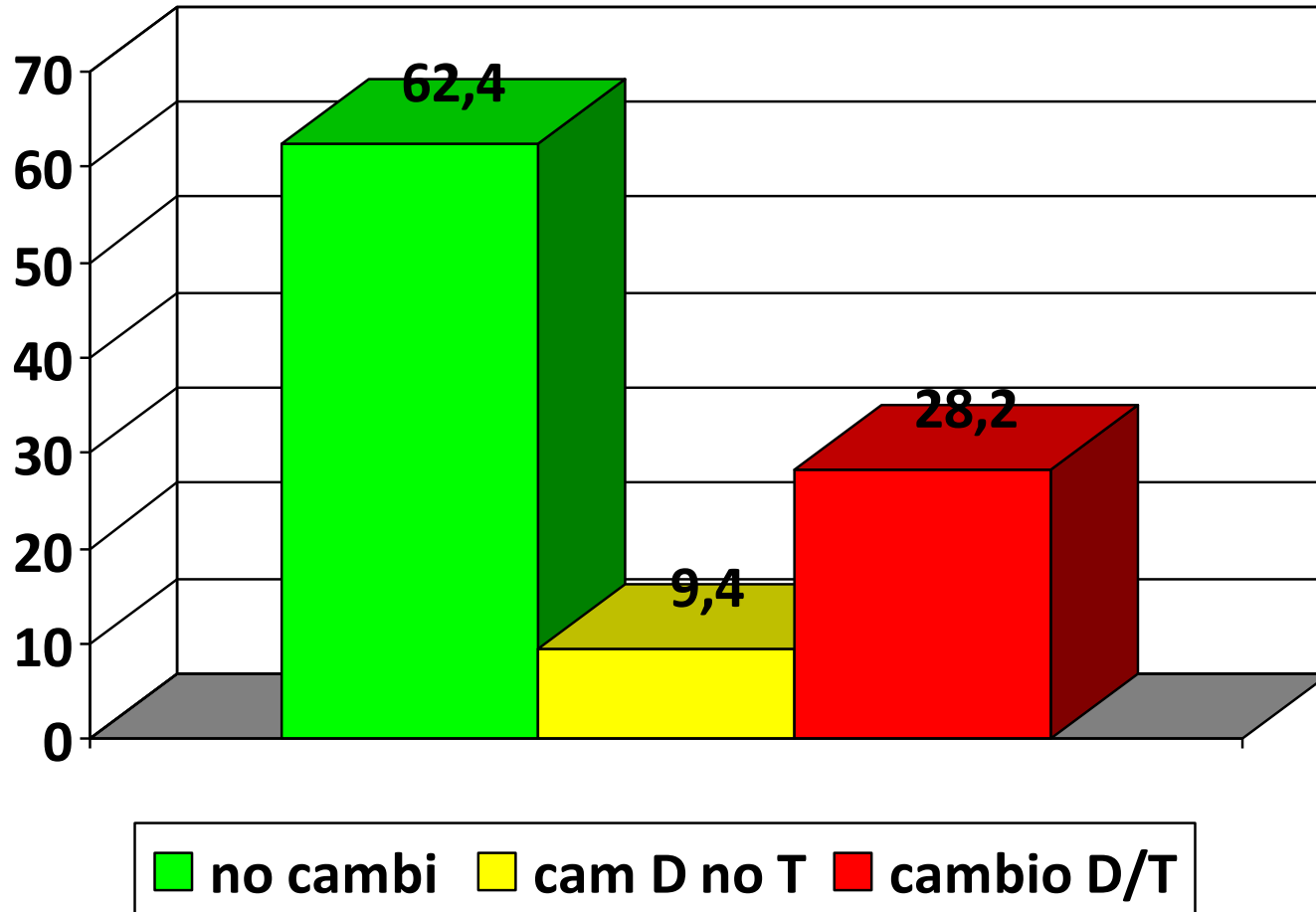
**Clinical implications: CRD, when the internationally proposed algorithms are applied, modifies the decision on SIT prescription in a large proportion of children affected by pollen-related AR.**

# Studio prospettico: real life



➤ **233** soggetti **polisensibilizzati** ad inalanti

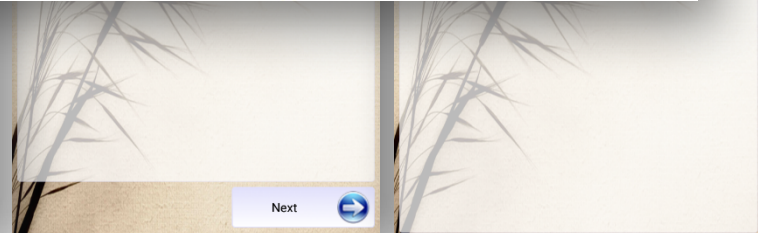
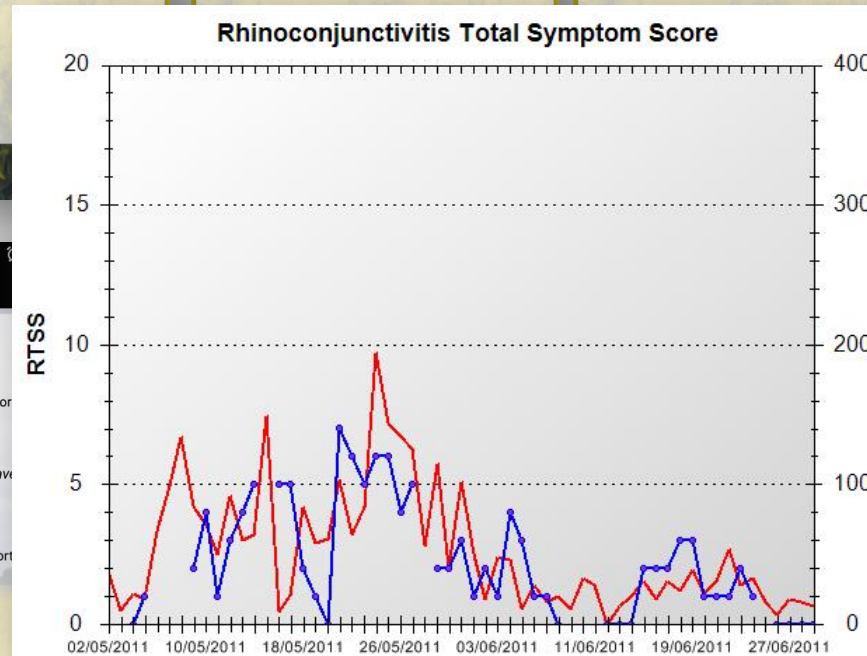
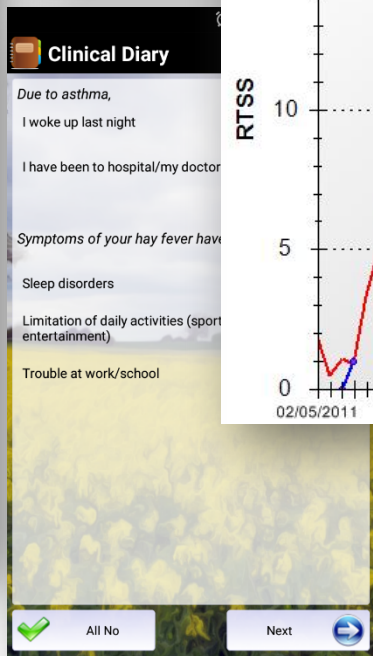
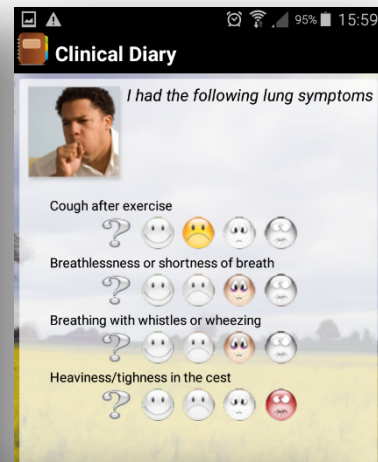
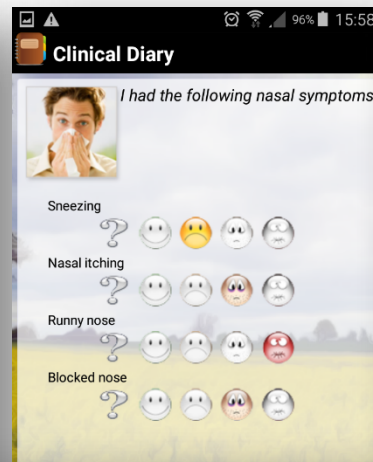
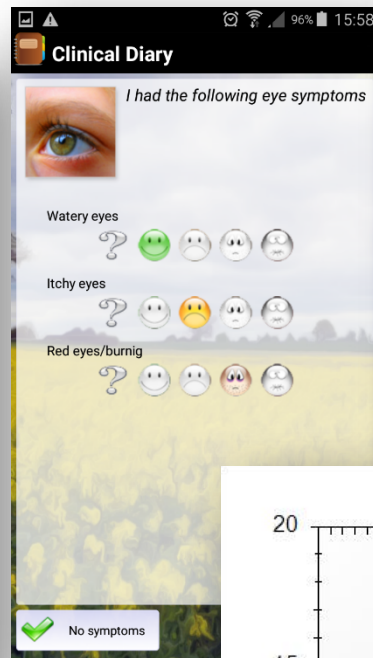
## CRD nelle allergie respiratorie





