



HAL
open science

Personalized medicine for allergy treatment: Allergen immunotherapy still a unique and unmatched model

Cristoforo Incorvaia, Mona Al-ahmad, Ignacio Ansotegui, Stefania Arasi, Claus Bachert, Catherine Bos, Jean Bousquet, Andrzej Bozek, Davide Caimmi, Moises Calderón, et al.

► To cite this version:

Cristoforo Incorvaia, Mona Al-ahmad, Ignacio Ansotegui, Stefania Arasi, Claus Bachert, et al.. Personalized medicine for allergy treatment: Allergen immunotherapy still a unique and unmatched model. *Allergy*, 2021, 76 (4), pp.1041-1052. 10.1111/all.14575 . hal-03613250

HAL Id: hal-03613250

<https://hal.science/hal-03613250>

Submitted on 23 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Personalized Medicine for allergy treatment: allergen immunotherapy still a unique and unmatched model

Journal:	<i>Allergy</i>
Manuscript ID	ALL-2020-00739.R2
Wiley - Manuscript type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Incorvaia, Cristoforo; ICP Hospital, Allergy/Pulmonary rehabilitation Al-Ahmad , Mona; Kuwait University, Microbiology Department Ansotegui, Ignacio J; Hospital Quironsalud Bizkaia, Allergy & Immunology Arasi, Stefania; Bambino Gesu Pediatric Hospital, Department of Allergy Bachert, Claus; Upper Airway Research Laboratory (URL),, Department of Oto-Rhino-Laryngology, University Hospital Ghent,; Division of ENT diseases, CLINTEC, Karolinska Institute,, Bos, Catherine; Stallergenes Greer, Medical Affairs Department Bousquet, Jean; Université Versailles, St-Quentin-en-Yvelines, 9. MACVIA-LR, Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc Roussillon, European Innovation Partnership on Active and Healthy Ageing Reference Site, and INSERM, VIMA: Ageing and Chronic Diseases, Epidemiological and Public Health Approaches, U1168, Paris, and UVSQ, UMR-S 1168 Bozek, Andrzej; Silesian Medical University, Katowice, Dept. of Internal Medicine, Dermatology and Allergology; Caimmi, Davide; Department of respiratory medicine and allergy, Hôpital Arnaud de Villeneuve, CHU Montpellier, Univ Montpellier, Allergy Unit; Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Calderon, Moises; Royal Brompton Hospital, Upper Respiratory Medicine Casale, Thomas; University of South Florida, Division of Allergy/Immunology Custovic, A; The University of Manchester, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair De Blay, Frédéric; University Hospital Strasbourg, 2Department of Chest Diseases Demoly, Pascal; University Hospital of Montpellier, Allergy Devillier, Philippe; Université Versailles Saint-Quentin-en-Yvelines, UPRES EA220; Hopital Foch, Department of Airway diseases Didier, Alain; CHU Toulouse, Respiratory disease Fiocchi, Alessandro; Bambino Gesu Pediatric Hospital, Allergy Fox, Adam; King's College London, Division of Asthma Allergy and Lung Biology Gevaert, Philippe; Ghent University, Otorhinolaryngology Gomez, Maximiliano; Hospital San Bernardo Salta, Allergy & Asthma Unit Heffler, Enrico; Humanitas University, Biomedical Sciences</p>

	<p>Ilina, Natalya; Novosibirsk State University, Medical Department Irani, Carla; Hotel Dieu de France hospital, Internal Medicine/Allergy and Immunology Section; Jutel, Marek; Wroclaw Medical University, Department of Clinical Immunology; ALL-MED Medical Research Institute,, Clinical Immunology Karagiannis, Efstrathios; Stallergenes GmbH, Medical Director Klimek, Ludger; Zentrum für Rhinologie und Allergologie, Studienzentrum Kuna, Piotr; University Clinical Hospital No 1 N Barlicki in Lodz, Division of Internal Medicine, Asthma and Allergy O'Hehir, Robyn; The Alfred Hospital, Department of Allergy, Immunology and Respiratory Medicine Kurbacheva, Oxana; Institute of Immunology FMBA, Department of Allergy and Immunotherapy Matricardi, Paolo; Charité University Medical Center, Paediatric Pneumology and Immunology Morais-Almeida, Mário; CUF-Descobertas Hospital, Immunoallergy Mosges, Ralph; Universität zu Köln, Institute of Medical Statistics, Informatics and Epidemiology (IMSIE Novak, Natalija; University of Bonn, Department of Dermatology and Allergy Okamoto, Yoshitaka; Chiba University, Graduate School of Medicine, Otolaryngology Panzner, Petr; Medical School in Plzen, Immunology and Allergology Papadopoulos, Nikolaos; Second Pediatric Clinic, Allergy Department; The University of Manchester, Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's Hospital Park, Hae-Sim; Ajou University School of Medicine, Allergy & Clinical Immunology; Passalacqua, Giovanni; Allergy & Respiratory Diseases - University of Genoa, Dept of Internal Medicine Pawankar, Ruby; Nippon Medical School, Div of Allergy, Dept of Pediatrics Pfaar, Oliver; University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany., Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy Schmid-Grendelmeier, Peter; University of Zurich Hospital, Dept. of Dermatology Scurati, Silvia; Stallergenes Greer, Medical Affairs Department Tortajada-Girbés , Miguel; University of Valencia, Pediatric Pulmonology and Allergy Unit, Department of Pediatrics Vidal, Carmen; Complejo Hospitalario Universitario Santiago, Allergy Virchow, Christian; University of Rostock, Department of Pneumology/Intensive Care Medicine Wahn, Ulrich; Charité Virchow-Klinikum, , Department of Paediatric Pulmonology and Immunology Worm, Margitta; Charité - Universitätsmedizin Berlin, Dpt. of Dermatology and Allergy Zieglmayer, Ursula; ENT- University Clinic, Allergy; Canonica, Giorgio Walter; Humanitas Clinical and Research Center, Personalized Medicine, Asthma and Allergy ; Humanitas University, Department of Biomedical Sciences</p>
Keywords:	allergy treatment, immunotherapy clinical, rhinitis

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

1
2
3 Dear Editor,

4
5 thank you very much for your provisional acceptance of our manuscript.

6
7 We here respond point-by-point to your comments:

8
9
10
11 Editor's comments:

12
13 1. Please communicate with our graphics editor to change the graphics to our journal's style.

14
15
16
17
18 RESPONSE: We will contact Anna Głobińska just after having completed this submission

19
20
21
22 2. Convert the below part to a text box.

23
24
25
26 The clinician should then evaluate:

27
28 The route of administration: presently SCIT and SLIT for aeroallergens, considering
29
30 evidences and patient's needs/preference

31
32 The AIT product to be chosen as recommended by WAO83 and EAACI84 among the
33
34 products supported by evidences.

35
36 SCIT: different schedules upon the products (i.e. depot or aqueous)

37
38 SLIT: preference for drops or tablet, both considering evidences and patient's
39
40 needs/preference

41
42 Dosages and schedules: continuous or pre-seasonal; long or short term.

43
44 Most of the above can be influenced by costs and/or reimbursements.

45
46
47
48
49 RESPONSE: We followed your suggestion and converted the text into a text-box

50
51
52
53 3. Make an algorithm graph for molecular diagnosis.

54
55
56
57
58 RESPONSE: We thank the Editor for this suggestion, but we do believe that this is out of scope of our article
59
60 and moreover almost impossible to produce a new graph and get the approval of it from all the Authors in

1
2
3 the due time (72 hours as requested). Therefore, we did not added such graph into this new version of the
4 manuscript, hoping that you will anyway considering the article suitable for publication.
5
6
7

8
9 COMMENTS FOR THE AUTHOR(S)

10
11 In this revision authors made significant changes and improvements in the manuscript and they included
12 some missing and most recent data to increase the quality of the paper. Im satisfied with the answers and
13 replies to my questions.
14
15
16

17
18 RESPONSE: We thank the Reviewer for his/her appreciation.
19
20

21
22 Best regards,

23
24 Enrico Heffler (on behalf of all my co-Authors)
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Personalized Medicine for allergy treatment: allergen immunotherapy** 2 **still a unique and unmatched model.**

3
4 Incorvaia Cristoforo¹, Al-Ahmad Mona^{2,3}, Ansotegui Ignacio⁴, Arasi Stefania⁵, Bachert
5 Claus^{6,7}, Bos Catherine⁸, Bousquet Jean⁹, Bozek Andrzej¹⁰, Caimmi Davide¹¹, Calderón
6 Moises¹², Casale Thomas¹³, Custovic Adnan¹⁴, De Blay Frédéric¹⁵, Demoly Pascal^{11,16},
7 Devillier Philippe¹⁷, Didier Alain¹⁸, Fiocchi Alessandro⁵, Fox Adam¹⁹, Gevaert Philippe⁶,
8 Gomez Maximiliano²⁰, Heffler Enrico^{21,22}, Iliina Natalia²³, Irani Carla²⁴, Jutel Marek²⁵,
9 Karagiannis Efstrathios⁸, Klimek Ludger²⁶, Kuna Piotr²⁷, O’Hehir Robin²⁸, Kurbacheva
10 Oxana²⁹, Matricardi Paolo Maria³⁰, Morais de Almeida Mario^{31,32}, Mosges Ralph^{33,34},
11 Novak Natalija³⁵, Okamoto Yoshitaka³⁶, Panzner Petr³⁷, Papadopoulos Nikolaos^{38,39}, Park
12 Hae-Sim⁴⁰, Passalacqua Giovanni⁴¹, Pawankar Ruby⁴², Pfaar Oliver⁴³, Schmid-
13 Grendelmeier Peter⁴⁴, Scurati Silvia⁸, Tortajada-Girbés Miguel^{45,46}, Vidal Carmen⁴⁷,
14 Virchow Christian⁴⁸, Wahn Ulrich³⁰, Worm Margitta³⁰, Ziegelmayer Petra⁴⁹, Canonica
15 Giorgio Walter^{21,22}.

17 **Affiliations**

- 18 1. Cardiac/Pulmonary Rehabilitation, ASST Pini/CTO, Milan, Italy
- 19 2. Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait
- 20 3. Drug Allergy Unit, Department of Allergy, Al-Rashed Allergy Center, Kuwait
- 21 4. Hospital Quirónsalud Bizkaia, Bilbao, Spain
- 22 5. Department of Allergy, Bambino Gesù' Childrens' Hospital IRCCS, Rome, Italy
- 23 6. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent,
24 Belgium.
- 25 7. Karolinska Institutet, Stockholm; Department of ENT Diseases, Karolinska University
26 Hospital, Stockholm.
- 27 8. Stallergenes Greer Medical Affairs Department, Antony, France
- 28 9. University Hospital Montpellier, France - MACVIA-France, Montpellier, France
- 29 10. Clinical Department of Internal Disease, Dermatology and Allergology, Medical
30 University of Silesia, Katowice , Poland
- 31 11. Department of Pulmonology and Addictology, Arnaud de Villeneuve Hospital,
32 Montpellier University, Montpellier, France
- 33 12. Imperial College London - National Heart and Lung Institute, Royal Brompton Hospital
34 NHS, London, United-Kingdom

- 1
- 2
- 3 35 13. Division of Allergy/Immunology, University of South Florida, Tampa, FL United-States
- 4
- 5 36 14. Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair,
- 6 37 University of Manchester and University Hospital of South Manchester, Manchester,
- 7 38 United-Kingdom
- 8
- 9 39 15. Allergy Division, Chest Diseases Department, Strasbourg University Hospital,
- 10 40 Strasbourg, France
- 11
- 12 41 16. Sorbonne Université, UMR-S 1136 INSERM, IPLESP, EPAR Team, Paris, France
- 13
- 14 42 17. Laboratoire de Recherche en Pharmacologie Respiratoire, Pôle des Maladies des
- 15 43 Voies Respiratoires, Hôpital Foch, Université Paris-Saclay, Suresnes, France
- 16
- 17 44 18. Respiratory Disease Dept, Larrey Hospital, University Hospital of Toulouse, Paul
- 18 45 Sabatier University, Toulouse, France
- 19
- 20 46 19. Department of Paediatric Allergy, Guy's & St Thomas' Hospitals NHS Foundation Trust,
- 21 47 London, United Kingdom
- 22
- 23 48 20. Allergy & Asthma Unit, Hospital San Bernardo Salta, Salta, Argentina
- 24
- 25 49 21. Personalized Medicine, Asthma & Allergy - Humanitas Clinical and Research Center
- 26 50 IRCCS, Rozzano (MI), Italy
- 27
- 28 51 22. Department of Biomedical Science, Humanitas University, Pieve Emanuele (MI), Italy.
- 29
- 30 52 23. Federal Institute of Immunology of Russia, Russia
- 31
- 32 53 24. Department of Internal Medicine and Clinical Immunology, Hotel Dieu de France
- 33 54 hospital. Faculty of Medicine, Saint Joseph University, Beirut, Lebanon.
- 34
- 35 55 25. Department of Clinical Immunology, Wrocław Medical University, Wrocław, Poland.
- 36
- 37 56 26. Center for Rhinology and Allergology, Wiesbaden, Germany
- 38
- 39 57 27. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical
- 40 58 University of Lodz, Lodz, Poland
- 41
- 42 59 28. Alfred Hospital and Monash University, Melbourne, Australia
- 43
- 44 60 29. National Research Center - Institute of Immunology Federal Medical-Biological Agency
- 45 61 of Russia, Moscow, Russia
- 46
- 47 62 30. Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine,
- 48 63 Charité - University Medicine Berlin, Berlin, Germany
- 49
- 50 64 31. Immunoallergy Department of CUF-Descobertas Hospital, Lisbon Portugal
- 51
- 52 65 32. CUF-Infante Santo Hospital, Lisbon, Portugal
- 53
- 54 66 33. Faculty of Medicine, Institute of Medical Statistics and Computational Biology,
- 55 67 University of Cologne, Cologne, Germany
- 56
- 57 68 34. CRI - Clinical Research International Ltd., Cologne, Germany
- 58
- 59
- 60

1

2

3 69 35. Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany

4 70 36. Department of Otorhinolaryngology, Chiba University Hospital, Chiba, Japan.

5 71 37. Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles
6 72 University in Prague, Pilsen, Czech Republic

7 73 38. Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's
8 74 Hospital, University of Manchester, Manchester, United-Kingdom

9 75 39. Allergy Department, 2nd Pediatric Clinic, Athens General Children's Hospital "P&A
10 76 Kyriakou", University of Athens, Athens, Greece

11 77 40. Department of Allergy and Clinical Immunology, Ajou University School of Medicine,
12 78 Suwon, South Korea

13 79 41. Allergy and Respiratory Diseases, Ospedale Policlinico San Martino -University of
14 80 Genoa, Genoa, Italy.

15 81 42. Department of Pediatrics, Nippon Medical School, Tokyo, Japan

16 82 43. Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and
17 83 Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

18 84 44. Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland

19 85 45. Pediatric Pulmonology and Allergy Unit, Department of Pediatrics, Dr. Peset University
20 86 Hospital, Valencia, Spain,

21 87 46. Department of Pediatrics, Obstetrics and Gynecology. University of Valencia, Valencia,
22 88 Spain., IVI Foundation, Valencia, Spain

23 89 47. Allergy Service, Complejo Hospitalario Universitario de Santiago, Santiago de
24 90 Compostela

25 91 48. Department of Pneumology/Intensive Care Medicine, University of Rostock, Germany

26 92 49. Vienna Challenge Chamber, Vienna, Austria

27 93

28 94 **Corresponding author**

29 95 Enrico Heffler, Personalized Medicine, Asthma and Allergy, Humanitas University and
30 96 Research, Hospital ICH, Via Alessandro Manzoni 56, Rozzano, Milan 20089, Italy,
31 97 heffler.enrico@gmail.com

32 98

33 99

34 100

35 101

36 102

37 103

38 104

39 105

40 106

1
2
3 **Abstract**
4

5 100 The introduction of personalized medicine (PM) has been a milestone in the history of
6 101 medical therapy, because it has revolutionized the previous approach of treating the
7 102 disease with that of treating the patient. It is known today that diseases can occur in
8 103 different genetic variants, making specific treatments of proven efficacy necessary for a
9 104 given endotype. Allergic diseases are particularly suitable for PM, because they meet the
10 105 therapeutic success requirements, including a known molecular mechanism of the
11 106 disease, a diagnostic tool for such disease, and a treatment blocking the mechanism. The
12 107 stakes of PM in allergic patients are molecular diagnostics, to detect specific IgE to single
13 108 allergen molecules and to distinguish the causative molecules from those merely cross-
14 109 reactive, pursuit of patient's treatable traits addressing genetic, phenotypic and
15 110 psychosocial features, and omics, such as proteomics, epi-genomics, metabolomics and
16 111 breathomics, to forecast patient's responsiveness to therapies, to detect biomarker and
17 112 mediators, and verify the disease control. This new approach has already improved the
18 113 precision of allergy diagnosis and is likely to significantly increase, through the higher
19 114 performance achieved with the personalized treatment, the effectiveness of allergen
20 115 immunotherapy by enhancing its already known and unique characteristics of treatment
21 116 that acts on the causes.
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 118 **Key words:** allergen immunotherapy, personalized medicine, molecular diagnosis,
37 119 treatable traits, omics.
38
39
40

41 121 **Short title:** Allergen immunotherapy: a model of personalized medicine.
42
43 122
44
45 123
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **124 Introduction**

4
5 125 In its millennial history, medicine has had the primary aim of treating diseases. The
6
7 126 development in the 1800s of pharmaceutical therapy with synthetic drugs was a
8
9 127 breakthrough¹, but the concept that a given drug was suitable for treating a given disease,
10 128 regardless of the characteristics of the individual patient, have survived for a long time.
11
12 129 The conceptual framework of genotypes, endotypes and phenotypes² has provided crucial
13
14 130 tools to understand that the characteristics of the individual also affect the response to
15 131 drugs and paved the way to the new era of personalized (otherwise defined precision)
16
17 132 medicine. The new approach was first applied on oncology, concerning both diagnosis and
18
19 133 treatment³, but soon, with a significant boost from President Obama's announcement on
20
21 134 the great potential of personalized medicine⁴, many other fields of medicine gained its
22 135 benefits. As far as allergic and immune-mediated diseases are concerned, the introduction
23
24 136 of biologics to treat severe asthma provided a significant advance in personalized
25
26 137 treatment, through their ability to work on asthma according on molecular phenotypes
27 138 defined as high type 2 immunity asthma and low type 2 immunity asthma⁵. However,
28
29 139 allergen immunotherapy (AIT), a treatment for respiratory allergy first proposed in 1911
30
31 140 which in its long road has gone from empiricism to full scientific evidence⁶ can actually be
32
33 141 proposed as "a medical model aiming to deliver customized healthcare, with medical
34 142 decisions, practices, and/or products tailored to the individual patient"⁷. The primary
35
36 143 therapeutic goal of AIT include reducing the frequency and intensity of symptoms, the use
37
38 144 of rescue medications, and improving the allergy-related quality of life. There is very strong
39
40 145 evidence to show that AIT achieves these goals in patients with allergic rhinitis⁸.
41 146 Furthermore, in mite-induced asthma AIT is likely to enable a successful step-down in the
42
43 147 inhaled corticosteroid dose in patients graded as step 3 or 4 of GINA scale⁹. Here we will
44
45 148 analyze the factors underlying the characteristics of AIT as an optimal model for
46 149 personalized medicine.