.... Ma

a volte la diagnostica molecolare  
da sola non è sufficiente



test:  ND **Prestazione:**

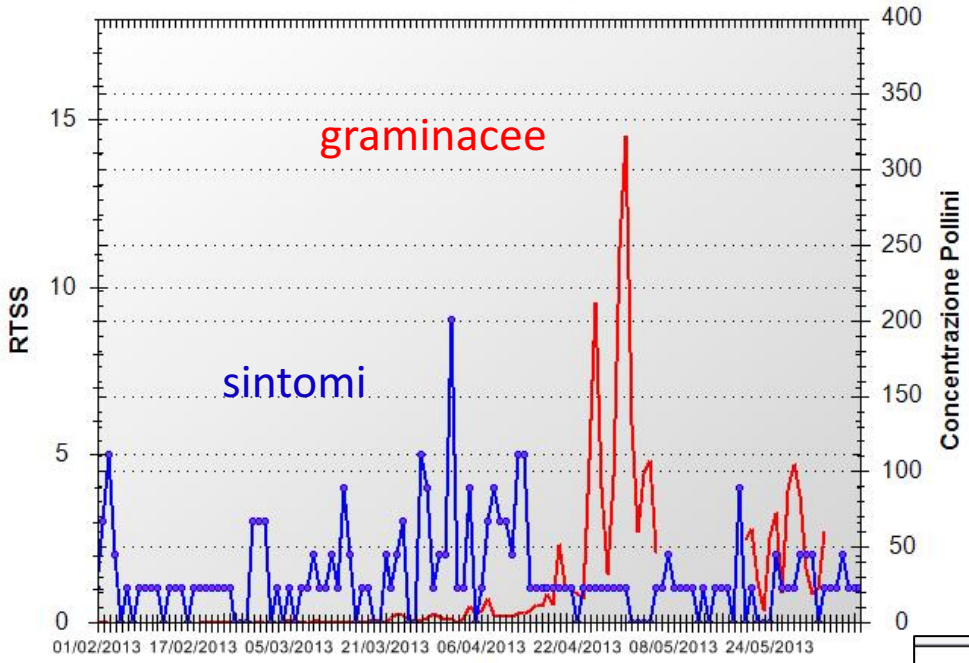
5,00 mm Controllo negativo 0,00 mm Eseguito da:

Allergene	Valore (mm)	Risultato	Skin index
Parietaria Judaica	12	++++	2,4
Graminacee Mix	11,5	++++	2,3
Dermatophagoides farinae	11	++++	2,2
Forfora di cane	7	+++	1,4
Epitelio di gatto	6,5	+++	1,3
Cupressus sempervirens	5,5	+++	1,1
Cynodon dactylon	5	+++	1,0
Olea europea	3	+	0,6
Blatella Germanica	3	+	0,6
Betula verrucosa (pendula)	0	NEG	0,0

3.484,00 KU/L Metodica:

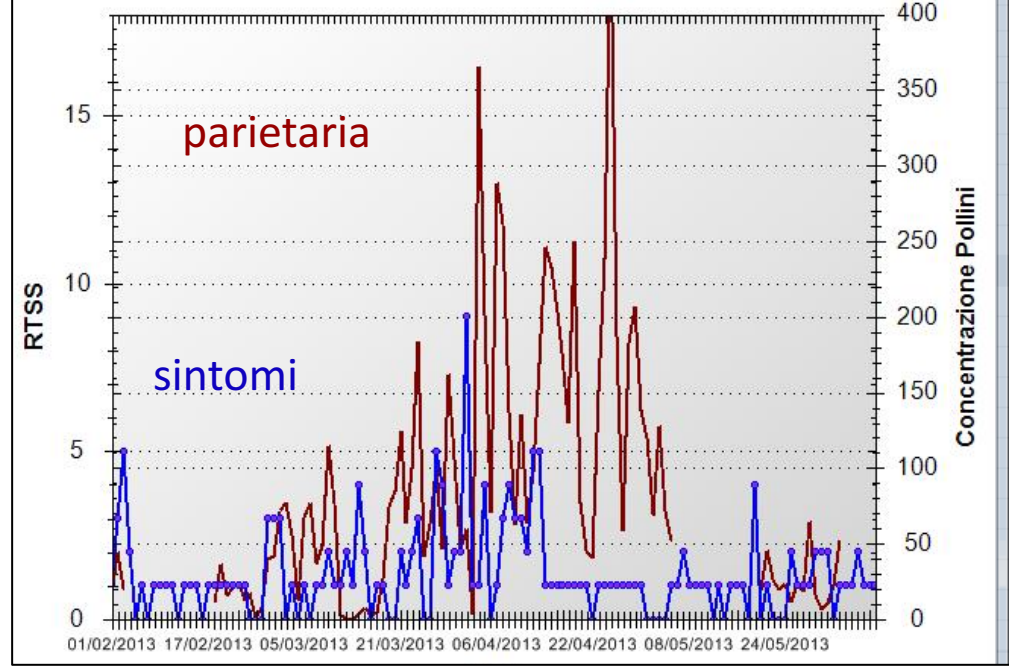
Allergene	KU/L
rPru p 3	0,11
Coda di topo	15,00
rPhl p 1	12,90
rPhl p 2	2,51
nPhl p 4	10,60
rPhl p 5b	0,01
rPhl p 6	0,12
rPhl p 11	0,33
Ulivo	1,46
Cipresso dell'Arizona	3,24
nCup a 1	7,79
Lanciuola	1,48
rPhl p 7	0,10
rPhl p 12	0,19
rBet v 1	0,12
nOle e 1	1,50
Parietaria judaica	139,00
rPar j 2	148,00