47
48 150 **The birth of AIT and its embryonic properties as a personalized treatment.**

49
50 151 As hinted above, AIT was introduced more than one hundred years ago, when the
51
52 152 knowledge on allergic disease was very limited⁶. Still, the different role of AIT compared
53 153 with the drug therapy available at the time was apparent, because drugs were aimed at
54
55 154 treating the symptoms of allergic rhinitis, while AIT was aimed at treating the specific
56
57 155 allergy of single patients, thus introducing a concept now acknowledged as personalized
58 156 medicine. The first studies addressed "hay fever" induced by grass pollen. It is obvious
59
60 157 that the quality of the products in that time, which consisted of extracts obtained from the

1
2
3 158 allergenic source directly from the doctor, was hugely lower than the allergen extracts
4
5 159 used today, but the positive results obtained paved the way to an evolution finally resulting
6
7 160 in high quality products. Another definition that underlines how the AIT was yet, but
8
9 161 improperly, proposed as personalized for the patient is “Named Patient Product” (NPP),
10 162 i.e. specifically prepared for a given patient according to the results of allergy testing.
11
12 163 Nevertheless, NPPs were not a guarantee of clinical efficacy, because alongside products
13
14 164 with evidence of efficacy proven by placebo-controlled trials, others without such evidence
15 165 were equally admitted to the prescription. Moreover, extracts containing several allergens,
16
17 166 namely all the allergens giving positive results to allergy testing, were frequently used,
18
19 167 especially in the U.S.A, but they were found to be ineffective in a pivotal double-blind,
20
21 168 placebo-controlled trial in 1997¹⁰. Nowadays, registered products, whose effectiveness
22 169 has been plainly demonstrated by controlled trials on large patient populations, are
23
24 170 considered ideal for AIT¹¹. However, good quality NPPs with demonstration of efficacy by
25
26 171 placebo-controlled trials, are still available to treat respiratory allergy with expectancy of
27 172 clinical success¹².

29 173 **Modern AIT as a prototype of personalized medicine.**

30
31 174 The traditional diagnosis by skin tests relay on extracts, whose composition in minor and
32
33 175 major allergens can play a crucial role in defining sensitizations, as in the AIT products for
34 176 inducing clinical efficacy. Another critical factor is the extract potency, concerning both skin
35
36 177 testing and AIT. As to the latter, Larenas-Linneman et al. found a substantial variability in
37
38 178 allergen extract potency as measured and reported worldwide^{13,14}. In particular, in Europe
39
40 179 the potency of extracts for sublingual immunotherapy (SLIT) is based on comparison with
41 180 in-house references, making it difficult to translate the dose to US extracts¹³. Moreover,
42
43 181 comparing SLIT maintenance solutions of grass pollen and *Dermatophagoides*
44
45 182 *pteronysinus* from 4 leading European manufacturers to standardized concentrate
46 183 extracts of 3 US manufacturers measure in bioequivalent allergen units (BAU), the relative
47
48 184 potency was around 10 times higher for US standardized extracts (to be diluted for SLIT)
49
50 185 than for European SLIT maintenance dosage. The authors argued that, based on the
51
52 186 efficacy demonstrations from controlled trials, SLIT efficacy is likely to depend on
53 187 additional factors apart from the extract dose¹⁴. Today, the pillars of AIT as a personalized
54
55 188 therapy are represented by molecular diagnostics for achieving the highest possible
56
57 189 precision, by the use of treatable traits, and by “omics”.

58 190
59
60 191

1) Molecular diagnostics and other *in vitro* tests

The diagnosis of allergy has been long based on skin prick test (SPT) with allergen extracts and *in vitro* test measuring specific IgE antibodies to the suspected allergens, but with both techniques the positive results indicated sensitization but not necessarily clinical allergy. A great advance in diagnostic precision was achieved by molecular diagnosis, which allows to detect specific IgEs (sIgEs) to each single molecule, distinguishing those really causative (genuine) from those simply cross-reactive. Such diagnostic approach was variously named, including “Component resolved diagnosis”¹⁵, molecular-based allergy diagnostics¹⁶, and molecular allergy diagnostics¹⁷. The updated WAO-ARIA- GA²LEN consensus document on molecular-based allergy proposed the unifying definition of “precision allergy molecular diagnostic applications” (PAMD@)¹⁸. This allergy diagnostics approach is aimed at mapping the allergen sensitization of a patient at a molecular level, using purified natural or recombinant allergenic molecules instead of allergen extracts. Each allergen molecule is identified, classified according to the family to which it belongs, and scientifically named according to the species to which it belongs. For example, the major allergen from cockroach is a lipocalin named Bla g 4 (after *Blattella germanica*¹⁹). Since its introduction, PAMD@ has been gradually used as a laboratory tool, and presently more than 130 allergenic molecules commercially are accessible for *in vitro* sIgE testing²⁰. Two platform to perform PAMD@ are available, which include a singleplex (i.e. a single assay per sample) or a multiplex (i.e. multiple assays per sample) measurement. With the former, the allergenic molecules thought to be responsible are selected by the physician²¹, while with the multiplex technique a large array of preselected allergens are tested. The commercially offered multiplex allergen arrays include the Immuno-CAP Immuno-solid-phase Allergen Chip (ISAC) from Thermo Fisher, containing 103 molecules from 51 allergen sources²², and the new ImmunoCAP ISAC 112i, including 112 components from 48 allergen sources, where some molecules from *Hymenoptera* venom and from walnut and plain tree have been eliminated, while others from cashew, hazelnut, dog, dust mites, and alpha-gal were added²³. The EUROLINE Southern European Pollen Profile [ESEP) was introduced to test pollen molecules of clinical relevance in Southern Europe²⁴, while the Microarray Diagnostics (MADx) Allergen Explorer (ALEX) include 126 molecules from different allergen sources²⁵. It is apparent that in order to properly interpret positive results for a high number of molecules, a great experience of the examining physician is necessary. To facilitate the matter, expert systems were developed to support the data analysis by dedicated decision-making

1
2
3 226 information systems. For instance, the expert system named Allergenius® is based on the
4
5 227 ImmunoCAP ISAC implemented with an advanced knowledge specification language
6
7 228 using more than 700 different rules to mimic the experts' opinions on a complex ISAC
8
9 229 result²⁶. In a study comparing sera from patients assayed with ImmunoCAP ISAC and
10 230 ALEX a good correlation between the results from the two methods was found²⁷.

11
12 231 By focusing on applications for personalized medicine, numerous studies have assessed
13
14 232 the benefits of attaining with PAMD@ a more appropriate prescription for AIT. Table 1
15 233 summarizes the observations from these studies²⁸⁻³⁷. A vast literature is available, as
16
17 234 recently reviewed³⁸⁻³⁹, also for the advantages of PAMD@ in the diagnosis of food allergy
18
19 235 compared to the conventional diagnosis, but this will not be treated here since the purpose
20
21 236 of our analysis is to examine the progress achieved by PAMD@ in the appropriate
22 237 prescription of AIT. In fact, despite the numerous controlled AIT trials for food allergy⁴⁰,
23
24 238 this therapy has not yet been approved.

25
26 239 As far as the identification of the really causative allergen in polysensitized patients is
27 240 concerned, the first *in vitro* test was the RAST inhibition⁴¹, which then evolved into CAP
28
29 241 inhibition assay. The latter has been shown to be comparable to PAMD@ in the ability to
30
31 242 identify the causative allergen^{35,42} and to have a lower cost⁴³ in patients with multiple
32
33 243 sensitization to *Hymenoptera* venom, in which a limited number of allergenic molecules
34 244 are responsible, while such outcomes was not reported for multi-sensitization to
35
36 245 respiratory allergens, involving a much higher number of molecules.

37
38 246 The basophil activation test (BAT), which measures basophil degranulation by flow
39
40 247 cytometry, has the unique characteristic to detect *in vitro* the reactivity of basophils to
41 248 allergens. Since these cells play a crucial role in allergic reactions, their *in vitro* detection
42
43 249 has a similar meaning to the *in vivo* provocation test with specific allergens, without
44
45 250 however the limit of false positive results from non-specific reactions, which represented a
46 251 limit of *in vivo* tests. BAT was found to be very useful in the personalized diagnosis of
47
48 252 patients with allergic conditions including respiratory, food and *Hymenoptera* venom
49
50 253 allergy who show multiple allergen reactivity, distinguishing the allergens as causative or
51
52 254 not based on the response of the basophils⁴⁴. As mentioned above, our review is focused
53 255 on the effects of personalized diagnosis on the outcomes of AIT. As for CAP inhibition, the
54
55 256 first studies concerned *Hymenoptera* venom allergy, demonstrating that BAT
56
57 257 accomplished with the recombinant allergens from *Vespula* spp Ves v 1, Ves v 2, Ves v 3
58 258 and Ves v 5 achieved a clear improvement in the specificity of diagnosis in patients with
59
60 259 anaphylactic reactions to wasp stings over IgE detection by Enzyme-Linked

1
2
3 260 ImmunoSorbent Test (ELISA) or ImmunoCAP⁴⁵ and that in patients with severe reactions
4
5 261 to stings, some of them with negative response to sIgE test and intradermal tests, BAT
6
7 262 was positive in 81% of patients compared with to a rate 57% with intradermal testing,
8
9 263 14% with IgE test, 19% of patients being negative to either test except BAT⁴⁶. A study
10
11 264 analyzed the correlation between the BAT changes during venom immunotherapy and
12
13 265 the treatment outcome. BAT was unchanged after one year, but in subsequent years a
14
15 266 fourfold reduction was detected in all patients who developed tolerance to stings, while
16
17 267 no change in BAT occurred in patients with a persistently positive sting challenge⁴⁷.
18
19 268 Such important outcome was found also in patients treated with subcutaneous
20
21 269 immunotherapy (SCIT) for grass pollen allergy. In fact, basophil sensitivity showed a
22
23 270 447-fold decrease in the first year of treatment, remaining 100-fold lower than baseline
24
25 271 in the 3 year-treatment period and 10-fold lower in the follow-up year. Notably, a
26
27 272 decline in basophil sensitivity after three weeks of SCIT predicted long-
28
29 273 term improvement in symptom and medication scores during the three years of
30
31 274 treatment⁴⁸. Further studies are needed to clarify the role of BAT as a biomarker or a
32
33 275 predictive marker of AIT efficacy.
34

35 276

36 277 **2 In vivo tests**

37 278 Theoretically, inducing allergic symptoms by a challenge with the suspected allergen in the
38
39 279 target organs can be a valuable in vivo test. However, as stated in the International
40
41 280 Consensus Statement on allergic rhinitis, the contrasting findings from different studies
42
43 281 and the absence thus far of a standardized technique limit the diagnostic utility of nasal
44
45 282 challenge, a pivotal role being currently acknowledged only in diagnosis of occupational
46
47 283 rhinitis and local allergic rhinitis⁴⁹. If future studies will achieve standardization of the
48
49 284 method, the nasal challenge could be used, alike BAT, as a test toward precision medicine.
50

51 285

52 286 **3. Treatable traits**

53 287 The term "Treatable traits" was suggested by Agusti and coworkers to indicate a precision
54
55 288 medicine methodology of diagnosis and treatment of chronic disorders of the airways
56
57 289 based on finding genetic, phenotypic and psychosocial features which are associated with
58
59 290 therapies able to improve respiratory health⁵⁰. The field of application considered as most
60
291 appropriate for the use of treatable traits is represented by chronic respiratory diseases
292 and in particular by asthma and chronic obstructive pulmonary disease (COPD), which
293 share various clinical aspects but whose drug therapy has significantly differentiated in

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

327

recent years⁵¹. For example, using treatable traits in a patient with COPD but symptoms compatible also with asthma and positivity of tests for respiratory allergy due to asymptomatic sensitization would prevent the incorrect prescription of AIT. The role of treatable traits in the management of chronic respiratory diseases has been outlined by some important studies. The first investigated the role of extra-pulmonary comorbidities as treatable traits in patients with difficult-to-control asthma. The proposed comorbidities were allergic and nonallergic rhinitis, chronic rhinosinusitis, vocal cord dysfunction, dysfunctional breathing, gastroesophageal reflux, obesity, obstructive sleep apnoea, and anxiety/depression, of which the prevalence, impact and outcome of treatment were assessed, also appraising the associations of single comorbidities and the potential of comorbidity clusters on asthma control. The authors concluded that extra-pulmonary comorbidities are important treatable traits to be evaluated in all asthmatic patients and especially in those with difficult asthma. Such comorbidities may have a significant influence on asthma control, thus their presence deserves treatment regardless of original asthma status and asthma control⁵². The number of treatable traits involved in acute exacerbation differed according to the respiratory disease, with a major role for C reacting protein in COPD, eosinophils count and fractionated exhaled nitric oxide (FeNO) measurement in asthma, and bacterial infections for bronchiectasis⁵³.

An important observation obtained through the review of the literature by Pavord and Agusti concerned the identification of eosinophilic airway inflammation, as assessed by the blood eosinophil count, as a treatable trait of particular importance in patients with airway disease (including asthma and COPD, being significantly associated with long-term outcomes⁵⁴. The recent European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project was aimed at identifying and quantifying, based on the hypothesis that treatable traits are more common in severe asthma and may significantly differ according to asthma phenotypes, the treatable traits recognized in the severe and mild/moderate adult asthma cohorts and across previously identified phenotypes⁵⁵.

All studies available thus far support a chief role of treatable traits in evaluating patients with respiratory diseases, however the preferable method of application and the cost-effectiveness of such a multidimensional intervention is still uncertain, making it necessary to conduct randomized controlled trials involving large populations of patients⁵⁶. Concerning AIT, treatable traits of clinical interest may consist of the treatment outcome, beyond the disease to be treated, on comorbidities⁵⁷. Another trait may concern the

1
2
3 328 possible synergistic effect of biologics and AIT. Precision medicine of allergic diseases is
4
5 329 nowadays highlighted by the consistent data of efficacy of biologics targeting cytokines ((IL
6
7 330 5) or their receptors (IL 5 rec. or IL4/IL13 rec.). Nonetheless, we should consider that the
8
9 331 eligibility of allergic patients to biologics or AIT is only partially overlapping, being the first
10 332 limited to severe asthma or CRSwNP whereas AIT has indication for allergic rhinitis and
11
12 333 mild/moderate asthma while severe asthma is a contraindication. Based on the
13
14 334 characteristics of the two treatments, a synergistic effect in allergic asthma is conceivable,
15 335 with biological achieving control of severe asthma but not changing its natural history while
16
17 336 AIT, once ceased the contraindication, can induce the long-term immunological changes.
18
19 337 Studies to investigate whether such synergy is achievable are warranted.

20 338

22 339 **4.Omics**

23
24 340 Following the definition of genomics in the 1960s as the complete nucleotide sequence of
25
26 341 an organism⁵⁸, a large number of other “omics” were recently proposed, such as
27 342 proteomics (the complete proteins of a cell in any organism), epi-genomics (the
28
29 343 modification of nucleotides in an organism), metabolomics (the changes in gene activity in
30
31 344 response to metabolites⁵⁹, breathomics (the multidimensional molecular analysis of
32
33 345 exhaled breath⁶⁰, but the list is very large and still expanding. In the field of allergy
34 346 diseases, asthma is the most investigated disease. In 2011, the detection of protein
35
36 347 changes by proteomics in different asthma stages was supported to improve the
37
38 348 understanding of the molecular mechanisms of the disease and to find novel mediators
39 349 and biomarkers⁶¹. Another omic of potential interest for personalized medicine is the
40
41 350 exposome, definable as a systematic approach to obtain large data sets on to
42
43 351 environmental exposures of an individual during the whole life⁶².

44
45 352 However, the available data on the state of omics technology in the management of
46 353 asthma and allergic diseases were recently analyzed by Donovan et al. After pointing out
47
48 354 that omics-based investigation are used increasingly to distinguish subtypes of
49
50 355 allergic diseases and asthma subtypes, forecast patient responsiveness to specific
51 356 therapies, detect biomarkers and mediators, and verify the disease control, the authors
52
53 357 concluded that omics testing in this field for are not yet a standard of care, and that key
54
55 358 factors need to be recognized before such technologies can be used successfully in
56
57 359 common clinical practice⁶³. On the other hand, according to Fitzgerald et al., the promise
58 360 of new technology must leave room to an humanomics perspective, i.e. the
59
60 361 acknowledgement of patient’s behavioral aspects⁶⁴.

1

2

3 362

4

5 363 Impact of personalized medicine on AIT

6

7 364 The great advance provided by the introduction of personalized medicine in diagnosis of

8

9 365 allergy is likely to enable solving the long-standing problem of AIT related to the great

10

11 366 qualitative variability of AIT products and the consequent heterogeneity of the clinical

12

13 367 results. Actually, an updated way to correctly evaluate the effectiveness of AIT products

14

15 368 must avoid the mistakes of the past, when the results of a valid tool such as meta-analysis,

16

17 370 extend the positive outcome to AIT in general⁶⁵. The latest generation of registered

18

19 371 products for SLIT, which were based on trials including large number of patients with

20

21 372 respiratory allergy to grass pollen and dust mites, meet the modern quality needs⁶⁶⁻⁷⁰. Still,

22

23 373 as mentioned above, the previous generation products include allergen extracts of efficacy

24

25 374 demonstrated by controlled trials, but also products missing such evidence. This implies

26

27 375 new properly designed clinical trials to demonstrate efficacy. Nonetheless, in order to

28

29 376 facilitate AIT product development it is advisable that the same product composition,

30

31 377 possibly using different formulation (i.e. drops/tablets) should have a mutual program and

32

33 378 recognition and possibly a full development program. Also, the relevance of testing all

34

35 380 allergens and the final cost of the studies for a limited effect size due to the huge placebo

36

37 381 effect in AIT trial is worthy of attention. These facets could provide a flexibility of treatment

38

39 382 otherwise difficult to reach in clinical practice, when batch to batch reproducibility is

40

41 383 ensured in terms of quality product and standardization.