Rhinoconjunctivitis Total Symptom Score



ITS solo per parietaria

Rhinoconjunctivitis Total Symptom Score



B. G. 45 aa

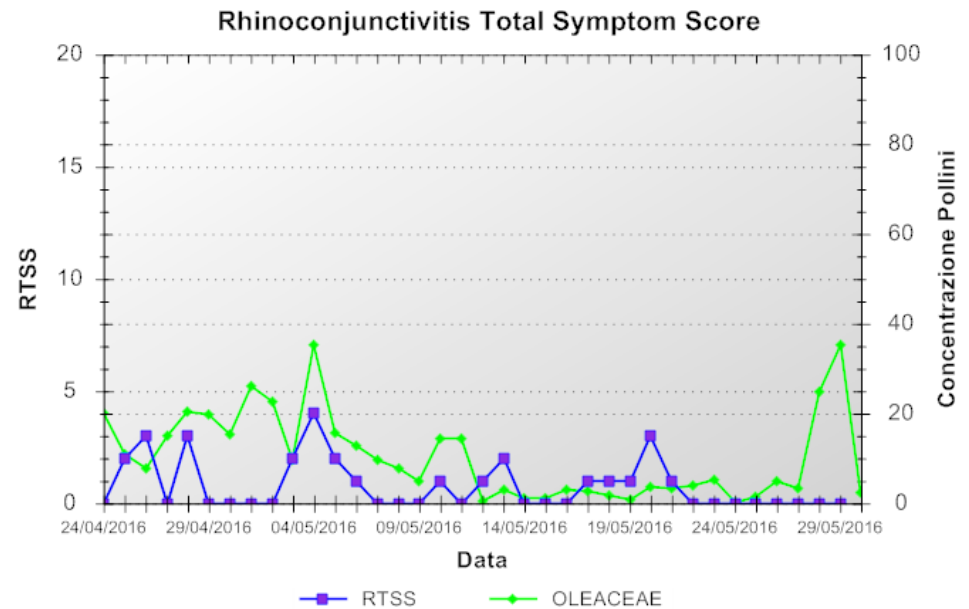
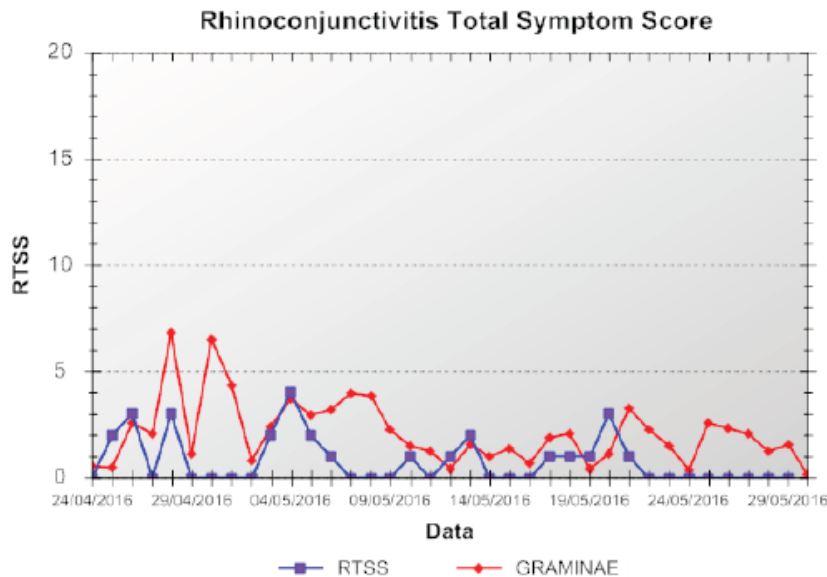
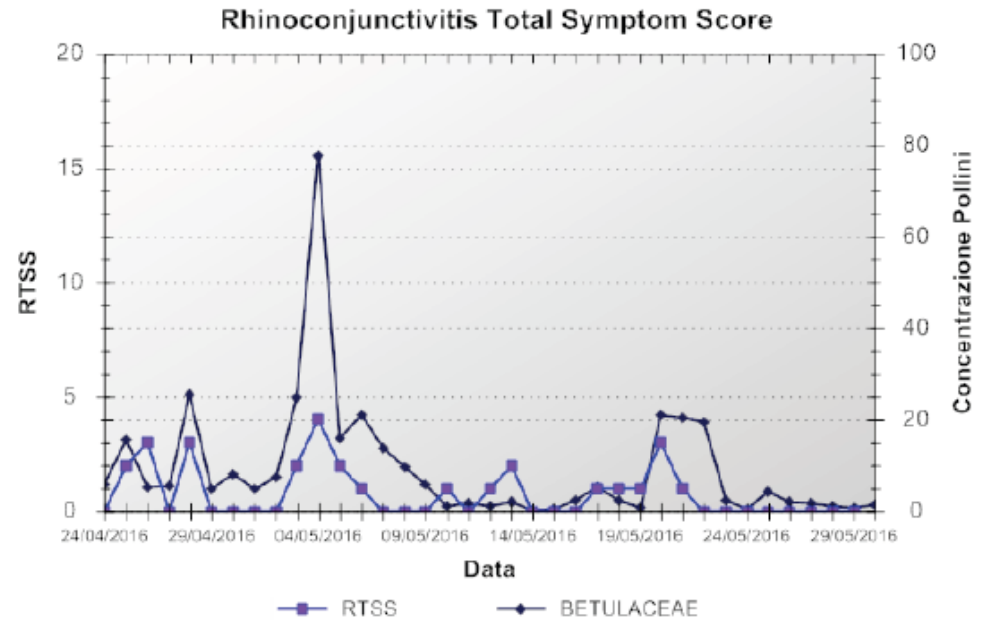
Sintomi marzo-maggio

Bet v 1 POS

Ole e 1 POS

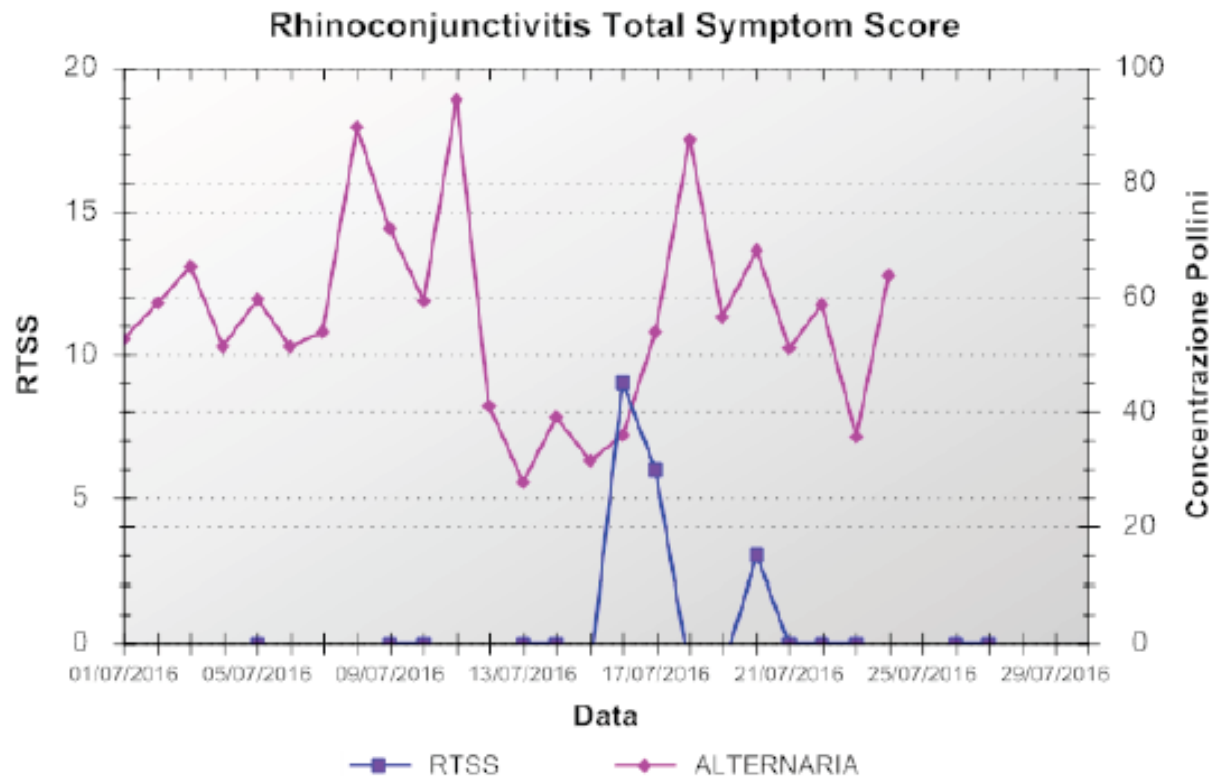
Phl p 1 POS

Phl p 5 POS

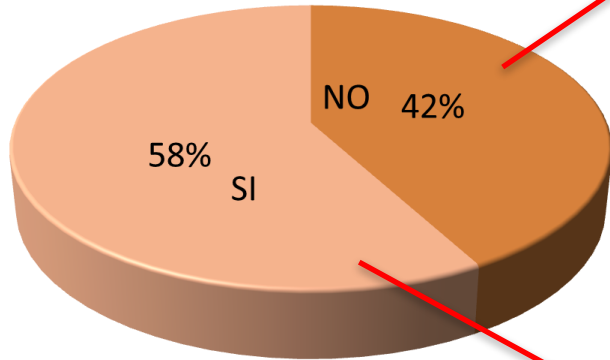


S.L. 42 aa

Già nota per ocuorinite primaverile con ipersensibilizzazioni a Graminaceae e Betulaceae. Nel 2015 riferisce rinite anche durante il periodo estivo. I test evidenziano nuova sensibilizzazione all'Alternaria alternata (Alt a 1 POS)

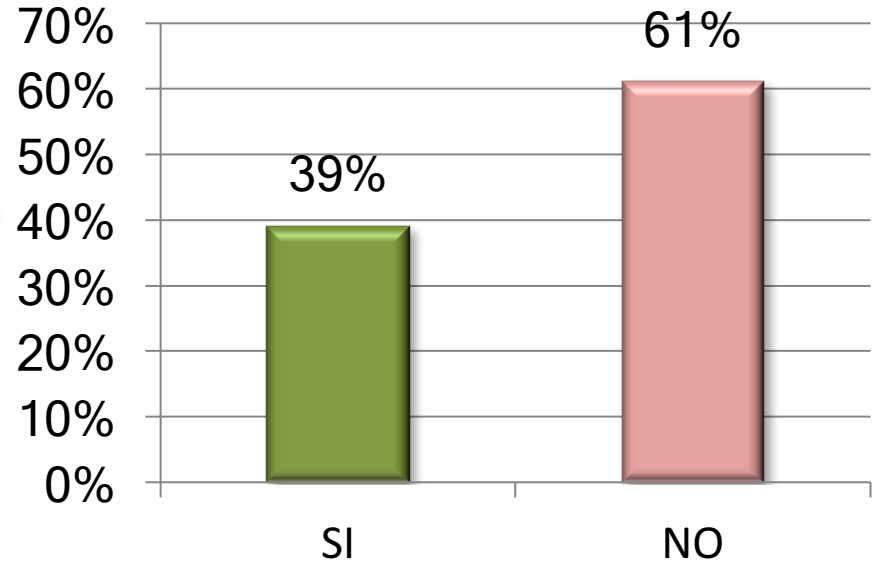


# Prescrizione ITS

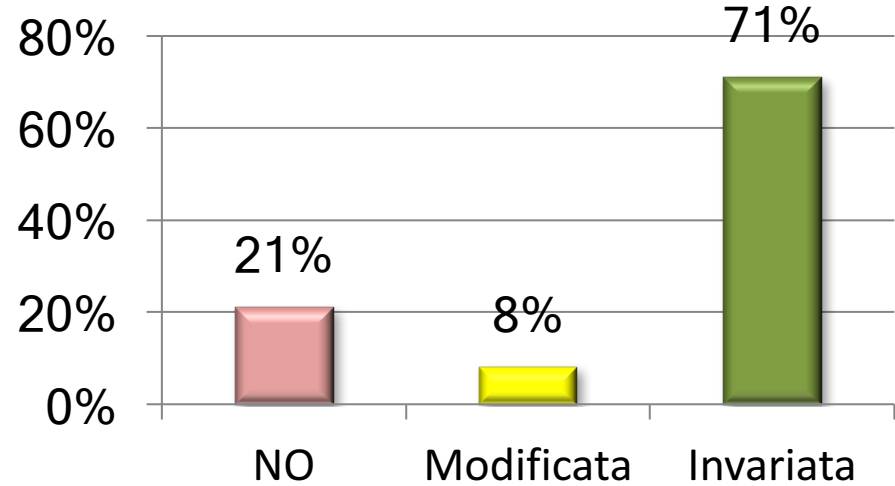


Modifica della prescrizione della ITS dopo analisi @M

# Prescrizione



# Prescrizione



# MONITORAGGIO DELL'EFFICACIA DELL'ITS



Paziente selezionato: **Giulia**

Rilevamento: Dal 22/05/2012 al 30/06/2012 (G)

- Raw Data
- Riassunto Diario
- Farmaci
- Effetti collaterali
- RCA Score**
- ASTHMA SCORE
- Grafico Sintomi
- Mapa

Tipologia curva:

RTSS

Periodo

Data inizio: 22/05/2012

Data fine: 29/06/2012

Concentrazione pollini

Comune

Roma

Polline

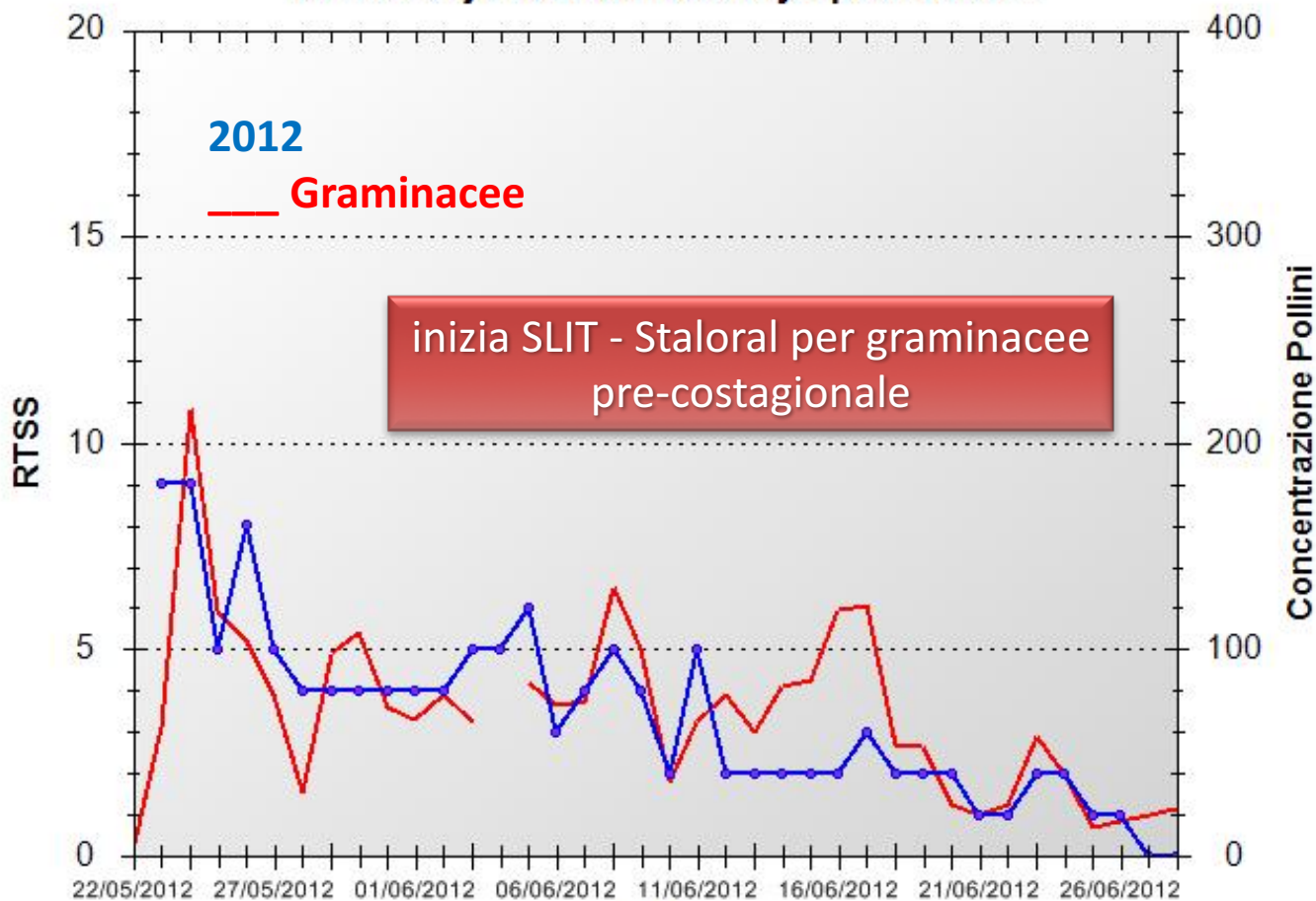
Pulisci

- ACERACEAE
- ALTERNARIA
- BETULACEAE
- CHENO/AMARANTH
- CORYLACEAE
- Cupressaceae/Taxa
- GRAMINAE
- MYRTACEAE
- OLEACEAE
- Parietaria

Aggiorna

Scarica dati

### Rhinoconjunctivitis Total Symptom Score



Chiudi

Paziente selezionato:                      **Giulia**

Rilevamento: Dal 01/04/2013 al 30/05/2013 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi   Mappa

Tipologia curva:

RTSS ?

Periodo

Data inizio: 01/04/2013

Data fine: 30/05/2013

Concentrazione pollini

Comune

Roma

Polline

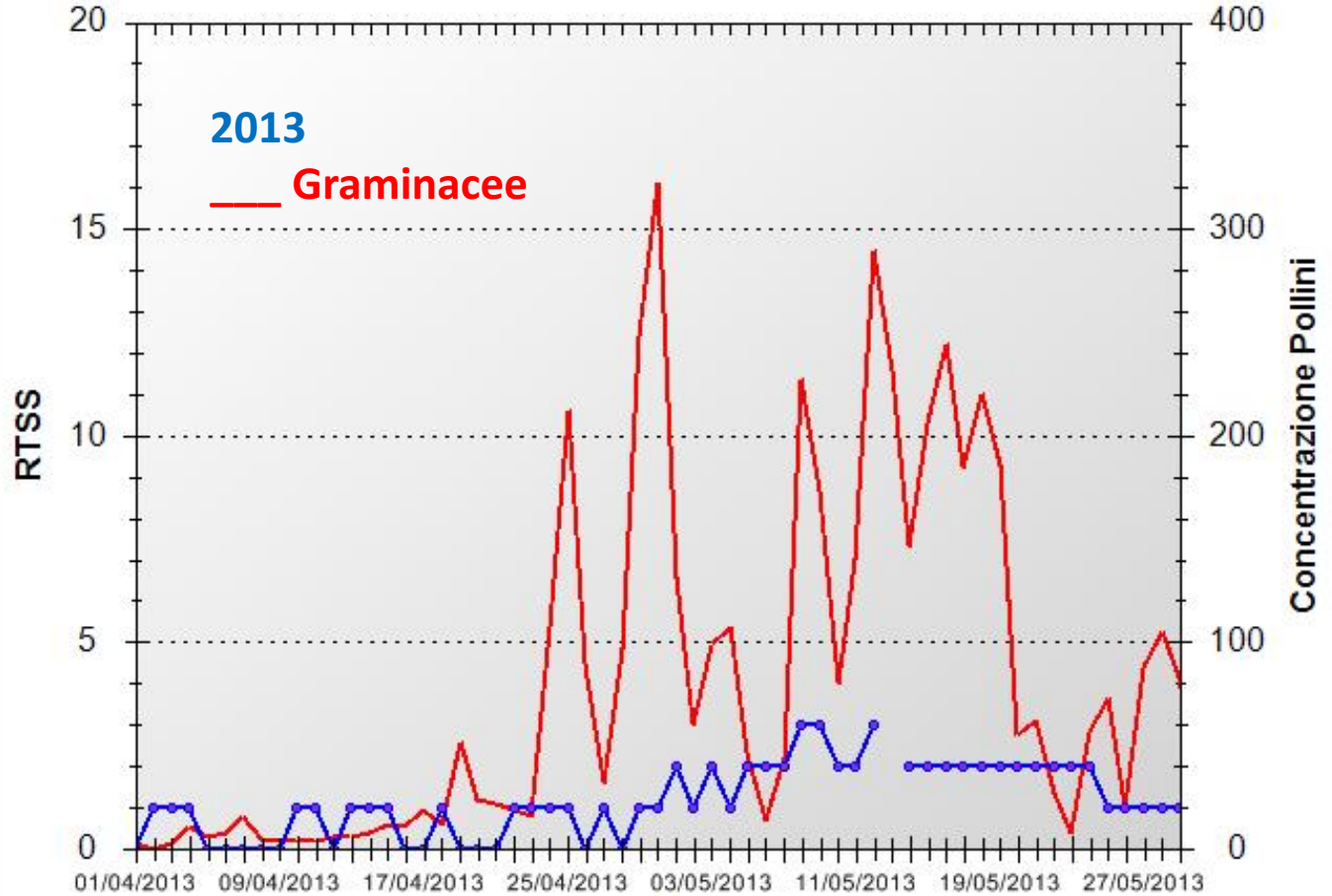
Pulisci

- ACERACEAE
- ALTERNARIA
- BETULACEAE
- CHENO/AMARANTH
- CORYLACEAE
- Cupressaceae/Taxa
- GRAMINAE
- MYRTACEAE
- OLEACEAE
- Parietaria

Aggiorna

Scarica dati

### Rhinoconjunctivitis Total Symptom Score



Chiudi

Paziente selezionato:                      Giulia

Rilevamento: Dal 01/04/2013 al 30/05/2013 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi   Mappa

Tipologia curva:

AdSS ?