42

43 384 Today, to achieve the highest quality any manufacturer of allergen products must follow

44

45 385 stringent scientific rules. The first is to ensure the presence in the allergen extracts of all

46

47 386 relevant allergens. As discussed above, PAMD@ provides the detections of all allergen

48

49 387 molecules, distinguishing those simply cross-reactive from genuine causative ones.

50

51 388 Similarly, the development of an AIT product requires during the manufacturing process

52

53 389 the identification of all component through mass-spectrometry based analysis, followed by

54

55 390 allergen extraction, purification and formulation, as well as yield cost, robustness and

56

57 391 scaling up. The subsequent step is the product characterization, which results in

58

59 392 development and implementation of analytical methods for identity, purity, consistency and

60

61 393 stability, which makes clinical development possible in its various phases. These phases

62

63 394 (I, II, III) are aimed at establishing safety, dosing and efficacy. For optimal quality level,

64

65 395 well-controlled source materials are also essential, which consist, for example for grass

66

67 pollen, in the harvesting and processing of pollens from cultured grasses, while for house

1

2

3 396 dust mites the development of a synthetic cultured medium free from proteins of animal
4
5 397 origin is needed⁷¹. As mentioned above, the use of omics is of marked importance in the
6
7 398 comprehensive characterization of allergen extracts, including transcriptome for *de novo*
8
9 399 sequencing, proteome for MS analysis, and allergome for IgE reactivity⁷².

10 400 In this context, the evaluation of the Real-World Evidences (RWE), should be properly
11
12 401 reappraised, since patients in clinical practice often do not meet the same criteria of the
13
14 402 subjects enrolled in the double-blind placebo-controlled trials (DBPCRT) leading to
15 403 registration by Regulatory Authorities⁷³. In fact, distinction is made between the final
16
17 404 outcome of DBPCT efficacy and the one in RWE. Nonetheless, a correct evaluation of
18
19 405 these RWE has to be methodologically performed. To this purpose an ongoing European
20
21 406 Academy of Allergy and Clinical Immunology (EAACI) initiative is designed to ascertain the
22 407 validity of the existing RWE concerning AIT, applying the recent tools proposed by
23
24 408 Respiratory Effectiveness Group (REG)/EAACI from one side (Relevant) and Grading of
25
26 409 Recommendations, Assessment, Development and Evaluation (GRADE) on the other side
27 410 ⁷⁴. Through this initiative we will be able define the real validity of the existing AIT RWEs.
28
29 411 This action has been also stated and promoted by the recent Real-Life Research
30
31 412 Manifesto, where it is pointed out the need to consider RWE in the complex scenario of
32
33 413 scientific clinical research⁷⁵. This document supported the use of tools, such as the ones
34 414 mentioned previously, to analyze RWE properly. Finally, the Manifesto also underlined the
35
36 415 major differences existing between retrospective and prospective RWE: where prospective
37
38 416 approach, whose typical example is a Disease or intervention's Registry, is the most
39
40 417 credible, as also stated by Sherman et al⁷⁶. In fact, it should be underlined that several AIT
41 418 RWE reports were retrospectively collected, combining different methodologies, thus
42
43 419 decreasing the validity of the final outcomes/conclusions. However, recent, well conducted
44
45 420 real-life studies, derived from a well-designed and set up database and including very
46 421 large patient populations, were of relevant importance, because they contributed to
47
48 422 increase the knowledge on the effectiveness of AIT in patients seen in daily clinical
49
50 423 practice, possibly not meeting the strict criteria to be included in a trial^{77,78}.

51 424

53 425 **Final message: AIT as personalized treatment**

54
55 426 All the above is in line with the current view that collecting Big Data can lead to precision
56
57 427 medicine^{79,80}. We previously pointed out AIT as a prototype of precision medicine⁷ and
58
59 428 now we would propose AIT as one of the best example of Personalized and Participatory
60 429 Medicine, aimed to satisfy the needs and preferences of patients and to strengthen the

1
2
3 430 cooperation patient/doctor in jointly choosing the best therapeutic option. AIT is the only
4
5 431 medical treatment that has the capacity to change the natural history of allergic diseases ⁸¹
6
7 432 and responds perfectly to the three major needs to be met in personalized medicine, which
8
9 433 are the identification of the molecular mechanism of the disease, the availability of
10 434 diagnostic tools to recognize this mechanism and the availability of a treatment capable of
11
12 435 blocking the mechanism⁸². In Figure 1 we summarized all the possible aspects of the
13
14 436 updated journey to reach the best prescription of AIT, through a detailed and modern
15 437 diagnosis (including PAMD@) and definition of patient's eligibility to AIT. As to diagnosis, it
16
17 438 must be kept in mind that the medical history collected by a skilled doctor is the basis for
18
19 439 deciding the subsequent investigations in accordance with the individual characteristics.
20
21 440 The current and future tools to reach a AIT personalized prescription are summarized in
22 441 Figure 2 . Their variable characteristics suggest that personalized care is valuable in this
23
24 442 setting and may be also be preventive (by focusing on quality of life), predictive (by
25
26 443 allowing treatment to be adjusted as a function of the individual's response) and
27 444 participative (empowering the patient). In particular, SLIT can be considered a precision
28
29 445 medicine treatment (especially with high quality NPP) that enable the physician to identify
30
31 446 the optimal treatment for each patient. This tailor-made approach to diagnosis, decision-
32
33 447 making, product choice and treatment schedules may enhance effectiveness, minimize
34 448 adverse events, improve patient's quality of live and reduce the socio-economic impact. A
35
36 449 number of SLIT drops up dosing regimens and maintenance treatment were shown to be
37
38 450 safe and effective. This means that SLIT liquid allergen extract formulations are extremely
39
40 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such
41 452 parameters can be fine-tuned to suit the patient's day-to-day treatment response and
42
43 453 intercurrent events. Depending on the sensitization profile and the clinical signs, the
44
45 454 specialist can develop a specific, tailor-made SLIT liquid-based approach that, due to its
46 455 ductility in clinical practice, may be an added value. In addition, SLIT liquid formulation
47
48 456 makes it possible to adapt the dose and regimen during the up dosing and/or the
49
50 457 maintenance phase to target optimal effectiveness.
51
52
53
54
55
56
57
58
59
60

The clinician should then evaluate:

- The route of administration: presently SCIT and SLIT for aeroallergens, considering evidences and patient's needs/preference
- The AIT product to be chosen as recommended by WAO⁸³ and EAACI⁸⁴ among the products supported by evidences.
- SCIT: different schedules upon the products (i.e. depot or aqueous)
- SLIT: preference for drops or tablet, both considering evidences and patient's needs/preference
- Dosages and schedules: continuous or pre-seasonal; long or short term.
- Most of the above can be influenced by costs and/or reimbursements.

Personalized medicine in AIT has the potential to improve various outcomes which have so far produced limited results. This is true for preventive ability, which until now has been shown only for the development of asthma in patients with allergic rhinitis⁸⁵, the identification of biomarkers predictive of treatment efficacy (still not known)⁵⁷ and cost-effectiveness compared to drug therapy, clearly demonstrated on the basis of the persistence over time of the control of symptoms after AIT withdrawal⁸⁶, but further improvable by greater diagnostic precision. Further issues could concern the expansion of e-health systems⁷ and the implementation of telemedicine⁸⁷.

This journey is leading to the most appropriate choice of the AIT treatment thanks to the multifaceted variety of AIT products empowering the professionalism of the clinician in choosing, through a shared decision that considers the patient's needs, a proper AIT product for each patient according to eligibility and acceptability.

It is so conceivable to conclude that AIT is still a unique and unmatched model of Personalized Medicine for allergy treatment, able to encompass the prediction of a successful treatment and the potential prevention or progression of an allergic disease, and possibly to face the challenge of providing such advances to at affordable costs. As well, the characteristics of Personalized Medicine for allergy are likely to enable to face challenges such as increasing prevalence, growing complexity and heterogeneity, impact on patients, problem of access to care, therapeutic wandering, and successful management of uncontrolled patients⁸⁸.

Disclosure of Interests

M. Al-Ahamad has nothing to disclose.

1

2

3 482 I. Ansotegui declares he has received fees from Abbott, Astra Zeneca, Faes Farma,
4 Hikma, Menarini, MSD, Mundipharma, Roxall, Sanofi, Stallergenes Greer, UCB.

6 484 S. Arasi has nothing to disclose.

8 485 C. Bachert declares he has received personal fees from Sanofi, personal fees from GSK,
9 personal fees from Novartis, personal fees from Astra-Zeneca.

11 487 J. Bousquet declares he has received lecture fees and/or participation at expert board
12 meetings from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-
13 Aventis, Takeda, Teva, Uriach (Advisory Board, consultant, meeting lectures fees),
14 488 Kyomed (shares).

17 490 A. Bozek has nothing to disclose.

18 491 D. Caimmi has nothing to disclose.

20 492 M. Calderon has nothing to disclose.

22 493 T. Casale has nothing to disclose.

24 494 A. Custovic has nothing to disclose.

25 495 GW. Canonica declares he has received lecture fees and/or participation at expert board
26 meetings BI, ALK, Stallergenes Greer (Grant/ research support), (Menarini, GSK, Sanofi,
27 Teva, Hal, AZ, Novartis (honoraria or consultation fees).

28 497 F. De Blay declares he has received grants from Stallergenes Greer, Chiesi, ALK,
29 Mundipharma, Novartis.

30 500 P. Demoly declares he had received personal fees for grants/lecture from Astra Zeneca,
31 Mylan, Sanofi, ASIT Biotech, ALK, Stallergènes Greer, Thermofisher Scientific, Menarini,
32 Chiesi, Bausch&Lomb, Yslab.

33 501 P. Devillier declares he has received has received consultancy fees, honoraria for
34 lectures, and/or research funding from ALKAbelló, Stallergenes Greer, AstraZeneca,
35 Chiesi, Boehringer-Ingelheim, GlaxoSmithKline.

36 502 A. Didier declares he has received personal fees for consultancy services for ALK and
37 grants for participation in clinical research projects with ALK.

38 503 A. Fiocchi has nothing to disclose.

39 504 A. Fox has nothing to disclose.

40 505 P. Gevaert declares he has received lecture fees and/or participation at expert board
41 meetings from Ablynx, ALK, Argenx, Astra-Zeneca, Genentech, HAL-Allergy, Novartis,
42 Roche, Regeneron, Sanofi, and Stallergenes Greer.

- 1
2
3 514 M. Gomez has nothing to disclose.
4
5
6 515 E. Heffler declares he has received lecture fees and/or participation at expert board
7
8 516 meetings from AstraZeneca, GSK, Sanofi, Novartis, Boehringer Ingelheim, Valeas,
9
10 517 Circassia, Nestlè Purina.
11 518 N. Ilina has nothing to disclose.
12
13 519 C. Irani has nothing to disclose.
14
15 520 L. Klimek has nothing to disclose.
16
17 521 P. Kuna declares he has received honorarium as speaker from Allergopharma, ALK.
18 522 Bencard and Stallergenes Greer.
19
20 523 R. O'Hehir C. has nothing to disclose.
21
22 524 Incorvaia declares he has received fees for consultancies from Bayer and Stallergenes
23 525 Greer.
24
25 526 M. Jutel declares he has received personal fees from ALK-Abello, Allergopharma,
26
27 527 Stallergenes Greer, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL.
28
29 528 O. Kurbacheva has nothing to disclose.
30
31 529 P. Matricardi declares he has received fees from Thermo Fisher Scientific, Hycor, Omron,
32 530 TPS, Stallergenes Greer, Euroimmun.
33
34 531 M. Morais de Almeida has nothing to disclose.
35
36 532 R. Mosges declares he has received fees from Allergopharma, ALK-Abelló, Glaxo, HAL
37 533 Allergy, Leti, Lofarma, Novartis, Parexel International, Stallergenes Greer.
38
39 534 N. Novak has nothing to disclose.
40
41 535 Y. Okamoto has nothing to disclose.
42
43 536 P. Panzner has nothing to disclose.
44
45 537 N. Papadopoulos declares he has received fees from Novartis, NUTRICIA, HAL, Menarini,
46 538 SANOFI, MEDA, AstraZeneca, GSK, MSD, ASIT BIOTECH, Boehringer Ingelheim.
47
48 539 H. Park has nothing to disclose.
49
50 540 G. Passalacqua has nothing to disclose.
51
52 541 R. Pawankar has nothing to disclose.
53
54 542 O.Pfaar declares he has received grants and personal fees from ALK-Abelló,
55 543 Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, from
56 544 Bencard Allergie GmbH/Allergy Therapeutics, Lofarma.
57
58 545 P. Schmid-Grendelmeier has nothing to disclose.
59
60 546 H. Tortajada has nothing to disclose.
547
C. Vidal has nothing to disclose.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

548 C Virchow declares he has received fees from Allergopharma, ALK, LETI, Stallergenes
549 Greer.

550 U. Wahn declares he has received honoraria for consultancy as well as lecture fees from
551 Allergopharma, Stallergenes Greer, ALK, Roxall, Sanofi-Aventis, Novartis, Berlin-Chemie

552 M. Worm declares she as received of honoraria or consultation fees by ALK-Abelló
553 Arzneimittel GmbH, Mylan Germany GmbH, Leo Pharma GmbH, Sanofi-Aventis
554 Deutschland GmbH, Regeneron Pharmaceuticals, DBV Technologies S.A, Stallergenes
555 Greer, HAL Allergie, Allergopharma, Bencard Allergie, Aimmune Therapeutics UK Limited,
556 Actelion Pharmaceuticals Deutschland G, Novartis AG, Biotest AG, AbbVie Deutschland &
557 Co. KG, Lilly Deutschland..

558 P. Zieglmayer has nothing to disclose.

559 C. Bos, E. Karagiannis and S. Scurati are employee of Stallergenes Greer

563 Acknowledgments

564 This is an initiative supported by Stallergenes Greer with an unrestricted grant

DRAFT REVIEW ARTICLE dated 17.05.20

1
2
3 565 **Table 1 Studies that have assessed the benefits of attaining with PAMD a more**
4
5 566 **appropriate prescription for AIT**

Author, year (ref)	Allergens tested	Population	Results
Mitterman, 2010 (28)	Bee and wasp venom.	43 patients (pts)	Recombinant nonglycosylated allergen molecules (Api m 1, rApi m 2, rVes v 5) allowed to define the sensitizing venom in the 14 patients with positive test both bee and wasp venom extracts.
Sastre, 2012 (29)	Pollens	141 pts	Agreement in AIT indication before and after ISAC(®) results in 62 (46%) patients; (kappa = 0.1057 ± 0.0413).
Moreno, 2014 (30)	Pollens	1263 pts	Based on history and SPT, 73% of patients would have been prescribed AIT with a mix of grass and olive pollens, while only in 56.8% of patients the double positivity was confirmed by molecular allergy diagnosis (MAD) with Ole e 1 and Phl p molecules.
Popescu, 2014 (31)	Grass pollen	Not defined (review of published data)	MAD biomarkers (including tolerogenic dendritic, regulatory T cells, IgE, IgA and IgG antibodies, and apoptosis biomarkers provide relevant

			information for allergists
Vidal, 2014 (32)	Pollens, dust mites, moulds, animal epithelia	62 Spanish allergists	SPTs are insufficient to establish the clinical relevance of each allergen. Serum specific IgE adds value to SPT but MAD is strongly recommended, particularly in pollen-allergic patients.
Saltabayeva, 2017 (33)	Pollens	95 pts (real-life study)	A lower number of AIT treatments (n = 119) was needed according to MAD compared to 275 AIT treatments based on conventional diagnosis, with large reduction of the total costs for a 3-year AIT treatment
Del-Rio Camacho, 2018 (34)	Pollens	70 children	MAD modified AIT prescription in 54.3% of cases, and increasing the indication of single-allergen therapy from 18% to 51% reversing the decision to prescribe AIT in 9.3% of cases
Savi, 2016 (35)	Hymenoptera venoms	40 pts.	By MAD data VIT would have been prescribed to 7 pts for Polistes spp, to 6 for Vespula spp, and to 41 for both venoms. With the data from CAP inhibition, it would have been a prescription to 15 patients for Polistes, to 28 for Vespula, and to 11

			for both venoms. A good concordance between the results of MAD and CAP-inhibition was found only when the value in kU/l of Ves v 5 were about twice those of Pol d 5, and vice versa.
Martinez-Canavate Burgos, 2018 (36)	Pollens	281 children	MAD results changed the specialist's composition of the prescribed AIT in 52.87% of cases.
Peveri, 2019 (37).	Various aeroallergens	272 pts.	In 50% of cases a change in the AIT prescription for respiratory allergy was found, resulting in a saving of financial resources.

567

568

569

570

571

572

573

574

575

576

577

578

579

580

581

582

583

584

585

586

587

588

589

590

591

592

593

594

595

596

597

598

599

600

References

- 1) Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. *Drug Test Anal.* 2011;3 (6)337-44.
- 2) Mahner, M. & Kary, M. (1997). "What exactly are genomes, genotypes and phenotypes? And what about phenomes?". *J Theoretical Biology* 186: 55–63.
- 3) Febbo PG, Ginsburg GS. Personalized diagnostic and therapeutic strategies in oncology. *Per Med.* 2005;2(2):97-110.
- 4) Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015 Feb 26;372(9):793-5
- 5) Busse WW. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int.* 2019;68(2):158-66.
- 6) Frew AJ. Hundred years of allergen immunotherapy. *Clin Exp Allergy.* 2011;41(9): 1221-225.
- 7) Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M, De Beaumont O, Bousquet J. Allergen Immunotherapy (AIT): A prototype of precision medicine. *World Allergy Organ J.* 2015;8 (1), 31 2015
- 8) Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, Halken S, Larenas-Linnemann D, Pawankar R, Pitsios C, Sheikh A, Worm M, Arasi S, Calderon MA, Cingi C, Dhimi S, Fauquert JL, Hamelmann E, Hellings P, Jacobsen L, Knol EF, Lin SY, Maggina P, Mösges R, Oude Elberink JNG, Pajno GB, Pastorello EA, Penagos M, Rotiroti G, Schmidt-Weber CB, Timmermans F, Tsilochristou O, Varga EM, Wilkinson JN, Williams A, Zhang L, Agache I, Angier E, Fernandez-Rivas M, Jutel M, Lau S, van Ree R, Ryan D, Sturm GJ, Muraro A. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy.* 2018;73(4):765-798.
- 9) Demoly P, Makatsori M, Casale TB, Calderon MA. The Potential Role of Allergen Immunotherapy in Stepping Down Asthma Treatment. *J Allergy Clin Immunol Pract.* 2017 May - Jun;5(3):640-648.
- 10) Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, Tonascia J, Wheeler B. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med.* 1997; 336(5):324-31.
- 11) Kaul S, May S, Lüttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy.* 2011;66(6):753-64.

1

2

3 602 12)Devillier P, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen
4 immunotherapy and pharmacotherapy in pollen-induced seasonal allergic
5 603 rhinoconjunctivitis. BMC Med. 2014;12:71
6 604

8 605 13)Larenas-Linnemann D, Cox LS; Immunotherapy and allergy diagnostics Committee of
9 the American Academy of Allergy, Asthma and Immunology European allergen extract
10 606 units and potency: review of available information. Ann Allergy Asthma Immunol.
11 607 2008;100(2):137-45.
12 608

15 609 14)Larenas-Linnemann D, Esch R, Plunkett G, Brown S, Maddox D, Barnes C, Constable
16 D. Maintenance dosing for sublingual immunotherapy by prominent European allergen
17 610 manufacturers expressed in bioequivalent allergy units. Ann Allergy Asthma Immunol.
18 611 2011;107(5):448-458.
19 612

22 613 15)Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Grönlund H. The recombinant
23 allergen-based concept of component-resolved diagnostics and immunotherapy (CRD
24 614 and CRIT). Clin Exp Allergy. 1999 Jul;29(7):896-904
25 615

27 616 16)Melioli G, Savi E, Crivellaro MA, Passalacqua G. Potential of molecular based
28 617 diagnostics and its impact on allergen immunotherapy. Asthma Res Pract. 2016 2;2:9.

29 618 17)Kespohl S, Raulf M. Mould allergens: Where do we stand with molecular allergy
30 619 diagnostics?: Part 13 of the series Molecular Allergology. Allergo J Int. 2014;23(4):120-
31 620 125.
32 621

36 621 18)A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnosis
37 622 (PAMD@): Update 2020. World Allergy Organ J. 2020 Mar 7;13(2):100091. Steering
38 623 Committee Authors; Review Panel Members. Collaborators (48) World Allergy Organ J.
39 624 2020;13(2):10009.
40 625

43 625 19)Pomes A, Davies JM, Gadermaier G, et al. WHO/IUIS allergen nomenclature: providing
44 626 a common language. Mol Immunol. 2018;100:3–13.

46 627 20)van Hage M, Hamsten C, Valenta R. ImmunoCAP assays: pros and cons in allergology.
47 628 J Allergy Clin Immunol. 2017;140: 974–977.

49 629 21)Garib V, Rigler E, Gastager F, et al. Determination of IgE and IgG reactivity to more
50 630 than 170 allergen molecules in paper dried blood spots. J Allergy Clin Immunol.
51 631 2019;143:437-440.
52 632

55 632 22)Jakob T, Forstenlechner P, Matricardi P, Kleine-Tebbe J. Molecular allergy diagnostics
56 633 using multiplex assays:methodological and practical considerations for use inresearch
57 634 and clinical routine: Part 21 of the Series Molecular Allergology. Allergo J Int.
58 635 2015;24:320-332.

1

2

- 3 636 23) van Hage M, Schmid-Grendelmeier P, Skevaki C, Plebani M, Canonica W, Kleine-
4 Tebbe J, Nystrand M, Jafari-Mamaghani M, Jakob T. Performance evaluation
5 637 of ImmunoCAP® ISAC 112: a multi-site study. *Clin Chem Lab Med*. 2017 Mar
6 638 1;55(4):571-577
8 639
- 10 640 24) Di Fraia M, Arasi S, Castelli S, et al. A new molecular multiplex IgE assay for the
11 diagnosis of pollen allergy in Mediterranean countries: a validation study. *Clin Exp*
12 641 *Allergy*. 2019;49:341-349.
13 642
- 15 643 25) Buzzulini F, Da Re M, Scala E, et al. Evaluation of a new multiplex IgE assay for
16 allergy diagnosis. *Clin Chim Acta*. 2019;493:73-78.
17 644
- 19 645 26) Melioli G, Spenser C, Reggiardo G, Passalacqua G, Compalati E, Rogkakou A, Riccio
20 646 AM, Di Leo E, Nettis E, Canonica GW. Allergenius, an expert system for the
21 interpretation of allergen microarray results. *World Allergy Organ J*. 2014 Jun
22 647 25;7(1):15.
23 648
- 25 649 27) Heffler E, Puggioni F, Peveri S, Montagni M, Canonica GW, Melioli G. Extended IgE
26 profile based on an allergen macroarray: a novel tool for precision medicine in allergy
27 650 diagnosis. *World Allergy Organ J*. 2018 Apr 26;11(1):7.
28 651
- 31 652 28) Mittermann I, Zidarn M, Silar M, Markovic-Housley Z, Aberer W, Korosec P, Kosnik M,
32 Valenta R. Recombinant allergen-based IgE testing to distinguish bee and wasp
33 653 allergy. *J Allergy Clin Immunol*. 2010 Jun;125(6):1300-1307.
34 654
- 36 655 29) Sastre J, Landivar ME, Ruiz-García M, Andregnette-Rosigno MV, Mahillo I.
37 How molecular diagnosis can change allergen-specific immunotherapy prescription in a
38 656 complex pollen area. *Allergy*. 2012 May;67(5):709-11.
39 657
- 41 658 30) Moreno C, Justicia JL, Quiralte J, Moreno-Ancillo A, Iglesias-Cadarso A, Torrecillas M,
42 Labarta N, García MA, Dávila I. Olive, grass or both? Molecular diagnosis for
43 659 the allergen immunotherapy selection in polysensitized pollinic patients. *Allergy*. 2014
44 660 Oct;69(10):1357-63.
46 661
- 48 662 31) Popescu FD. Molecular biomarkers for grass pollen immunotherapy. *World J Methodol*.
49 2014 Mar 26;4(1):26-45.
50 663
- 51 664 32) Vidal C, Enrique E, Gonzalo A, Moreno C, Tabar AI; Expert Clinical Participants.
52 Diagnosis and allergen immunotherapy treatment of polysensitized patients with
53 665 respiratory allergy in Spain: an Allergists' Consensus. *Clin Transl Allergy*. 2014 Nov
54 666 7;4:36.
56 667
- 58 668 33) Saltabayeva U, Garib V, Morenko M, Rosenson R, Ispayeva Z, Gatauova M, Zulus L,
59 Karaulov A, Gastager F, Valenta R. Greater Real-Life Diagnostic Efficacy
60 669

1

2

3 670 of Allergen Molecule Based Diagnosis for Prescription of Immunotherapy in an Area
4 with Multiple Pollen Exposure. *Int Arch Allergy Immunol*. 2017;173(2):93-98.

5 671
6 672 34) Del-Río Camacho G, Montes Arjona AM, Fernández-Cantalejo Padial J, Rodríguez
7 673 Catalán J. How molecular diagnosis may modify immunotherapy prescription in multi-
8 674 sensitized pollen-allergic children. *Allergol Immunopathol (Madr)*. 2018 Nov -
9 675 Dec;46(6):552-556.

10 676 35) Savi E, Peveri S, Makri E, Pravettoni V, Incorvaia C. Comparing the ability of molecular
11 677 diagnosis and CAP-inhibition in identifying the really causative venom in patients with
12 678 positive tests to *Vespula* and *Polistes* species. *Clin Mol Allergy*. 2016 Feb 8;14:3.

13 679 36) Martínez-Cañavate Burgos A, Torres-Borrego J, Molina Terán AB, Corzo JL, García
14 680 BE, Rodríguez Pacheco R, Moreno Aguilar C, Dávila I. Molecular sensitization patterns
15 681 and influence of molecular diagnosis in immunotherapy prescription in children
16 682 sensitized to both grass and olive pollen. *Pediatr Allergy Immunol*. 2018 Jun;29(4):369-
17 683 374.

18 684 37) Peveri S, Pattini S, Costantino MT, Incorvaia C, Montagni M, Roncallo C, Villalta D,
19 685 Savi E. Molecular diagnostics improves diagnosis and treatment of respiratory allergy
20 686 and food allergy with economic optimization and cost saving. *Allergol Immunopathol*
21 687 (Madr). 2019 Jan - Feb;47(1):64-72.

22 688 38) Gupta M, Cox A, Nowak-Węgrzyn A, Wang J. Diagnosis of food allergy.
23 689 *Immunol Allergy Clin North Am*. 2018 Feb;38(1):39-52. Doi

24 690 39) Volpicella M, Leoni C, Dileo MCG, Ceci LR. Progress in the analysis of food allergens
25 691 through molecular biology approaches. *Cells*. 2019 Sep 12;8(9).

26 692 40) Wai CYY, Leung NYH, Leung PSC, Chu KH. Immunotherapy of Food Allergy: a
27 693 Comprehensive Review. *Clin Rev Allergy Immunol*. 2019 Aug;57(1):55-73.

28 694 41) Schröder H, Yman L. Standardization of the RAST inhibition assay. *Allergy*. 1980
29 695 Apr;35(3):234-6.

30 696 42) Quercia O, Cova V, Martini M, Cortellini G, Murzilli F, Bignardi D, Cilia M, Scarpa A,
31 697 Bilò MB. CAP-Inhibition, molecular diagnostics, and total IgE in the evaluation of
32 698 *Polistes* and *Vespula* double sensitization. *Int Arch Allergy Immunol*. 2018;177(4):365-
33 699 369.

34 700 43) Caruso B, Bonadonna P, Bovo C, Melloni N, Lombardo C, Senna G, Lippi G. Wasp
35 701 venom allergy screening with recombinant allergen testing. Diagnostic performance of
36 702 rPol d 5 and rVes v 5 for differentiating sensitization to *Vespula* and *Polistes*
37 703 subspecies. *Clin Chim Acta*. 2016 Jan 30;453:170-3.

1

2

3 704 44)Hemmings O, Kwok M, McKendry R, Santos AF. Basophil activation test: old and new
4 applications in allergy. *Curr Allergy Asthma Rep.* 2018 Nov 15;18(12):77.

6 706 45)Balzer L, Pennino D, Blank S, Seismann H, Darsow U, Schnedler M, McIntyre M, Ollert
8 707 MW, Durham SR, Spillner E, Ring J, Cifuentes L. Basophil activation test using
9 recombinant allergens: highly specific diagnostic method complementing routine tests
10 708 in wasp venom allergy. *PLoS One.* 2014 Oct 17;9(10)
11 709

13 710 46)Korošec P, Šilar M, Eržen R, Čelesnik N, Bajrović N, Zidarn M, Košnik M. Clinical
15 711 routine utility of basophil activation testing for diagnosis of hymenoptera-allergic
16 712 patients with emphasis on individuals with negative venom-specific IgE antibodies. *Int
17 713 Arch Allergy Immunol.* 2013;161(4):363.

20 714 47)Eržen R, Košnik M, Silar M, Korošec P. Basophil response and the induction of a
21 tolerance in venom immunotherapy: a long-term sting challenge study. *Allergy.* 2012
22 715 Jun;67(6):822-30.
23 716

25 717 48)Schmid JM, Würtzen PA, Siddhuraj P, Jogdand P, Petersen CG, Dahl R, Erjefält JS,
27 718 Hoffmann HJ. Basophil sensitivity reflects long-term clinical outcome of subcutaneous
28 immunotherapy in grass pollen-allergic patients. *Allergy.* 2020 Mar 7. [Epub ahead of
29 719 print].
30 720

32 721 49)Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, Azar A, Baroody FM,
34 722 Bachert C, Canonica GW, Chacko T, Cingi C, Ciprandi G, Corey J, Cox LS, Creticos
35 723 PS, Custovic A, Damask C, DeConde A, DelGaudio JM, Ebert CS, Eloy JA, Flanagan
37 724 CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ,
39 725 Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M,
41 726 Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU,
42 727 Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson
44 728 HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L,
46 729 Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL,
47 730 Tantilipikorn P, Tversky JR, Veling MC, Wang Y, Westman M, Wickman M, Zacharek
49 731 M. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int
51 732 Forum Allergy Rhinol.* 2018;8(2):108-352

53 733 50)Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones
54 734 P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision
56 735 medicine of chronic airway diseases. *Eur Respir J.* 2016 Feb;47(2):410-9
58
59
60

1

2

3 736 51) Woodruff PG, Agusti A, Roche N, Singh D, Martinez FJ. Current concepts
4
5 737 in targeting chronic obstructive pulmonary disease pharmacotherapy: making
6
7 738 progress towards personalised management. *Lancet*. 2015;385(9979):1789-1798.

8 739 52) Tay TR, Hew M. Comorbid, "treatable traits" in difficult asthma: current evidence and
9
10 740 clinical evaluation. *Allergy*. 2017;101:130.

11
12 741 53) McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of
13
14 742 chronic airway diseases. *Chron Respir Dis*. 2019;16:1479973119867954.

15 743 54) Pavord ID, Agusti A. Blood eosinophil count: a biomarker of an important treatable trait
16
17 744 in patients with airway disease. *Eur Respir J*. 2016;47(5):1299-303.

18
19 745 55) Simpson AJ, Hekking PP, Shaw DE, Fleming LJ, Roberts G, Riley JH, Bates S, Sousa
20
21 746 AR, Bansal AT, Pandis I, Sun K, Bakke PS, Caruso M, Dahlén B, Dahlén SE, Horvath
22 747 I, Krug N, Montuschi P, Sandstrom T, Singer F, Adcock IM, Wagers SS, Djukanovic
23
24 748 R, Chung KF, Sterk PJ, Fowler SJ; U-BIOPRED Study Group. Treatable traits in
25
26 749 the European U-BIOPRED adult asthma cohorts. *Allergy*. 2019 Feb;74(2):406-411.

27 750 56) Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. *Curr Opin*
28
29 751 *Pulm Med*. 2018;24(1):24-31.

30
31 752 57) Bousquet J, Pfaar O, Togias A, Schünemann HJ, Ansotegui I, Papadopoulos NG,
32
33 753 Tsiligianni I, Agache I, Anto JM, Bachert C, Bedbrook A, Bergmann KC, Bosnic-
34 754 Anticevich S, Bosse I, Brozek J, Calderon MA, Canonica GW, Caraballo L, Cardona V,
35
36 755 Casale T, Cecchi L, Chu D, Costa E, Cruz AA, Czarlewski W, Durham SR, Du Toit G,
37
38 756 Dykewicz M, Ebisawa M, Fauquert JL, Fernandez-Rivas M, Fokkens WJ, Fonseca J,
39 757 Fontaine JF, Gerth van Wijk R, Haahtela T, Halcken S, Hellings PW, Ierodiakonou D,
40
41 758 Iinuma T, Ivancevich JC, Jacobsen L, Jutel M, Kaidashev I, Khaitov M, Kalayci O,
42
43 759 Kleine Tebbe J, Klimek L, Kowalski ML, Kuna P, Kvedariene V, La Grutta S, Larenas-
44
45 760 Linemann D, Lau S, Laune D, Le L, Lodrup Carlsen K, Lourenço O, Malling HJ, Marien
46 761 G, Menditto E, Mercier G, Mullol J, Muraro A, O'Hehir R, Okamoto Y, Pajno GB, Park
47
48 762 HS, Panzner P, Passalacqua G, Pham-Thi N, Roberts G, Pawankar R, Rolland C,
49
50 763 Rosario N, Ryan D, Samolinski B, Sanchez-Borges M, Scadding G, Shamji MH, Sheikh
51
52 764 A, Sturm GJ, Todo Bom A, Toppila-Salmi S, Valentin-Rostan M, Valiulis A, Valovirta E,
53 765 Ventura MT, Wahn U, Walker S, Wallace D, Wasserman S, Yorgancioglu A, Zuberbier
54
55 766 T; ARIA Working Group. 2019 ARIA Care pathways for allergen immunotherapy.
56
57 767 *Allergy*. 2019;74(11):2087-2102.

58 768 58) Mushra R. Science of omics: Perspectives and prospects for human health care. *Integr*
59
60 769 *Mol. Med*. 2016;IMM.1000258.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 59) Abdel-Aziz MI, Neerincx AH, Vijverberg SJ, Kraneveld AD, Maitland-van der Zee AH. Omics for the future in asthma. *Semin Immunopathol.* 2020;42(1):111-126.
- 60) Devillier P, Salvator H, Naline E, Couderc LJ, Gtassin-Delyle S. Metabolomics in the diagnosis and pharmacotherapeutic management of respiratory diseases. *Curr Pharm Des.* 2017;23(14):2050-2059.
- 61) Park CS, Rhim T. Application of proteomics in asthma research. *Expert Rev Proteomics.* 2011;8(2):221-30
- 62) Martin-Sanchez F, Bellazzi R, Casella V, Dixon W, Lopez-Campos G, Peek N. Progress in Characterizing the Human Exposome: a Key Step for Precision Medicine. *Yearb Med Inform.* 2020 [Epub ahead of print]
- 63) Donovan BM, Bastarache L, Turi KN, Zutter MM, Hartert TV. The current state of omics technologies in the clinical management of asthma and allergic diseases. *Ann Allergy Asthma Immunol.* 2019;123(6):550-557.
- 64) FitzGerald JM, Poureslami I. The need for humanomics in the era of genomics and the challenge of chronic disease management. *Chest.* 2014 Jul;146(1):10-12.
- 65) Canonica GW, Bagnasco D, Ferrantino G, Ferrando M, Passalacqua G. Update on immunotherapy for the treatment of asthma. *Curr Opin Pulm Med.* 2016;22(1):18-2
- 66) Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once daily grass allergen tablet: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 2006;117:802-809.
- 67) Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 2007; 120:1338-1345.
- 68) Wahn U, Tabar A, Kuna P, et al. SLIT Study Group. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 2009;123:160-166.
- 69) Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2014;134(3):568-75.
- 70) Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133(6):1608-14.

1

2

3 803 71)Batard T, Hrabina A, Bi XZ, Chabre H, Lemoine P, Couret MN, Faccenda D, Villet
4 B, Harzic P, André F, Goh SY, André C, Chew FT, Moingeon P. Production and
5 804 proteomic characterization of pharmaceutical-grade *Dermatophagoides pteronyssinus*
6 805 and *Dermatophagoides farinae* extracts for allergy vaccines. *Int Arch Allergy*
7 806 *Immunol.* 2006;140(4):295-305)

10 807

11

12 808 72)Bordas-Le Floch V, Le Mignon M, Bussièrès L, Jain K, Martelet A, Baron-Bodo V, Nony
13 809 E, Mascarell L, Moingeon P. A combined transcriptome and proteome analysis extends
14 810 the allergome of house dust mite *Dermatophagoides* species. *PLoS One.* 2017 Oct
15 811 5;12(10):e0185830

17 811

18

19 812 73)Herland K, Akselsen JP, Skjønberg OH, Bjermer LHow representative are clinical
20 813 study patients with asthma or COPD for a larger "real life" population of patients with
21 814 obstructive lung disease? *Respir Med.* 2005;99(1):11-9.