Periodo

Data inizio: 01/04/2013

Data fine: 30/05/2013

Concentrazione pollini

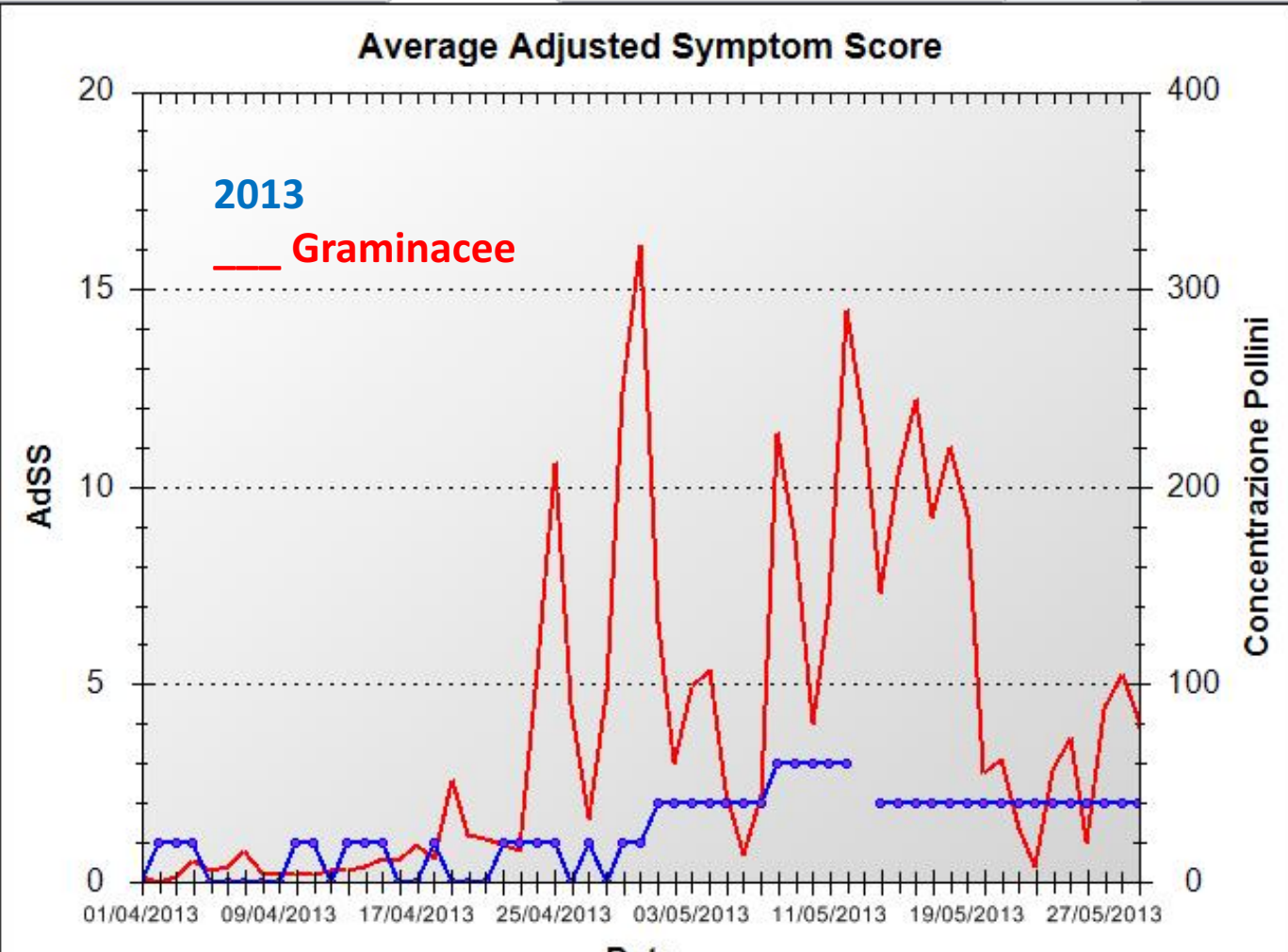
Comune  
Roma

Polline Pulisci

- ACERACEAE
- ALTERNARIA
- ▷  BETULACEAE
- CHENO/AMARANTH
- ▷  CORYLACEAE
- Cupressaceae/Taxa
- ▷  GRAMINAE
- MYRTACEAE
- ▷  OLEACEAE
- Parietaria

Aggiorna

Scarica dati



Chiudi

Paziente selezionato:                      Giulia

Rilevamento: Dal 03/04/2014 al 30/06/2014 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi   Mappa

Tipologia curva:

RTSS ?

Periodo

Data inizio: 03/04/2014

Data fine: 30/06/2014

Concentrazione pollini

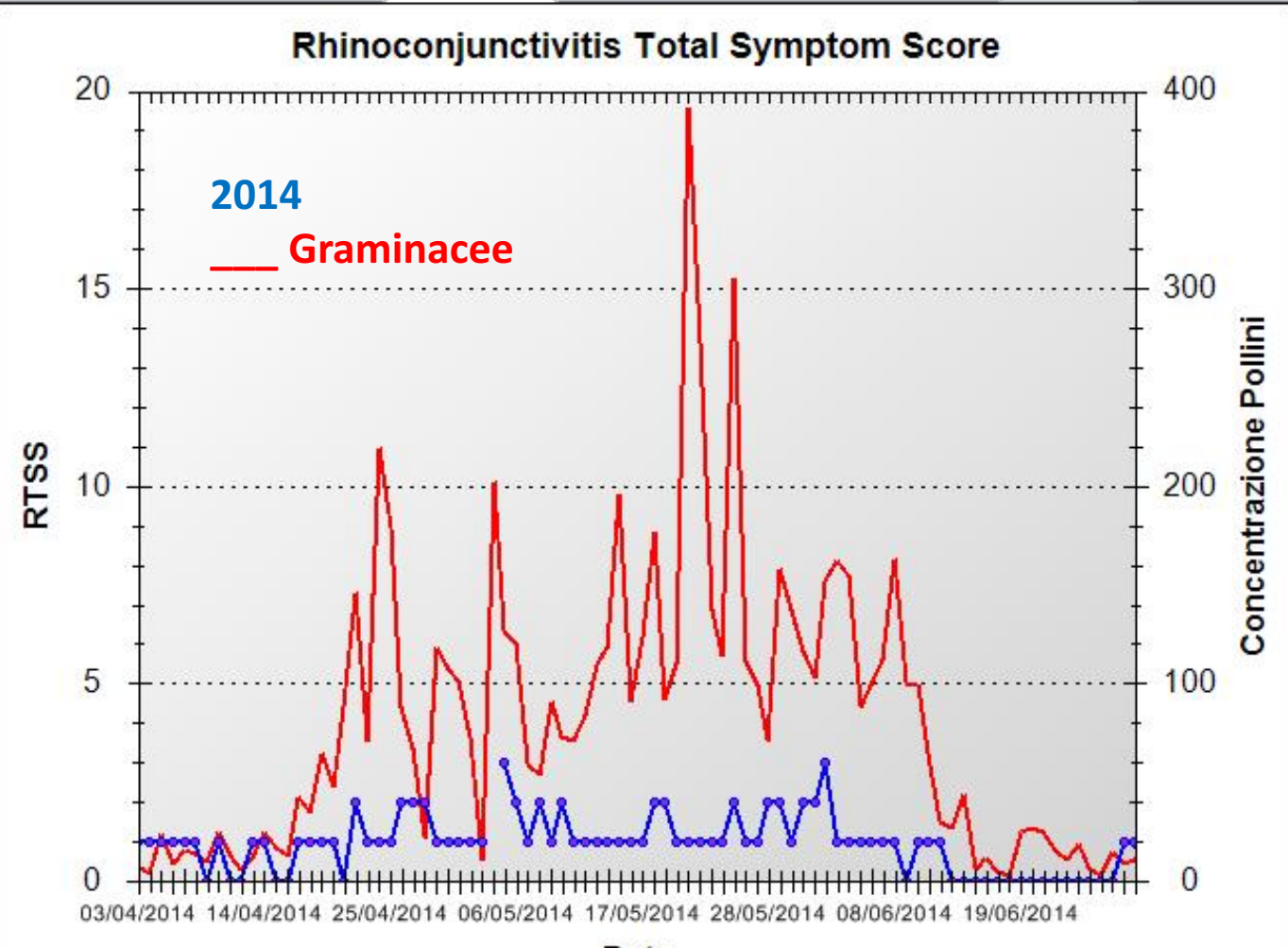
Comune  
Roma

Polline Pulisci

- ACERACEAE
- ALTERNARIA
- ▷  BETULACEAE
- CHENO/AMARANTH
- ▷  CORYLACEAE
- Cupressaceae/Taxa
- ▷  GRAMINAE
- MYRTACEAE
- ▷  OLEACEAE
- Parietaria

Aggiorna

Scarica dati



Chiudi

Paziente selezionato:                      Giulia

Rilevamento: Dal 03/04/2014 al 30/06/2014 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi   Mappa

Tipologia curva:

AdSS ?

Periodo

Data inizio: 03/04/2014

Data fine: 30/06/2014

Concentrazione pollini

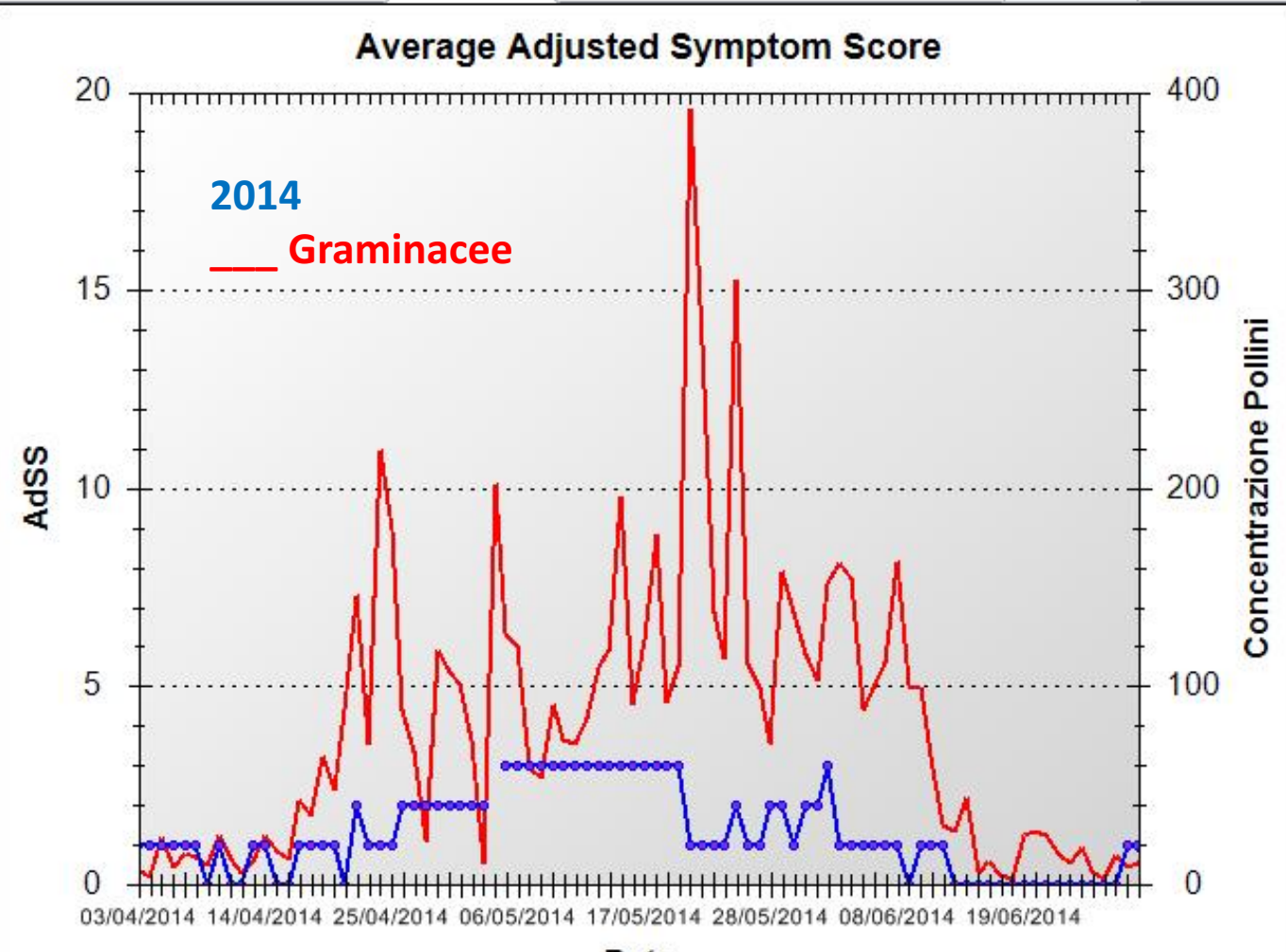
Comune  
Roma

Polline Pulisci

- ACERACEAE
- ALTERNARIA
- ▷  BETULACEAE
- CHENO/AMARANTH
- ▷  CORYLACEAE
- Cupressaceae/Taxa
- ▷  GRAMINAE
- MYRTACEAE
- ▷  OLEACEAE
- Parietaria

Aggiorna

Scarica dati



Chiudi

Paziente selezionato:                      giulia

Rilevamento: Dal 01/04/2015 al 31/05/2015 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi

Tipologia curva:

RTSS ?