24 815

25

26 816 74)Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, Morgan
27 817 RL, Gartlehner G, Kunz R, Katikireddi SV, Sterne J, Higgins JP, Guyatt
28 818 G; GRADE Working Group. GRADE guidelines: 18. How ROBINS-I and other tools to
29 819 assess risk of bias in nonrandomized studies should be used to rate the certainty of a
30 820 body of evidence. *J Clin Epidemiol.* 2019 Jul;111:105-114.

32 820

33

34 821 75)Roche N, Anzueto A, Bosnic Anticevich S, Kaplan A, Miravittles M, Ryan D, Soriano JB,
35 822 Usmani O, Papadopoulos NG, Canonica GW; Respiratory Effectiveness Group
36 823 Collaborators. The importance of real-life research in respiratory medicine: manifesto of
37 824 the Respiratory Effectiveness Group: Endorsed by the International Primary Care
38 825 Respiratory Group and the World Allergy Organization. *Eur Respir J.* 2019 19;54(3)

41 825

42

43 826 76)Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, LaVange
44 827 L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue
45 828 LQ, Califf RM . Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J*
46 829 *Med.* 2016;375(23):2293-2297..

48 829

49

50 830 77)Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefit of allergen
51 831 immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy.* 2018;
52 832 74(3):594-604.

53 832

54

55 833 78)Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy
56 834 provides long-term relief in allergic rhinitis and reduces the risk of asthma: a
57 835 retrospective, real-world database analysis. *Allergy.* 2018;165-177.

58 835

59

60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 79)Hulsen T, Jamuar SS, Moody AR, Karnes JH, Varga O, Hedensted S, Spreafico R, Hafler DA, McKinney EF. From Big Data to Precision Medicine. Front Med (Lausanne). 2019;6:34. 2019.
- 80)Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010; 22; 363(4):301-4.
- 81)Calderon M, Demoly P, Gert van Wijk R, Bousquez J, Sheikh A, Frew A, Scadding G, Bachert c, et al. EAACI: a European declaration on immunotherapy. Designing the future of allergen specific immunotherapy. Clin Transl Allergy 2012 30;2(1):20.
- 82)Passalacqua G, Canonica GW. AIT (allergen immunotherapy): a model for the "precision medicine". Clin Mol Allergy. 2015; 8;13:24
- 83)Bachert C, Larché M, Bonini S, Canonica GW, Kündig T, Larenas-Linnemann D, Ledford D, Neffen H, Pawankar R, Passalacqua G. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. World Allergy Organ J. 2015;8(1):29.
- 84)Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M, Kleine-Tebbe J, Klimek L, Klysner S, Kopp MV, Kuna P, Larché M, Muraro A, Schmidt-Weber CB, Shamji MH, Simonsen K, Somoza C, Valovirta E, Ziegelmayer P, Zuberbier T, Wahn U; FASIT group. Perspectives in allergen immunotherapy: 2017 and beyond. Allergy. 2018;73 Suppl 104:5-23.
- 85)Jacobsen L, Wahn U, Bilo MB. Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: the effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy. Clin Transl Allergy. 2012 Apr 13;2:8.
- 86)Cox LS, Murphey A, Hankin C.The Cost effectiveness of allergen immunotherapy compared with pharmacotherapy for treatment of allergic rhinitis and asthma. Immunol Allergy Clin North Am. 2020;40(1):69-85.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

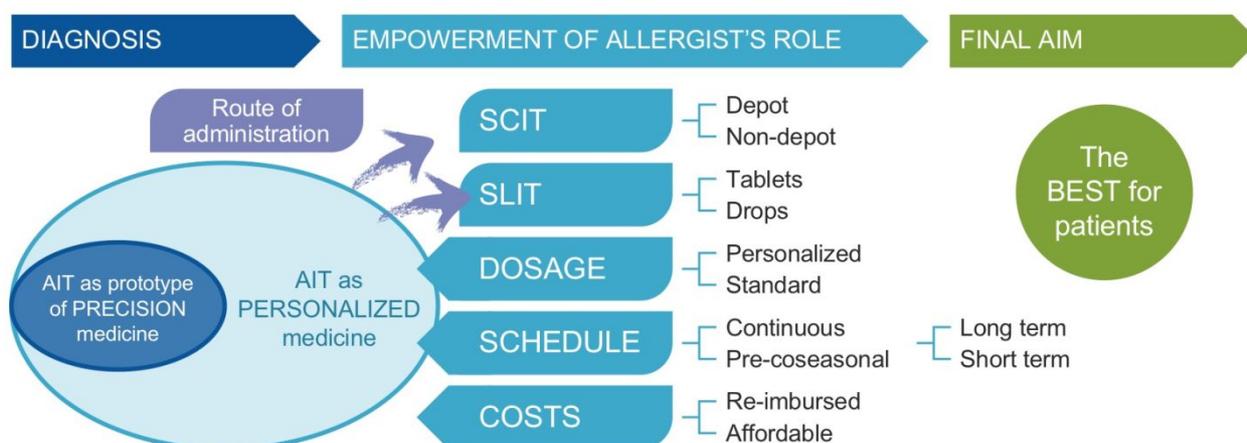
871 87) Krishna MT, Knibb RC, Huissoon AP. Is there a role for telemedicine in adult allergy
872 services?. Clin Exp Allergy. 2016;46(5):668-77.

873
874
875 88) Gómez RM, Ansotegui I, Canonica GW. Will precision medicine be available for all
876 patients in the near future? Curr Opin Allergy Clin Immunol. 2019;19(1):75-80.

DRAFT REVIEW ARTICLE dated 11.11.2020
For Peer Review

880 **Figure 1** - Allergen Immunotherapy as personalized treatment

AIT AS PERSONALIZED TREATMENT



881

882

883

884

883 **Figure 2** - Tools for personalized Allergen Immunotherapy

Tools for personalized AIT

Validated tools for AIT

- Clinical history
- Skin tests with allergen extracts
- Serum-specific IgE
- Component-resolved diagnosis
- CAP-inhibition (*limited*)



Tools still to be validated for AIT

- Basophil activation test
- Nasal cytology
- Nasal challenge with the suspected allergen



Tools of future applications

- Treatable traits (*genetic, phenotypic, psychosocial features*)
- Omics (*proteomics, epigenomics, metabolomics, breathomics*)



885

886

887

888

889

890

891

892

893

894

895

896

897

898

899

900

901

902

903

904

905

906

907

908

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Personalized Medicine for allergy treatment: allergen immunotherapy**
2 **still a unique and unmatched model.**

3
4 Incorvaia Cristoforo¹, Al-Ahmad Mona^{2,3}, Ansotegui Ignacio⁴, Arasi Stefania⁵, Bachert
5 Claus^{6,7}, Bos Catherine⁸, Bousquet Jean⁹, Bozek Andrzej¹⁰, Caimmi Davide¹¹, Calderón
6 Moises¹², Casale Thomas¹³, Custovic Adnan¹⁴, De Blay Frédéric¹⁵, Demoly Pascal^{11,16},
7 Devillier Philippe¹⁷, Didier Alain¹⁸, Fiocchi Alessandro⁵, Fox Adam¹⁹, Gevaert Philippe⁶,
8 Gomez Maximiliano²⁰, Heffler Enrico^{21,22}, Iliina Natalia²³, Irani Carla²⁴, Jutel Marek²⁵,
9 Karagiannis Efstrathios⁸, Klimek Ludger²⁶, Kuna Piotr²⁷, O’Hehir Robin²⁸, Kurbacheva
10 Oxana²⁹, Matricardi Paolo Maria³⁰, Morais de Almeida Mario^{31,32}, Mosges Ralph^{33,34},
11 Novak Natalija³⁵, Okamoto Yoshitaka³⁶, Panzner Petr³⁷, Papadopoulos Nikolaos^{38,39}, Park
12 Hae-Sim⁴⁰, Passalacqua Giovanni⁴¹, Pawankar Ruby⁴², Pfaar Oliver⁴³, Schmid-
13 Grendelmeier Peter⁴⁴, Scurati Silvia⁸, Tortajada-Girbés Miguel^{45,46}, Vidal Carmen⁴⁷,
14 Virchow Christian⁴⁸, Wahn Ulrich³⁰, Worm Margitta³⁰, Ziegelmayer Petra⁴⁹, Canonica
15 Giorgio Walter^{21,22}.

16
17 **Affiliations**

- 18 1. Cardiac/Pulmonary Rehabilitation, ASST Pini/CTO, Milan, Italy
- 19 2. Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait
- 20 3. Drug Allergy Unit, Department of Allergy, Al-Rashed Allergy Center, Kuwait
- 21 4. Hospital Quirónsalud Bizkaia, Bilbao, Spain
- 22 5. Department of Allergy, Bambino Gesù' Childrens' Hospital IRCCS, Rome, Italy
- 23 6. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent,
24 Belgium.
- 25 7. Karolinska Institutet, Stockholm; Department of ENT Diseases, Karolinska University
26 Hospital, Stockholm.
- 27 8. Stallergenes Greer Medical Affairs Department, Antony, France
- 28 9. University Hospital Montpellier, France - MACVIA-France, Montpellier, France
- 29 10. Clinical Department of Internal Disease, Dermatology and Allergology, Medical
30 University of Silesia, Katowice , Poland
- 31 11. Department of Pulmonology and Addictology, Arnaud de Villeneuve Hospital,
32 Montpellier University, Montpellier, France
- 33 12. Imperial College London - National Heart and Lung Institute, Royal Brompton Hospital
34 NHS, London, United-Kingdom

1

2

3 35 13. Division of Allergy/Immunology, University of South Florida, Tampa, FL United-States

4 36 14. Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair,

5 37 University of Manchester and University Hospital of South Manchester, Manchester,

6 38 United-Kingdom

7 39 15. Allergy Division, Chest Diseases Department, Strasbourg University Hospital,

8 40 Strasbourg, France

9 41 16. Sorbonne Université, UMR-S 1136 INSERM, IPLESP, EPAR Team, Paris, France

10 42 17. Laboratoire de Recherche en Pharmacologie Respiratoire, Pôle des Maladies des

11 43 Voies Respiratoires, Hôpital Foch, Université Paris-Saclay, Suresnes, France

12 44 18. Respiratory Disease Dept, Larrey Hospital, University Hospital of Toulouse, Paul

13 45 Sabatier University, Toulouse, France

14 46 19. Department of Paediatric Allergy, Guy's & St Thomas' Hospitals NHS Foundation Trust,

15 47 London, United Kingdom

16 48 20. Allergy & Asthma Unit, Hospital San Bernardo Salta, Salta, Argentina

17 49 21. Personalized Medicine, Asthma & Allergy - Humanitas Clinical and Research Center

18 50 IRCCS, Rozzano (MI), Italy

19 51 22. Department of Biomedical Science, Humanitas University, Pieve Emanuele (MI), Italy.

20 52 23. Federal Institute of Immunology of Russia, Russia

21 53 24. Department of Internal Medicine and Clinical Immunology, Hotel Dieu de France

22 54 hospital. Faculty of Medicine, Saint Joseph University, Beirut, Lebanon.

23 55 25. Department of Clinical Immunology, Wrocław Medical University, Wrocław, Poland.

24 56 26. Center for Rhinology and Allergology, Wiesbaden, Germany

25 57 27. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical

26 58 University of Lodz, Lodz, Poland

27 59 28. Alfred Hospital and Monash University, Melbourne, Australia

28 60 29. National Research Center - Institute of Immunology Federal Medical-Biological Agency

29 61 of Russia, Moscow, Russia

30 62 30. Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine,

31 63 Charité - University Medicine Berlin, Berlin, Germany

32 64 31. Immunoallergy Department of CUF-Descobertas Hospital, Lisbon Portugal

33 65 32. CUF-Infante Santo Hospital, Lisbon, Portugal

34 66 33. Faculty of Medicine, Institute of Medical Statistics and Computational Biology,

35 67 University of Cologne, Cologne, Germany

36 68 34. CRI - Clinical Research International Ltd., Cologne, Germany

1

2

3 69 35. Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany

4 70 36. Department of Otorhinolaryngology, Chiba University Hospital, Chiba, Japan.

5 71 37. Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles
6 72 University in Prague, Pilsen, Czech Republic

7 73 38. Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's
8 74 Hospital, University of Manchester, Manchester, United-Kingdom

9 75 39. Allergy Department, 2nd Pediatric Clinic, Athens General Children's Hospital "P&A
10 76 Kyriakou", University of Athens, Athens, Greece

11 77 40. Department of Allergy and Clinical Immunology, Ajou University School of Medicine,
12 78 Suwon, South Korea

13 79 41. Allergy and Respiratory Diseases, Ospedale Policlinico San Martino -University of
14 80 Genoa, Genoa, Italy.

15 81 42. Department of Pediatrics, Nippon Medical School, Tokyo, Japan

16 82 43. Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and
17 83 Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

18 84 44. Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland

19 85 45. Pediatric Pulmonology and Allergy Unit, Department of Pediatrics, Dr. Peset University
20 86 Hospital, Valencia, Spain,

21 87 46. Department of Pediatrics, Obstetrics and Gynecology. University of Valencia, Valencia,
22 88 Spain., IVI Foundation, Valencia, Spain

23 89 47. Allergy Service, Complejo Hospitalario Universitario de Santiago, Santiago de
24 90 Compostela

25 91 48. Department of Pneumology/Intensive Care Medicine, University of Rostock, Germany

26 92 49. Vienna Challenge Chamber, Vienna, Austria

27 93

28 94 **Corresponding author**

29 95 Enrico Heffler, Personalized Medicine, Asthma and Allergy, Humanitas University and
30 96 Research, Hospital ICH, Via Alessandro Manzoni 56, Rozzano, Milan 20089, Italy,
31 97 heffler.enrico@gmail.com

32 98

33 99

34 100

35 101

36 102

37 103

38 104

39 105

1
2
3 99 **Abstract**

4
5 100 The introduction of personalized medicine (PM) has been a milestone in the history of
6
7 101 medical therapy, because it has revolutionized the previous approach of treating the
8
9 102 disease with that of treating the patient. It is known today that diseases can occur in
10 103 different genetic variants, making specific treatments of proven efficacy necessary for a
11
12 104 given endotype. Allergic diseases are particularly suitable for PM, because they meet the
13
14 105 therapeutic success requirements, including a known molecular mechanism of the
15 106 disease, a diagnostic tool for such disease, and a treatment blocking the mechanism. The
16
17 107 stakes of PM in allergic patients are molecular diagnostics, to detect specific IgE to single
18
19 108 allergen molecules and to distinguish the causative molecules from those merely cross-
20
21 109 reactive, pursuit of patient's treatable traits addressing genetic, phenotypic and
22 110 psychosocial features, and omics, such as proteomics, epi-genomics, metabolomics and
23
24 111 breathomics, to forecast patient's responsiveness to therapies, to detect biomarker and
25
26 112 mediators, and verify the disease control. This new approach has already improved the
27
28 113 precision of allergy diagnosis and is likely to significantly increase, through the higher
29 114 performance achieved with the personalized treatment, the effectiveness of allergen
30
31 115 immunotherapy by enhancing its already known and unique characteristics of treatment
32
33 116 that acts on the causes.

34 117
35
36 118 **Key words:** allergen immunotherapy, personalized medicine, molecular diagnosis,
37
38 119 treatable traits, omics.

39 120
40
41 121 **Short title:** Allergen immunotherapy: a model of personalized medicine.
42
43 122
44
45 123
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 2 3 124 **Introduction**

4
5 125 In its millennial history, medicine has had the primary aim of treating diseases. The
6
7 126 development in the 1800s of pharmaceutical therapy with synthetic drugs was a
8
9 127 breakthrough¹, but the concept that a given drug was suitable for treating a given disease,
10 128 regardless of the characteristics of the individual patient, have survived for a long time.
11
12 129 The conceptual framework of genotypes, endotypes and phenotypes² has provided crucial
13
14 130 tools to understand that the characteristics of the individual also affect the response to
15 131 drugs and paved the way to the new era of personalized (otherwise defined precision)
16
17 132 medicine. The new approach was first applied on oncology, concerning both diagnosis and
18
19 133 treatment³, but soon, with a significant boost from President Obama's announcement on
20
21 134 the great potential of personalized medicine⁴, many other fields of medicine gained its
22 135 benefits. As far as allergic and immune-mediated diseases are concerned, the introduction
23
24 136 of biologics to treat severe asthma provided a significant advance in personalized
25
26 137 treatment, through their ability to work on asthma according on molecular phenotypes
27 138 defined as high type 2 immunity asthma and low type 2 immunity asthma⁵. However,
28
29 139 allergen immunotherapy (AIT), a treatment for respiratory allergy first proposed in 1911
30
31 140 which in its long road has gone from empiricism to full scientific evidence⁶ can actually be
32
33 141 proposed as "a medical model aiming to deliver customized healthcare, with medical
34 142 decisions, practices, and/or products tailored to the individual patient"⁷. The primary
35
36 143 therapeutic goal of AIT include reducing the frequency and intensity of symptoms, the use
37
38 144 of rescue medications, and improving the allergy-related quality of life. There is very strong
39
40 145 evidence to show that AIT achieves these goals in patients with allergic rhinitis⁸.
41 146 Furthermore, in mite-induced asthma AIT is likely to enable a successful step-down in the
42
43 147 inhaled corticosteroid dose in patients graded as step 3 or 4 of GINA scale⁹. Here we will
44
45 148 analyze the factors underlying the characteristics of AIT as an optimal model for
46 149 personalized medicine.

48 150 **The birth of AIT and its embryonic properties as a personalized treatment.**

49
50 151 As hinted above, AIT was introduced more than one hundred years ago, when the
51
52 152 knowledge on allergic disease was very limited⁶. Still, the different role of AIT compared
53 153 with the drug therapy available at the time was apparent, because drugs were aimed at
54
55 154 treating the symptoms of allergic rhinitis, while AIT was aimed at treating the specific
56
57 155 allergy of single patients, thus introducing a concept now acknowledged as personalized
58
59 156 medicine. The first studies addressed "hay fever" induced by grass pollen. It is obvious
60 157 that the quality of the products in that time, which consisted of extracts obtained from the

1
2
3 158 allergenic source directly from the doctor, was hugely lower than the allergen extracts
4
5 159 used today, but the positive results obtained paved the way to an evolution finally resulting
6
7 160 in high quality products. Another definition that underlines how the AIT was yet, but
8
9 161 improperly, proposed as personalized for the patient is “Named Patient Product” (NPP),
10 162 i.e. specifically prepared for a given patient according to the results of allergy testing.
11
12 163 Nevertheless, NPPs were not a guarantee of clinical efficacy, because alongside products
13
14 164 with evidence of efficacy proven by placebo-controlled trials, others without such evidence
15 165 were equally admitted to the prescription. Moreover, extracts containing several allergens,
16
17 166 namely all the allergens giving positive results to allergy testing, were frequently used,
18
19 167 especially in the U.S.A, but they were found to be ineffective in a pivotal double-blind,
20
21 168 placebo-controlled trial in 1997¹⁰. Nowadays, registered products, whose effectiveness
22 169 has been plainly demonstrated by controlled trials on large patient populations, are
23
24 170 considered ideal for AIT¹¹. However, good quality NPPs with demonstration of efficacy by
25
26 171 placebo-controlled trials, are still available to treat respiratory allergy with expectancy of
27 172 clinical success¹².

29 173 **Modern AIT as a prototype of personalized medicine.**

30
31 174 The traditional diagnosis by skin tests relay on extracts, whose composition in minor and
32
33 175 major allergens can play a crucial role in defining sensitizations, as in the AIT products for
34 176 inducing clinical efficacy. Another critical factor is the extract potency, concerning both skin
35
36 177 testing and AIT. As to the latter, Larenas-Linneman et al. found a substantial variability in
37
38 178 allergen extract potency as measured and reported worldwide^{13,14}. In particular, in Europe
39
40 179 the potency of extracts for sublingual immunotherapy (SLIT) is based on comparison with
41 180 in-house references, making it difficult to translate the dose to US extracts¹³. Moreover,
42
43 181 comparing SLIT maintenance solutions of grass pollen and *Dermatophagoides*
44
45 182 *pteronysinus* from 4 leading European manufacturers to standardized concentrate
46 183 extracts of 3 US manufacturers measure in bioequivalent allergen units (BAU), the relative
47
48 184 potency was around 10 times higher for US standardized extracts (to be diluted for SLIT)
49
50 185 than for European SLIT maintenance dosage. The authors argued that, based on the
51
52 186 efficacy demonstrations from controlled trials, SLIT efficacy is likely to depend on
53 187 additional factors apart from the extract dose¹⁴. Today, the pillars of AIT as a personalized
54
55 188 therapy are represented by molecular diagnostics for achieving the highest possible
56
57 189 precision, by the use of treatable traits, and by “omics”.

58 190
59
60 191

1) Molecular diagnostics and other *in vitro* tests

The diagnosis of allergy has been long based on skin prick test (SPT) with allergen extracts and *in vitro* test measuring specific IgE antibodies to the suspected allergens, but with both techniques the positive results indicated sensitization but not necessarily clinical allergy. A great advance in diagnostic precision was achieved by molecular diagnosis, which allows to detect specific IgEs (sIgEs) to each single molecule, distinguishing those really causative (genuine) from those simply cross-reactive. Such diagnostic approach was variously named, including “Component resolved diagnosis”¹⁵, molecular-based allergy diagnostics¹⁶, and molecular allergy diagnostics¹⁷. The updated WAO-ARIA- GA²LEN consensus document on molecular-based allergy proposed the unifying definition of “precision allergy molecular diagnostic applications” (PAMD@)¹⁸. This allergy diagnostics approach is aimed at mapping the allergen sensitization of a patient at a molecular level, using purified natural or recombinant allergenic molecules instead of allergen extracts. Each allergen molecule is identified, classified according to the family to which it belongs, and scientifically named according to the species to which it belongs. For example, the major allergen from cockroach is a lipocalin named Bla g 4 (after *Blattella germanica*¹⁹). Since its introduction, PAMD@ has been gradually used as a laboratory tool, and presently more than 130 allergenic molecules commercially are accessible for *in vitro* sIgE testing²⁰. Two platform to perform PAMD@ are available, which include a singleplex (i.e. a single assay per sample) or a multiplex (i.e. multiple assays per sample) measurement. With the former, the allergenic molecules thought to be responsible are selected by the physician²¹, while with the multiplex technique a large array of preselected allergens are tested. The commercially offered multiplex allergen arrays include the Immuno-CAP Immuno-solid-phase Allergen Chip (ISAC) from Thermo Fisher, containing 103 molecules from 51 allergen sources²², and the new ImmunoCAP ISAC 112i, including 112 components from 48 allergen sources, where some molecules from *Hymenoptera* venom and from walnut and plain tree have been eliminated, while others from cashew, hazelnut, dog, dust mites, and alpha-gal were added²³. The EUROLINE Southern European Pollen Profile [ESEP) was introduced to test pollen molecules of clinical relevance in Southern Europe²⁴, while the Microarray Diagnostics (MADx) Allergen Explorer (ALEX) include 126 molecules from different allergen sources²⁵. It is apparent that in order to properly interpret positive results for a high number of molecules, a great experience of the examining physician is necessary. To facilitate the matter, expert systems were developed to support the data analysis by dedicated decision-making

1
2
3 226 information systems. For instance, the expert system named Allergenius® is based on the
4
5 227 ImmunoCAP ISAC implemented with an advanced knowledge specification language
6
7 228 using more than 700 different rules to mimic the experts' opinions on a complex ISAC
8
9 229 result²⁶. In a study comparing sera from patients assayed with ImmunoCAP ISAC and
10 230 ALEX a good correlation between the results from the two methods was found²⁷.

11
12 231 By focusing on applications for personalized medicine, numerous studies have assessed
13
14 232 the benefits of attaining with PAMD@ a more appropriate prescription for AIT. Table 1
15 233 summarizes the observations from these studies²⁸⁻³⁷. A vast literature is available, as
16
17 234 recently reviewed³⁸⁻³⁹, also for the advantages of PAMD@ in the diagnosis of food allergy
18
19 235 compared to the conventional diagnosis, but this will not be treated here since the purpose
20
21 236 of our analysis is to examine the progress achieved by PAMD@ in the appropriate
22 237 prescription of AIT. In fact, despite the numerous controlled AIT trials for food allergy⁴⁰,
23
24 238 this therapy has not yet been approved.

25
26 239 As far as the identification of the really causative allergen in polysensitized patients is
27 240 concerned, the first *in vitro* test was the RAST inhibition⁴¹, which then evolved into CAP
28
29 241 inhibition assay. The latter has been shown to be comparable to PAMD@ in the ability to
30
31 242 identify the causative allergen^{35,42} and to have a lower cost⁴³ in patients with multiple
32
33 243 sensitization to *Hymenoptera* venom, in which a limited number of allergenic molecules
34 244 are responsible, while such outcomes was not reported for multi-sensitization to
35
36 245 respiratory allergens, involving a much higher number of molecules.

37
38 246 The basophil activation test (BAT), which measures basophil degranulation by flow
39 247 cytometry, has the unique characteristic to detect *in vitro* the reactivity of basophils to
40
41 248 allergens. Since these cells play a crucial role in allergic reactions, their *in vitro* detection
42
43 249 has a similar meaning to the *in vivo* provocation test with specific allergens, without
44
45 250 however the limit of false positive results from non-specific reactions, which represented a
46 251 limit of *in vivo* tests. BAT was found to be very useful in the personalized diagnosis of
47
48 252 patients with allergic conditions including respiratory, food and *Hymenoptera* venom
49
50 253 allergy who show multiple allergen reactivity, distinguishing the allergens as causative or
51
52 254 not based on the response of the basophils⁴⁴. As mentioned above, our review is focused
53 255 on the effects of personalized diagnosis on the outcomes of AIT. As for CAP inhibition, the
54
55 256 first studies concerned *Hymenoptera* venom allergy, demonstrating that BAT
56
57 257 accomplished with the recombinant allergens from *Vespula* spp Ves v 1, Ves v 2, Ves v 3
58 258 and Ves v 5 achieved a clear improvement in the specificity of diagnosis in patients with
59
60 259 anaphylactic reactions to wasp stings over IgE detection by Enzyme-Linked

1
2

3 260 ImmunoSorbent Test (ELISA) or ImmunoCAP⁴⁵ and that in patients with severe reactions
4
5 261 to stings, some of them with negative response to sIgE test and intradermal tests, BAT
6
7 262 was positive in 81% of patients compared with to a rate 57% with intradermal testing,
8
9 263 14% with IgE test, 19% of patients being negative to either test except BAT⁴⁶. A study
10
11 264 analyzed the correlation between the BAT changes during venom immunotherapy and
12
13 265 the treatment outcome. BAT was unchanged after one year, but in subsequent years a
14
15 266 fourfold reduction was detected in all patients who developed tolerance to stings, while
16
17 267 no change in BAT occurred in patients with a persistently positive sting challenge⁴⁷.
18
19 268 Such important outcome was found also in patients treated with subcutaneous
20
21 269 immunotherapy (SCIT) for grass pollen allergy. In fact, basophil sensitivity showed a
22
23 270 447-fold decrease in the first year of treatment, remaining 100-fold lower than baseline
24
25 271 in the 3 year-treatment period and 10-fold lower in the follow-up year. Notably, a
26
27 272 decline in basophil sensitivity after three weeks of SCIT predicted long-
28
29 273 term improvement in symptom and medication scores during the three years of
30
31 274 treatment⁴⁸. Further studies are needed to clarify the role of BAT as a biomarker or a
32
33 275 predictive marker of AIT efficacy.

32 276

33 277 **2 In vivo tests**

35 278 Theoretically, inducing allergic symptoms by a challenge with the suspected allergen in the
36
37 279 target organs can be a valuable in vivo test. However, as stated in the International
38
39 280 Consensus Statement on allergic rhinitis, the contrasting findings from different studies
40
41 281 and the absence thus far of a standardized technique limit the diagnostic utility of nasal
42
43 282 challenge, a pivotal role being currently acknowledged only in diagnosis of occupational
44
45 283 rhinitis and local allergic rhinitis⁴⁹. If future studies will achieve standardization of the
46
47 284 method, the nasal challenge could be used, alike BAT, as a test toward precision medicine.

47 285

49 286 **3. Treatable traits**

51 287 The term "Treatable traits" was suggested by Agusti and coworkers to indicate a precision
52
53 288 medicine methodology of diagnosis and treatment of chronic disorders of the airways
54
55 289 based on finding genetic, phenotypic and psychosocial features which are associated with
56
57 290 therapies able to improve respiratory health⁵⁰. The field of application considered as most
58
59 291 appropriate for the use of treatable traits is represented by chronic respiratory diseases
60
292 and in particular by asthma and chronic obstructive pulmonary disease (COPD), which
293 share various clinical aspects but whose drug therapy has significantly differentiated in

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

327

recent years⁵¹. For example, using treatable traits in a patient with COPD but symptoms compatible also with asthma and positivity of tests for respiratory allergy due to asymptomatic sensitization would prevent the incorrect prescription of AIT. The role of treatable traits in the management of chronic respiratory diseases has been outlined by some important studies. The first investigated the role of extra-pulmonary comorbidities as treatable traits in patients with difficult-to-control asthma. The proposed comorbidities were allergic and nonallergic rhinitis, chronic rhinosinusitis, vocal cord dysfunction, dysfunctional breathing, gastroesophageal reflux, obesity, obstructive sleep apnoea, and anxiety/depression, of which the prevalence, impact and outcome of treatment were assessed, also appraising the associations of single comorbidities and the potential of comorbidity clusters on asthma control. The authors concluded that extra-pulmonary comorbidities are important treatable traits to be evaluated in all asthmatic patients and especially in those with difficult asthma. Such comorbidities may have a significant influence on asthma control, thus their presence deserves treatment regardless of original asthma status and asthma control⁵². The number of treatable traits involved in acute exacerbation differed according to the respiratory disease, with a major role for C reacting protein in COPD, eosinophils count and fractionated exhaled nitric oxide (FeNO) measurement in asthma, and bacterial infections for bronchiectasis⁵³.

An important observation obtained through the review of the literature by Pavord and Agusti concerned the identification of eosinophilic airway inflammation, as assessed by the blood eosinophil count, as a treatable trait of particular importance in patients with airway disease (including asthma and COPD, being significantly associated with long-term outcomes⁵⁴. The recent European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project was aimed at identifying and quantifying, based on the hypothesis that treatable traits are more common in severe asthma and may significantly differ according to asthma phenotypes, the treatable traits recognized in the severe and mild/moderate adult asthma cohorts and across previously identified phenotypes⁵⁵.

All studies available thus far support a chief role of treatable traits in evaluating patients with respiratory diseases, however the preferable method of application and the cost-effectiveness of such a multidimensional intervention is still uncertain, making it necessary to conduct randomized controlled trials involving large populations of patients⁵⁶. Concerning AIT, treatable traits of clinical interest may consist of the treatment outcome, beyond the disease to be treated, on comorbidities⁵⁷. Another trait may concern the

1

2

3 328 possible synergistic effect of biologics and AIT. Precision medicine of allergic diseases is
4
5 329 nowadays highlighted by the consistent data of efficacy of biologics targeting cytokines ((IL
6
7 330 5) or their receptors (IL 5 rec. or IL4/IL13 rec.). Nonetheless, we should consider that the
8
9 331 eligibility of allergic patients to biologics or AIT is only partially overlapping, being the first
10 332 limited to severe asthma or CRSwNP whereas AIT has indication for allergic rhinitis and
11
12 333 mild/moderate asthma while severe asthma is a contraindication. Based on the
13
14 334 characteristics of the two treatments, a synergistic effect in allergic asthma is conceivable,
15 335 with biological achieving control of severe asthma but not changing its natural history while
16
17 336 AIT, once ceased the contraindication, can induce the long-term immunological changes.
18
19 337 Studies to investigate whether such synergy is achievable are warranted.

20 338

21 339

22 340

23 341

24 342

25 343

26 344

27 345

28 346

29 347

30 348

31 349

32 350

33 351

34 352

35 353

36 354

37 355

38 356

39 357

40 358

41 359

42 360

43 361

44 362

45 363

46 364

47 365

48 366

49 367

50 368

51 369

52 370

53 371

54 372

55 373

56 374

57 375

58 376

59 377

60 378

61 379

62 380

63 381

64 382

65 383

66 384

67 385

68 386

69 387

70 388

71 389

72 390

73 391

74 392

75 393

76 394

77 395

78 396

79 397

80 398

81 399

82 400

83 401

84 402

85 403

86 404

87 405

88 406

89 407

90 408

91 409

92 410

93 411

94 412

95 413

96 414

97 415

98 416

99 417

100 418

101 419

102 420

103 421

104 422

105 423

106 424

107 425

108 426

109 427

110 428

111 429

112 430

113 431

114 432

115 433

116 434

117 435

118 436

119 437

120 438

121 439

122 440

123 441

124 442

125 443

126 444

127 445

128 446

129 447

130 448

131 449

132 450

133 451

134 452

135 453

136 454

137 455

138 456

139 457

140 458

141 459

142 460

143 461

144 462

145 463

146 464

147 465

148 466

149 467

150 468

151 469

152 470

153 471

154 472

155 473

156 474

157 475

158 476

159 477

160 478

161 479

162 480

163 481

164 482

165 483

166 484

167 485

168 486

169 487

170 488

171 489

172 490

173 491

174 492

175 493

176 494

177 495

178 496

179 497

180 498

181 499

182 500

183 501

184 502

185 503

186 504

187 505

188 506

189 507

190 508

191 509

192 510

193 511

194 512

195 513

196 514

197 515

198 516

199 517

200 518

201 519

202 520

203 521

204 522

205 523

206 524

207 525

208 526

209 527

210 528

211 529

212 530

213 531

214 532

215 533

216 534

217 535

218 536

219 537

220 538

221 539

222 540

223 541

224 542

225 543

226 544

227 545

228 546

229 547

230 548

231 549

232 550

233 551

234 552

235 553

236 554

237 555

238 556

239 557

240 558

241 559

242 560

243 561

244 562

245 563

246 564

247 565

248 566

249 567

250 568

251 569

252 570

253 571

254 572

255 573

256 574

257 575

258 576

259 577

260 578

261 579

262 580

263 581

264 582

265 583

266 584

267 585

268 586

269 587

270 588

271 589

272 590

273 591

274 592

275 593

276 594

277 595

278 596

279 597

280 598

281 599

282 600

283 601

284 602

285 603

286 604

287 605

288 606

289 607

290 608

291 609

292 610

293 611

294 612

295 613

296 614

297 615

298 616

299 617

300 618

301 619

302 620

303 621

304 622

305 623

306 624

307 625

308 626

309 627

310 628

311 629

312 630

313 631

314 632

315 633

316 634

317 635

318 636

319 637

320 638

321 639

322 640

323 641

324 642

325 643

326 644

327 645

328 646

329 647

330 648

331 649

332 650

333 651

334 652

335 653

336 654

337 655

338 656

339 657

340 658

341 659

342 660

343 661

344 662

345 663

346 664

347 665

348 666

349 667

350 668

351 669

352 670

353 671

354 672

355 673

356 674

357 675

358 676

359 677

360 678

361 679

362 680

363 681

364 682

3

1

2

3 362

4

5 363 Impact of personalized medicine on AIT

6

7 364 The great advance provided by the introduction of personalized medicine in diagnosis of

8

9 365 allergy is likely to enable solving the long-standing problem of AIT related to the great

10

11 366 qualitative variability of AIT products and the consequent heterogeneity of the clinical

12

13 367 results. Actually, an updated way to correctly evaluate the effectiveness of AIT products

14

15 368 must avoid the mistakes of the past, when the results of a valid tool such as meta-analysis,

16

17 370 extend the positive outcome to AIT in general⁶⁵. The latest generation of registered

18

19 371 products for SLIT, which were based on trials including large number of patients with

20

21 372 respiratory allergy to grass pollen and dust mites, meet the modern quality needs⁶⁶⁻⁷⁰. Still,

22

23 373 as mentioned above, the previous generation products include allergen extracts of efficacy

24

25 374 demonstrated by controlled trials, but also products missing such evidence. This implies

26

27 375 new properly designed clinical trials to demonstrate efficacy. Nonetheless, in order to

28

29 376 facilitate AIT product development it is advisable that the same product composition,

30

31 377 possibly using different formulation (i.e. drops/tablets) should have a mutual program and

32

33 378 recognition and possibly a full development program. Also, the relevance of testing all

34

35 380 allergens and the final cost of the studies for a limited effect size due to the huge placebo

36

37 381 effect in AIT trial is worthy of attention. These facets could provide a flexibility of treatment

38

39 382 otherwise difficult to reach in clinical practice, when batch to batch reproducibility is

40

41 383 ensured in terms of quality product and standardization.

42

43 384 Today, to achieve the highest quality any manufacturer of allergen products must follow

44

45 385 stringent scientific rules. The first is to ensure the presence in the allergen extracts of all

46

47 386 relevant allergens. As discussed above, PAMD@ provides the detections of all allergen

48

49 387 molecules, distinguishing those simply cross-reactive from genuine causative ones.