Periodo

Data inizio: 01/04/2015

Data fine: 31/05/2015

Concentrazione pollini

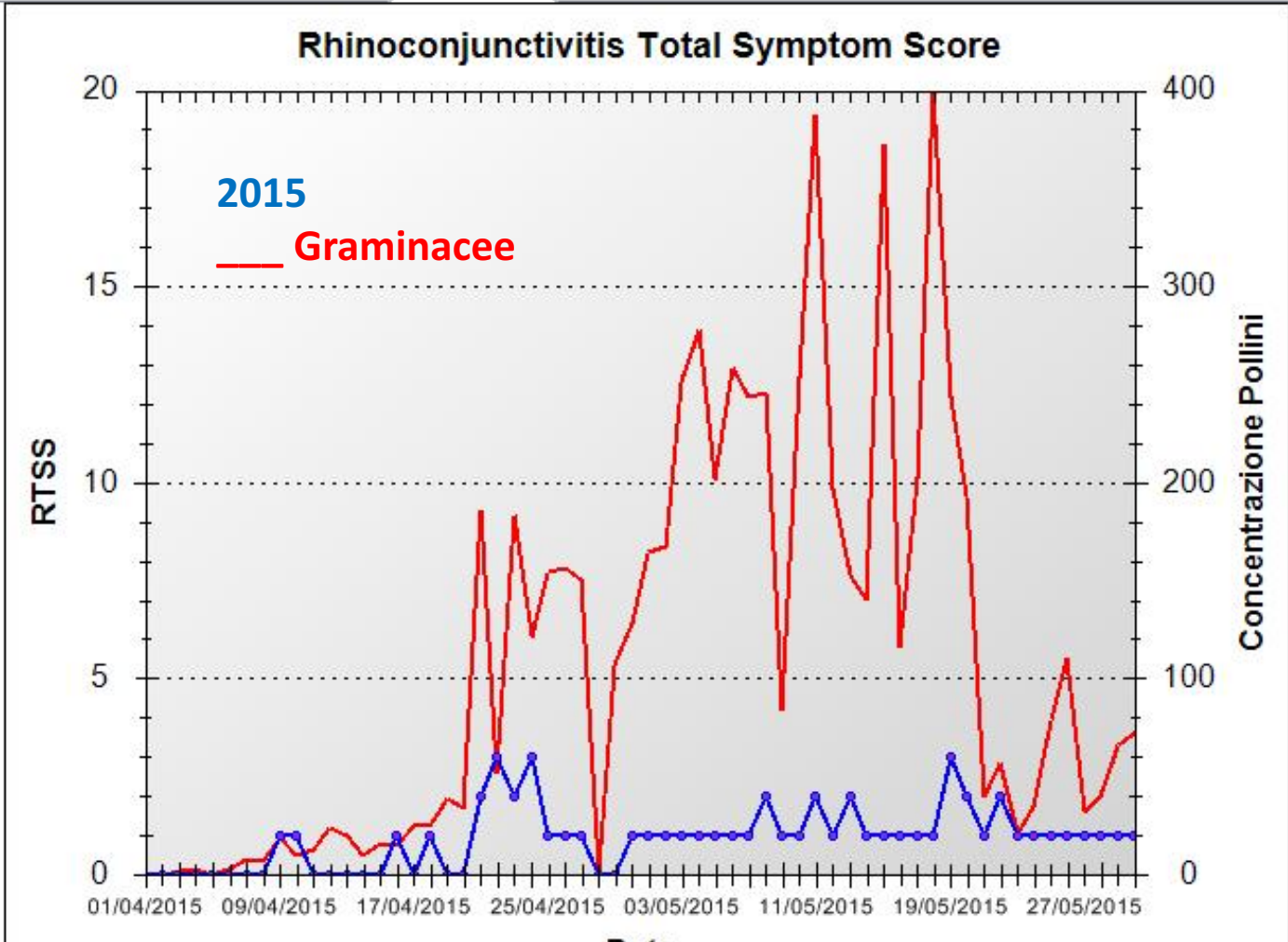
Comune  
Roma

Polline Pulisci

- ACERACEAE
- ALTERNARIA
- BETULACEAE
- CHENO/AMARANTH
- CORYLACEAE
- Cupressaceae/Taxa
- GRAMINAE
- MYRTACEAE
- OLEACEAE
- Parietaria

Aggiorna

Scarica dati



Chiudi

Paziente selezionato:                      giulia

Rilevamento: Dal 01/04/2015 al 31/05/2015 (G)

Raw Data   Riassunto Diario   Farmaci   Effetti collaterali   **RCA Score**   ASTHMA SCORE   Grafico Sintomi

Tipologia curva:

AdSS ?

Periodo

Data inizio: 01/04/2015

Data fine: 31/05/2015

Concentrazione pollini

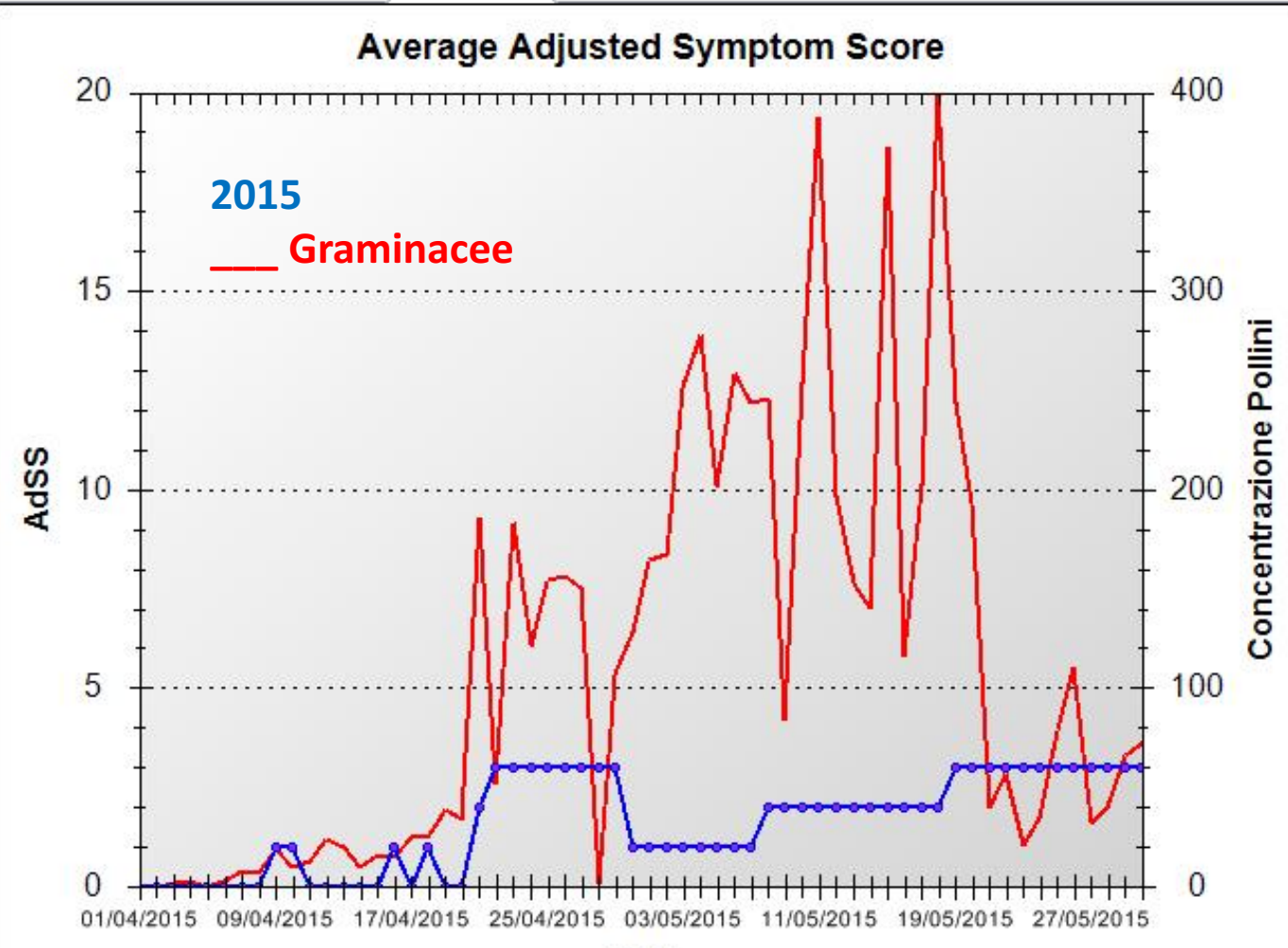
Comune  
Roma

Polline Pulisci

- ACERACEAE
- ALTERNARIA
- ▶  BETULACEAE
- CHENO/AMARANTH
- ▶  CORYLACEAE
- Cupressaceae/Taxa
- ▶  GRAMINAE
- MYRTACEAE
- ▶  OLEACEAE
- Parietaria

Aggiorna

Scarica dati



Chiudi





REVIEW

Open Access

# Allergen Immunotherapy (AIT): a prototype of Precision Medicine



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

Precise information and biomarkers provided by systems medicine and network medicine will address the discovery of Allergen immunotherapy biomarkers for (i) identification of the causes, (ii) stratification of eligible patients for AIT and (iii) the assessment of AIT efficacy.

This area of **medical technology** is evolving rapidly and, **complemented by e e-health** will change the way we practice medicine. It will help to monitor patients' disease control and data for (i) patient stratification, (ii) clinical trials, (iii) monitoring the efficacy and safety of targeted therapies which are critical for reaching an appropriate reimbursement. **Biomarkers associated with e-health combined with a clinical decision support system (CDSS) will change the scope of Allergen immunotherapy.**