50

51 388 Similarly, the development of an AIT product requires during the manufacturing process

52

53 389 the identification of all component through mass-spectrometry based analysis, followed by

54

55 390 allergen extraction, purification and formulation, as well as yield cost, robustness and

56

57 391 scaling up. The subsequent step is the product characterization, which results in

58

59 392 development and implementation of analytical methods for identity, purity, consistency and

60

61 393 stability, which makes clinical development possible in its various phases. These phases

62

63 394 (I, II, III) are aimed at establishing safety, dosing and efficacy. For optimal quality level,

64

65 395 well-controlled source materials are also essential, which consist, for example for grass

66

67 pollen, in the harvesting and processing of pollens from cultured grasses, while for house

1

2

3 396 dust mites the development of a synthetic cultured medium free from proteins of animal
4
5 397 origin is needed⁷¹. As mentioned above, the use of omics is of marked importance in the
6
7 398 comprehensive characterization of allergen extracts, including transcriptome for *de novo*
8
9 399 sequencing, proteome for MS analysis, and allergome for IgE reactivity⁷².

10 400 In this context, the evaluation of the Real-World Evidences (RWE), should be properly
11
12 401 reappraised, since patients in clinical practice often do not meet the same criteria of the
13
14 402 subjects enrolled in the double-blind placebo-controlled trials (DBPCRT) leading to
15 403 registration by Regulatory Authorities⁷³. In fact, distinction is made between the final
16
17 404 outcome of DBPCT efficacy and the one in RWE. Nonetheless, a correct evaluation of
18
19 405 these RWE has to be methodologically performed. To this purpose an ongoing European
20
21 406 Academy of Allergy and Clinical Immunology (EAACI) initiative is designed to ascertain the
22 407 validity of the existing RWE concerning AIT, applying the recent tools proposed by
23
24 408 Respiratory Effectiveness Group (REG)/EAACI from one side (Relevant) and Grading of
25
26 409 Recommendations, Assessment, Development and Evaluation (GRADE) on the other side
27 410 ⁷⁴. Through this initiative we will be able define the real validity of the existing AIT RWEs.
28
29 411 This action has been also stated and promoted by the recent Real-Life Research
30
31 412 Manifesto, where it is pointed out the need to consider RWE in the complex scenario of
32
33 413 scientific clinical research⁷⁵. This document supported the use of tools, such as the ones
34 414 mentioned previously, to analyze RWE properly. Finally, the Manifesto also underlined the
35
36 415 major differences existing between retrospective and prospective RWE: where prospective
37
38 416 approach, whose typical example is a Disease or intervention's Registry, is the most
39
40 417 credible, as also stated by Sherman et al⁷⁶. In fact, it should be underlined that several AIT
41 418 RWE reports were retrospectively collected, combining different methodologies, thus
42
43 419 decreasing the validity of the final outcomes/conclusions. However, recent, well conducted
44
45 420 real-life studies, derived from a well-designed and set up database and including very
46 421 large patient populations, were of relevant importance, because they contributed to
47
48 422 increase the knowledge on the effectiveness of AIT in patients seen in daily clinical
49
50 423 practice, possibly not meeting the strict criteria to be included in a trial^{77,78}.

51 424

53 425 **Final message: AIT as personalized treatment**

54
55 426 All the above is in line with the current view that collecting Big Data can lead to precision
56
57 427 medicine^{79,80}. We previously pointed out AIT as a prototype of precision medicine⁷ and
58
59 428 now we would propose AIT as one of the best example of Personalized and Participatory
60 429 Medicine, aimed to satisfy the needs and preferences of patients and to strengthen the

1
2
3 430 cooperation patient/doctor in jointly choosing the best therapeutic option. AIT is the only
4
5 431 medical treatment that has the capacity to change the natural history of allergic diseases ⁸¹
6
7 432 and responds perfectly to the three major needs to be met in personalized medicine, which
8
9 433 are the identification of the molecular mechanism of the disease, the availability of
10 434 diagnostic tools to recognize this mechanism and the availability of a treatment capable of
11
12 435 blocking the mechanism⁸². In Figure 1 we summarized all the possible aspects of the
13
14 436 updated journey to reach the best prescription of AIT, through a detailed and modern
15 437 diagnosis (including PAMD@) and definition of patient's eligibility to AIT. As to diagnosis, it
16
17 438 must be kept in mind that the medical history collected by a skilled doctor is the basis for
18
19 439 deciding the subsequent investigations in accordance with the individual characteristics.
20
21 440 The current and future tools to reach a AIT personalized prescription are summarized in
22 441 Figure 2 . Their variable characteristics suggest that personalized care is valuable in this
23
24 442 setting and may be also be preventive (by focusing on quality of life), predictive (by
25
26 443 allowing treatment to be adjusted as a function of the individual's response) and
27 444 participative (empowering the patient). In particular, SLIT can be considered a precision
28
29 445 medicine treatment (especially with high quality NPP) that enable the physician to identify
30
31 446 the optimal treatment for each patient. This tailor-made approach to diagnosis, decision-
32
33 447 making, product choice and treatment schedules may enhance effectiveness, minimize
34 448 adverse events, improve patient's quality of live and reduce the socio-economic impact. A
35
36 449 number of SLIT drops up dosing regimens and maintenance treatment were shown to be
37
38 450 safe and effective. This means that SLIT liquid allergen extract formulations are extremely
39
40 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such
41 452 parameters can be fine-tuned to suit the patient's day-to-day treatment response and
42
43 453 intercurrent events. Depending on the sensitization profile and the clinical signs, the
44
45 454 specialist can develop a specific, tailor-made SLIT liquid-based approach that, due to its
46 455 ductility in clinical practice, may be an added value. In addition, SLIT liquid formulation
47
48 456 makes it possible to adapt the dose and regimen during the up dosing and/or the
49
50 457 maintenance phase to target optimal effectiveness.
51
52
53
54
55
56
57
58
59
60

The clinician should then evaluate:

- The route of administration: presently SCIT and SLIT for aeroallergens, considering evidences and patient's needs/preference
- The AIT product to be chosen as recommended by WAO⁸³ and EAACI⁸⁴ among the products supported by evidences.
- SCIT: different schedules upon the products (i.e. depot or aqueous)
- SLIT: preference for drops or tablet, both considering evidences and patient's needs/preference
- Dosages and schedules: continuous or pre-seasonal; long or short term.
- Most of the above can be influenced by costs and/or reimbursements.

Personalized medicine in AIT has the potential to improve various outcomes which have so far produced limited results. This is true for preventive ability, which until now has been shown only for the development of asthma in patients with allergic rhinitis⁸⁵, the identification of biomarkers predictive of treatment efficacy (still not known)⁵⁷ and cost-effectiveness compared to drug therapy, clearly demonstrated on the basis of the persistence over time of the control of symptoms after AIT withdrawal⁸⁶, but further improvable by greater diagnostic precision. Further issues could concern the expansion of e-health systems⁷ and the implementation of telemedicine⁸⁷.

This journey is leading to the most appropriate choice of the AIT treatment thanks to the multifaceted variety of AIT products empowering the professionalism of the clinician in choosing, through a shared decision that considers the patient's needs, a proper AIT product for each patient according to eligibility and acceptability.

It is so conceivable to conclude that AIT is still a unique and unmatched model of Personalized Medicine for allergy treatment, able to encompass the prediction of a successful treatment and the potential prevention or progression of an allergic disease, and possibly to face the challenge of providing such advances to at affordable costs. As well, the characteristics of Personalized Medicine for allergy are likely to enable to face challenges such as increasing prevalence, growing complexity and heterogeneity, impact on patients, problem of access to care, therapeutic wandering, and successful management of uncontrolled patients⁸⁸.

Disclosure of Interests

M. Al-Ahamad has nothing to disclose.

1

2

3 482 I. Ansotegui declares he has received fees from Abbott, Astra Zeneca, Faes Farma,
4 Hikma, Menarini, MSD, Mundipharma, Roxall, Sanofi, Stallergenes Greer, UCB.

6 484 S. Arasi has nothing to disclose.

8 485 C. Bachert declares he has received personal fees from Sanofi, personal fees from GSK,
9 personal fees from Novartis, personal fees from Astra-Zeneca.

11
12 487 J. Bousquet declares he has received lecture fees and/or participation at expert board
13 meetings from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-
14 488 Aventis, Takeda, Teva, Uriach (Advisory Board, consultant, meeting lectures fees),
15 489 Kyomed (shares).

18
19 491 A. Bozek has nothing to disclose.

20
21 492 D. Caimmi has nothing to disclose.

22 493 M. Calderon has nothing to disclose.

23
24 494 T. Casale has nothing to disclose.

25
26 495 A. Custovic has nothing to disclose.

27 496 GW. Canonica declares he has received lecture fees and/or participation at expert board
28 meetings BI, ALK, Stallergenes Greer (Grant/ research support), (Menarini, GSK, Sanofi,
29 497 Teva, Hal, AZ, Novartis (honoraria or consultation fees).

31 498
32 499 F. De Blay declares he has received grants from Stallergenes Greer, Chiesi, ALK,
33 500 Mundipharma, Novartis.

36
37 501 P. Demoly declares he had received personal fees for grants/lecture from Astra Zeneca,
38 502 Mylan, Sanofi, ASIT Biotech, ALK, Stallergènes Greer, Thermofisher Scientific, Menarini,
39 503 Chiesi, Bausch&Lomb, Yslab.

41
42
43 504 P. Devillier declares he has received has received consultancy fees, honoraria for
44 lectures, and/or research funding from ALKAbelló, Stallergenes Greer, AstraZeneca,
45 505 Chiesi, Boehringer-Ingelheim, GlaxoSmithKline.

48
49 507 A. Didier declares he has received personal fees for consultancy services for ALK and
50 grants for participation in clinical research projects with ALK.

51 508
52
53 509 A. Fiocchi has nothing to disclose.

54
55 510 A. Fox has nothing to disclose.

56
57 511 P. Gevaert declares he has received lecture fees and/or participation at expert board
58 meetings from Ablynx, ALK, Argenx, Astra-Zeneca, Genentech, HAL-Allergy, Novartis,
59 512 Roche, Regeneron, Sanofi, and Stallergenes Greer.
60
513

- 1
2
3 514 M. Gomez has nothing to disclose.
4
5
6 515 E. Heffler declares he has received lecture fees and/or participation at expert board
7
8 516 meetings from AstraZeneca, GSK, Sanofi, Novartis, Boehringer Ingelheim, Valeas,
9
10 517 Circassia, Nestlè Purina.
11 518 N. Ilina has nothing to disclose.
12
13 519 C. Irani has nothing to disclose.
14
15 520 L. Klimek has nothing to disclose.
16
17 521 P. Kuna declares he has received honorarium as speaker from Allergopharma, ALK.
18 522 Bencard and Stallergenes Greer.
19
20 523 R. O'Hehir C. has nothing to disclose.
21
22 524 Incorvaia declares he has received fees for consultancies from Bayer and Stallergenes
23 525 Greer.
24
25 526 M. Jutel declares he has received personal fees from ALK-Abello, Allergopharma,
26
27 527 Stallergenes Greer, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL.
28
29 528 O. Kurbacheva has nothing to disclose.
30 529 P. Matricardi declares he has received fees from Thermo Fisher Scientific, Hycor, Omron,
31
32 530 TPS, Stallergenes Greer, Euroimmun.
33
34 531 M. Morais de Almeida has nothing to disclose.
35
36 532 R. Mosges declares he has received fees from Allergopharma, ALK-Abelló, Glaxo, HAL
37 533 Allergy, Leti, Lofarma, Novartis, Parexel International, Stallergenes Greer.
38
39 534 N. Novak has nothing to disclose.
40
41 535 Y. Okamoto has nothing to disclose.
42 536 P. Panzner has nothing to disclose.
43
44 537 N. Papadopoulos declares he has received fees from Novartis, NUTRICIA, HAL, Menarini,
45
46 538 SANOFI, MEDA, AstraZeneca, GSK, MSD, ASIT BIOTECH, Boehringer Ingelheim.
47
48 539 H. Park has nothing to disclose.
49 540 G. Passalacqua has nothing to disclose.
50
51 541 R. Pawankar has nothing to disclose.
52
53 542 O.Pfaar declares he has received grants and personal fees from ALK-Abelló,
54 543 Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, from
55
56 544 Bencard Allergie GmbH/Allergy Therapeutics, Lofarma.
57
58 545 P. Schmid-Grendelmeier has nothing to disclose.
59
60 546 H. Tortajada has nothing to disclose.
547 C. Vidal has nothing to disclose.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

548 C Virchow declares he has received fees from Allergopharma, ALK, LETI, Stallergenes
549 Greer.

550 U. Wahn declares he has received honoraria for consultancy as well as lecture fees from
551 Allergopharma, Stallergenes Greer, ALK, Roxall, Sanofi-Aventis, Novartis, Berlin-Chemie

552 M. Worm declares she as received of honoraria or consultation fees by ALK-Abelló
553 Arzneimittel GmbH, Mylan Germany GmbH, Leo Pharma GmbH, Sanofi-Aventis
554 Deutschland GmbH, Regeneron Pharmaceuticals, DBV Technologies S.A, Stallergenes
555 Greer, HAL Allergie, Allergopharma, Bencard Allergie, Aimmune Therapeutics UK Limited,
556 Actelion Pharmaceuticals Deutschland G, Novartis AG, Biotest AG, AbbVie Deutschland &
557 Co. KG, Lilly Deutschland..

558 P. Zieglmayer has nothing to disclose.

559 C. Bos, E. Karagiannis and S. Scurati are employee of Stallergenes Greer

563 Acknowledgments

564 This is an initiative supported by Stallergenes Greer with an unrestricted grant

DRAFT REVIEW ARTICLE dated 17.05.20

1
2
3 565 **Table 1 Studies that have assessed the benefits of attaining with PAMD a more**
4
5 566 **appropriate prescription for AIT**

Author, year (ref)	Allergens tested	Population	Results
Mitterman, 2010 (28)	Bee and wasp venom.	43 patients (pts)	Recombinant nonglycosylated allergen molecules (Api m 1, rApi m 2, rVes v 5) allowed to define the sensitizing venom in the 14 patients with positive test both bee and wasp venom extracts.
Sastre, 2012 (29)	Pollens	141 pts	Agreement in AIT indication before and after ISAC(®) results in 62 (46%) patients; (kappa = 0.1057 ± 0.0413).
Moreno, 2014 (30)	Pollens	1263 pts	Based on history and SPT, 73% of patients would have been prescribed AIT with a mix of grass and olive pollens, while only in 56.8% of patients the double positivity was confirmed by molecular allergy diagnosis (MAD) with Ole e 1 and Phl p molecules.
Popescu, 2014 (31)	Grass pollen	Not defined (review of published data)	MAD biomarkers (including tolerogenic dendritic, regulatory T cells, IgE, IgA and IgG antibodies, and apoptosis biomarkers provide relevant

			information for allergists
Vidal, 2014 (32)	Pollens, dust mites, moulds, animal epithelia	62 Spanish allergists	SPTs are insufficient to establish the clinical relevance of each allergen. Serum specific IgE adds value to SPT but MAD is strongly recommended, particularly in pollen-allergic patients.
Saltabayeva, 2017 (33)	Pollens	95 pts (real-life study)	A lower number of AIT treatments (n = 119) was needed according to MAD compared to 275 AIT treatments based on conventional diagnosis, with large reduction of the total costs for a 3-year AIT treatment
Del-Rio Camacho, 2018 (34)	Pollens	70 children	MAD modified AIT prescription in 54.3% of cases, and increasing the indication of single-allergen therapy from 18% to 51% reversing the decision to prescribe AIT in 9.3% of cases
Savi, 2016 (35)	Hymenoptera venoms	40 pts.	By MAD data VIT would have been prescribed to 7 pts for Polistes spp, to 6 for Vespula spp, and to 41 for both venoms. With the data from CAP inhibition, it would have been a prescription to 15 patients for Polistes, to 28 for Vespula, and to 11

			for both venoms. A good concordance between the results of MAD and CAP-inhibition was found only when the value in kU/l of Ves v 5 were about twice those of Pol d 5, and vice versa.
Martinez-Canavate Burgos, 2018 (36)	Pollens	281 children	MAD results changed the specialist's composition of the prescribed AIT in 52.87% of cases.
Peveri, 2019 (37).	Various aeroallergens	272 pts.	In 50% of cases a change in the AIT prescription for respiratory allergy was found, resulting in a saving of financial resources.

567

568

569

570

571

572

573

574

575

576

577

578

579

580

581

582

583

584

585

586

587

588

589

590

591

592

593

594

595

596

597

598

References

- 1) Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. *Drug Test Anal.* 2011;3 (6)337-44.
- 2) Mahner, M. & Kary, M. (1997). "What exactly are genomes, genotypes and phenotypes? And what about phenomes?". *J Theoretical Biology* 186: 55–63.
- 3) Febbo PG, Ginsburg GS. Personalized diagnostic and therapeutic strategies in oncology. *Per Med.* 2005;2(2):97-110.
- 4) Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015 Feb 26;372(9):793-5
- 5) Busse WW. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int.* 2019;68(2):158-66.
- 6) Frew AJ. Hundred years of allergen immunotherapy. *Clin Exp Allergy.* 2011;41(9): 1221-225.
- 7) Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M, De Beaumont O, Bousquet J. Allergen Immunotherapy (AIT): A prototype of precision medicine. *World Allergy Organ J.* 2015;8 (1), 31 2015
- 8) Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, Halken S, Larenas-Linnemann D, Pawankar R, Pitsios C, Sheikh A, Worm M, Arasi S, Calderon MA, Cingi C, Dhimi S, Fauquert JL, Hamelmann E, Hellings P, Jacobsen L, Knol EF, Lin SY, Maggina P, Mösges R, Oude Elberink JNG, Pajno GB, Pastorello EA, Penagos M, Rotiroti G, Schmidt-Weber CB, Timmermans F, Tsilochristou O, Varga EM, Wilkinson JN, Williams A, Zhang L, Agache I, Angier E, Fernandez-Rivas M, Jutel M, Lau S, van Ree R, Ryan D, Sturm GJ, Muraro A. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy.* 2018;73(4):765-798.
- 9) Demoly P, Makatsori M, Casale TB, Calderon MA. The Potential Role of Allergen Immunotherapy in Stepping Down Asthma Treatment. *J Allergy Clin Immunol Pract.* 2017 May - Jun;5(3):640-648.
- 10) Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, Tonascia J, Wheeler B. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med.* 1997; 336(5):324-31.
- 11) Kaul S, May S, Lüttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy.* 2011;66(6):753-64.

1

2

3 602 12)Devillier P, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen
4
5 603 immunotherapy and pharmacotherapy in pollen-induced seasonal allergic
6
7 604 rhinoconjunctivitis. *BMC Med.* 2014;12:71

8 605 13)Larenas-Linnemann D, Cox LS; Immunotherapy and allergy diagnostics Committee of
9
10 606 the American Academy of Allergy, Asthma and Immunology European allergen extract
11
12 607 units and potency: review of available information. *Ann Allergy Asthma Immunol.*
13
14 608 2008;100(2):137-45.

15 609 14)Larenas-Linnemann D, Esch R, Plunkett G, Brown S, Maddox D, Barnes C, Constable
16
17 610 D. Maintenance dosing for sublingual immunotherapy by prominent European allergen
18
19 611 manufacturers expressed in bioequivalent allergy units. *Ann Allergy Asthma Immunol.*
20
21 612 2011;107(5):448-458.

22 613 15)Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Grönlund H. The recombinant
23
24 614 allergen-based concept of component-resolved diagnostics and immunotherapy (CRD
25
26 615 and CRIT). *Clin Exp Allergy.* 1999 Jul;29(7):896-904

27 616 16)Melioli G, Savi E, Crivellaro MA, Passalacqua G. Potential of molecular based
28
29 617 diagnostics and its impact on allergen immunotherapy. *Asthma Res Pract.* 2016 2;2:9.

30
31 618 17)Kespohl S, Raulf M. Mould allergens: Where do we stand with molecular allergy
32
33 619 diagnostics?: Part 13 of the series Molecular Allergology. *Allergo J Int.* 2014;23(4):120-
34 620 125.

35
36 621 18)A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnosis
37
38 622 (PAMD@): Update 2020. *World Allergy Organ J.* 2020 Mar 7;13(2):100091. Steering
39 623 Committee Authors; Review Panel Members. Collaborators (48) *World Allergy Organ J.*
40 624 2020;13(2):10009.

41 625 19)Pomes A, Davies JM, Gadermaier G, et al. WHO/IUIS allergen nomenclature: providing
42
43 626 a common language. *Mol Immunol.* 2018;100:3–13.

44
45 627 20)van Hage M, Hamsten C, Valenta R. ImmunoCAP assays: pros and cons in allergology.
46
47 628 *J Allergy Clin Immunol.* 2017;140: 974–977.

48 629 21)Garib V, Rigler E, Gastager F, et al. Determination of IgE and IgG reactivity to more
49
50 630 than 170 allergen molecules in paper dried blood spots. *J Allergy Clin Immunol.*
51 631 2019;143:437-440.

52
53 632 22)Jakob T, Forstenlechner P, Matricardi P, Kleine-Tebbe J. Molecular allergy diagnostics
54
55 633 using multiplex assays:methodological and practical considerations for use inresearch
56
57 634 and clinical routine: Part 21 of the Series Molecular Allergology. *Allergo J Int.*
58 635 2015;24:320-332.

1

2

- 3 636 23) van Hage M, Schmid-Grendelmeier P, Skevaki C, Plebani M, Canonica W, Kleine-
4 637 Tebbe J, Nystrand M, Jafari-Mamaghani M, Jakob T. Performance evaluation
5 638 of ImmunoCAP® ISAC 112: a multi-site study. *Clin Chem Lab Med*. 2017 Mar
6 639 1;55(4):571-577
- 10 640 24) Di Fraia M, Arasi S, Castelli S, et al. A new molecular multiplex IgE assay for the
11 641 diagnosis of pollen allergy in Mediterranean countries: a validation study. *Clin Exp*
12 642 *Allergy*. 2019;49:341-349.
- 15 643 25) Buzzulini F, Da Re M, Scala E, et al. Evaluation of a new multiplex IgE assay for
16 644 allergy diagnosis. *Clin Chim Acta*. 2019;493:73-78.
- 19 645 26) Melioli G, Spenser C, Reggiardo G, Passalacqua G, Compalati E, Rogkakou A, Riccio
20 646 AM, Di Leo E, Nettis E, Canonica GW. Allergenius, an expert system for the
21 647 interpretation of allergen microarray results. *World Allergy Organ J*. 2014 Jun
22 648 25;7(1):15.
- 25 649 27) Heffler E, Puggioni F, Peveri S, Montagni M, Canonica GW, Melioli G. Extended IgE
26 650 profile based on an allergen macroarray: a novel tool for precision medicine in allergy
27 651 diagnosis. *World Allergy Organ J*. 2018 Apr 26;11(1):7.
- 31 652 28) Mittermann I, Zidarn M, Silar M, Markovic-Housley Z, Aberer W, Korosec P, Kosnik M,
32 653 Valenta R. Recombinant allergen-based IgE testing to distinguish bee and wasp
33 654 allergy. *J Allergy Clin Immunol*. 2010 Jun;125(6):1300-1307.
- 36 655 29) Sastre J, Landivar ME, Ruiz-García M, Andregnette-Rosigno MV, Mahillo I.
37 656 How molecular diagnosis can change allergen-specific immunotherapy prescription in a
38 657 complex pollen area. *Allergy*. 2012 May;67(5):709-11.
- 41 658 30) Moreno C, Justicia JL, Quiralte J, Moreno-Ancillo A, Iglesias-Cadarso A, Torrecillas M,
42 659 Labarta N, García MA, Dávila I. Olive, grass or both? Molecular diagnosis for
43 660 the allergen immunotherapy selection in polysensitized pollinic patients. *Allergy*. 2014
44 661 Oct;69(10):1357-63.
- 48 662 31) Popescu FD. Molecular biomarkers for grass pollen immunotherapy. *World J Methodol*.
49 663 2014 Mar 26;4(1):26-45.
- 51 664 32) Vidal C, Enrique E, Gonzalo A, Moreno C, Tabar AI; Expert Clinical Participants.
52 665 Diagnosis and allergen immunotherapy treatment of polysensitized patients with
53 666 respiratory allergy in Spain: an Allergists' Consensus. *Clin Transl Allergy*. 2014 Nov
54 667 7;4:36.
- 58 668 33) Saltabayeva U, Garib V, Morenko M, Rosenson R, Ispayeva Z, Gatauova M, Zulus L,
59 669 Karaulov A, Gastager F, Valenta R. Greater Real-Life Diagnostic Efficacy

1

2

3 670 of Allergen Molecule Based Diagnosis for Prescription of Immunotherapy in an Area
4 with Multiple Pollen Exposure. *Int Arch Allergy Immunol*. 2017;173(2):93-98.

5 671
6 672 34) Del-Río Camacho G, Montes Arjona AM, Fernández-Cantalejo Padial J, Rodríguez
7 673 Catalán J. How molecular diagnosis may modify immunotherapy prescription in multi-
8 674 sensitized pollen-allergic children. *Allergol Immunopathol (Madr)*. 2018 Nov -
9 675 Dec;46(6):552-556.

10 676
11 677 35) Savi E, Peveri S, Makri E, Pravettoni V, Incorvaia C. Comparing the ability of molecular
12 678 diagnosis and CAP-inhibition in identifying the really causative venom in patients with
13 679 positive tests to *Vespula* and *Polistes* species. *Clin Mol Allergy*. 2016 Feb 8;14:3.

14 680
15 681 36) Martínez-Cañavate Burgos A, Torres-Borrego J, Molina Terán AB, Corzo JL, García
16 682 BE, Rodríguez Pacheco R, Moreno Aguilar C, Dávila I. Molecular sensitization patterns
17 683 and influence of molecular diagnosis in immunotherapy prescription in children
18 684 sensitized to both grass and olive pollen. *Pediatr Allergy Immunol*. 2018 Jun;29(4):369-
19 685 374.

20 686
21 687 37) Peveri S, Pattini S, Costantino MT, Incorvaia C, Montagni M, Roncallo C, Villalta D,
22 688 Savi E. Molecular diagnostics improves diagnosis and treatment of respiratory allergy
23 689 and food allergy with economic optimization and cost saving. *Allergol Immunopathol*
24 690 (Madr). 2019 Jan - Feb;47(1):64-72.

25 691
26 692 38) Gupta M, Cox A, Nowak-Węgrzyn A, Wang J. Diagnosis of food allergy.
27 693 *Immunol Allergy Clin North Am*. 2018 Feb;38(1):39-52. Doi

28 694
29 695 39) Volpicella M, Leoni C, Dileo MCG, Ceci LR. Progress in the analysis of food allergens
30 696 through molecular biology approaches. *Cells*. 2019 Sep 12;8(9).

31 697
32 698 40) Wai CYY, Leung NYH, Leung PSC, Chu KH. Immunotherapy of Food Allergy: a
33 699 Comprehensive Review. *Clin Rev Allergy Immunol*. 2019 Aug;57(1):55-73.

34 700
35 701 41) Schröder H, Yman L. Standardization of the RAST inhibition assay. *Allergy*. 1980
36 702 Apr;35(3):234-6.

37 703
38 704 42) Quercia O, Cova V, Martini M, Cortellini G, Murzilli F, Bignardi D, Cilia M, Scarpa A,
39 705 Bilò MB. CAP-Inhibition, molecular diagnostics, and total IgE in the evaluation of
40 706 *Polistes* and *Vespula* double sensitization. *Int Arch Allergy Immunol*. 2018;177(4):365-
41 707 369.

42 708
43 709 43) Caruso B, Bonadonna P, Bovo C, Melloni N, Lombardo C, Senna G, Lippi G. Wasp
44 710 venom allergy screening with recombinant allergen testing. Diagnostic performance of
45 711 rPol d 5 and rVes v 5 for differentiating sensitization to *Vespula* and *Polistes*
46 712 subspecies. *Clin Chim Acta*. 2016 Jan 30;453:170-3.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

- 44)Hemmings O, Kwok M, McKendry R, Santos AF. Basophil activation test: old and new applications in allergy. *Curr Allergy Asthma Rep.* 2018 Nov 15;18(12):77.
- 45)Balzer L, Pennino D, Blank S, Seismann H, Darsow U, Schnedler M, McIntyre M, Ollert MW, Durham SR, Spillner E, Ring J, Cifuentes L. Basophil activation test using recombinant allergens: highly specific diagnostic method complementing routine tests in wasp venom allergy. *PLoS One.* 2014 Oct 17;9(10)
- 46)Korošec P, Šilar M, Eržen R, Čelesnik N, Bajrović N, Zidarn M, Košnik M. Clinical routine utility of basophil activation testing for diagnosis of hymenoptera-allergic patients with emphasis on individuals with negative venom-specific IgE antibodies. *Int Arch Allergy Immunol.* 2013;161(4):363.
- 47)Eržen R, Košnik M, Silar M, Korošec P. Basophil response and the induction of a tolerance in venom immunotherapy: a long-term sting challenge study. *Allergy.* 2012 Jun;67(6):822-30.
- 48)Schmid JM, Würtzen PA, Siddhuraj P, Jogdand P, Petersen CG, Dahl R, Erjefält JS, Hoffmann HJ. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. *Allergy.* 2020 Mar 7. [Epub ahead of print].
- 49)Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, Azar A, Baroody FM, Bachert C, Canonica GW, Chacko T, Cingi C, Ciprandi G, Corey J, Cox LS, Creticos PS, Custovic A, Damask C, DeConde A, DelGaudio JM, Ebert CS, Eloy JA, Flanagan CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ, Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M, Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU, Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L, Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL, Tantilipikorn P, Tversky JR, Veling MC, Wang Y, Westman M, Wickman M, Zacharek M. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol.* 2018;8(2):108-352
- 50)Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J.* 2016 Feb;47(2):410-9

1

2

3 736 51) Woodruff PG, Agusti A, Roche N, Singh D, Martinez FJ. Current concepts
4
5 737 in targeting chronic obstructive pulmonary disease pharmacotherapy: making
6
7 738 progress towards personalised management. *Lancet*. 2015;385(9979):1789-1798.

8 739 52) Tay TR, Hew M. Comorbid, "treatable traits" in difficult asthma: current evidence and
9
10 740 clinical evaluation. *Allergy*. 2017;101:130.

11
12 741 53) McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of
13
14 742 chronic airway diseases. *Chron Respir Dis*. 2019;16:1479973119867954.

15 743 54) Pavord ID, Agusti A. Blood eosinophil count: a biomarker of an important treatable trait
16
17 744 in patients with airway disease. *Eur Respir J*. 2016;47(5):1299-303.

18
19 745 55) Simpson AJ, Hekking PP, Shaw DE, Fleming LJ, Roberts G, Riley JH, Bates S, Sousa
20
21 746 AR, Bansal AT, Pandis I, Sun K, Bakke PS, Caruso M, Dahlén B, Dahlén SE, Horvath
22 747 I, Krug N, Montuschi P, Sandstrom T, Singer F, Adcock IM, Wagers SS, Djukanovic
23
24 748 R, Chung KF, Sterk PJ, Fowler SJ; U-BIOPRED Study Group. Treatable traits in
25
26 749 the European U-BIOPRED adult asthma cohorts. *Allergy*. 2019 Feb;74(2):406-411.

27 750 56) Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. *Curr Opin*
28
29 751 *Pulm Med*. 2018;24(1):24-31.

30
31 752 57) Bousquet J, Pfaar O, Togias A, Schünemann HJ, Ansotegui I, Papadopoulos NG,
32
33 753 Tsiligianni I, Agache I, Anto JM, Bachert C, Bedbrook A, Bergmann KC, Bosnic-
34 754 Anticevich S, Bosse I, Brozek J, Calderon MA, Canonica GW, Caraballo L, Cardona V,
35
36 755 Casale T, Cecchi L, Chu D, Costa E, Cruz AA, Czarlewski W, Durham SR, Du Toit G,
37
38 756 Dykewicz M, Ebisawa M, Fauquert JL, Fernandez-Rivas M, Fokkens WJ, Fonseca J,
39 757 Fontaine JF, Gerth van Wijk R, Haahtela T, Halcken S, Hellings PW, Ierodiakonou D,
40
41 758 Iinuma T, Ivancevich JC, Jacobsen L, Jutel M, Kaidashev I, Khaitov M, Kalayci O,
42
43 759 Kleine Tebbe J, Klimek L, Kowalski ML, Kuna P, Kvedariene V, La Grutta S, Larenas-
44
45 760 Linemann D, Lau S, Laune D, Le L, Lodrup Carlsen K, Lourenço O, Malling HJ, Marien
46 761 G, Menditto E, Mercier G, Mullol J, Muraro A, O'Hehir R, Okamoto Y, Pajno GB, Park
47
48 762 HS, Panzner P, Passalacqua G, Pham-Thi N, Roberts G, Pawankar R, Rolland C,
49
50 763 Rosario N, Ryan D, Samolinski B, Sanchez-Borges M, Scadding G, Shamji MH, Sheikh
51
52 764 A, Sturm GJ, Todo Bom A, Toppila-Salmi S, Valentin-Rostan M, Valiulis A, Valovirta E,
53 765 Ventura MT, Wahn U, Walker S, Wallace D, Wasserman S, Yorgancioglu A, Zuberbier
54
55 766 T; ARIA Working Group. 2019 ARIA Care pathways for allergen immunotherapy.
56
57 767 *Allergy*. 2019;74(11):2087-2102.

58 768 58) Mushra R. Science of omics: Perspectives and prospects for human health care. *Integr*
59
60 769 *Mol. Med*. 2016;IMM.1000258.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 59) Abdel-Aziz MI, Neerincx AH, Vijverberg SJ, Kraneveld AD, Maitland-van der Zee AH. Omics for the future in asthma. *Semin Immunopathol.* 2020;42(1):111-126.
- 60) Devillier P, Salvator H, Naline E, Couderc LJ, Gtassin-Delyle S. Metabolomics in the diagnosis and pharmacotherapeutic management of respiratory diseases. *Curr Pharm Des.* 2017;23(14):2050-2059.
- 61) Park CS, Rhim T. Application of proteomics in asthma research. *Expert Rev Proteomics.* 2011;8(2):221-30
- 62) Martin-Sanchez F, Bellazzi R, Casella V, Dixon W, Lopez-Campos G, Peek N. Progress in Characterizing the Human Exposome: a Key Step for Precision Medicine. *Yearb Med Inform.* 2020 [Epub ahead of print]
- 63) Donovan BM, Bastarache L, Turi KN, Zutter MM, Hartert TV. The current state of omics technologies in the clinical management of asthma and allergic diseases. *Ann Allergy Asthma Immunol.* 2019;123(6):550-557.
- 64) FitzGerald JM, Poureslami I. The need for humanomics in the era of genomics and the challenge of chronic disease management. *Chest.* 2014 Jul;146(1):10-12.
- 65) Canonica GW, Bagnasco D, Ferrantino G, Ferrando M, Passalacqua G. Update on immunotherapy for the treatment of asthma. *Curr Opin Pulm Med.* 2016;22(1):18-2
- 66) Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once daily grass allergen tablet: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 2006;117:802-809.
- 67) Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 2007; 120:1338-1345.
- 68) Wahn U, Tabar A, Kuna P, et al. SLIT Study Group. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 2009;123:160-166.
- 69) Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2014;134(3):568-75.
- 70) Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133(6):1608-14.

1

2

3 803 71)Batard T, Hrabina A, Bi XZ, Chabre H, Lemoine P, Couret MN, Faccenda D, Villet
4 B, Harzic P, André F, Goh SY, André C, Chew FT, Moingeon P. Production and
5 804 proteomic characterization of pharmaceutical-grade *Dermatophagoides pteronyssinus*
6 805 and *Dermatophagoides farinae* extracts for allergy vaccines. *Int Arch Allergy*
7 806 *Immunol.* 2006;140(4):295-305)

10 807

11

12 808 72)Bordas-Le Floch V, Le Mignon M, Bussièrès L, Jain K, Martelet A, Baron-Bodo V, Nony
13 809 E, Mascarell L, Moingeon P. A combined transcriptome and proteome analysis extends
14 810 the allergome of house dust mite *Dermatophagoides* species. *PLoS One.* 2017 Oct
15 811 5;12(10):e0185830

17 811

18

19 812 73)Herland K, Akselsen JP, Skjønberg OH, Bjermer L How representative are clinical
20 813 study patients with asthma or COPD for a larger "real life" population of patients with
21 814 obstructive lung disease? *Respir Med.* 2005;99(1):11-9.

22 814

23

24 815 74)Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, Morgan
25 816 RL, Gartlehner G, Kunz R, Katikireddi SV, Sterne J, Higgins JP, Guyatt
26 817 G; GRADE Working Group GRADE guidelines: 18. How ROBINS-I and other tools to
27 818 assess risk of bias in nonrandomized studies should be used to rate the certainty of a
28 819 body of evidence. *J Clin Epidemiol.* 2019 Jul;111:105-114.

29 818

30

31 819 75)Roche N, Anzueto A, Bosnic Anticevich S, Kaplan A, Miravittles M, Ryan D, Soriano JB,
32 820 Usmani O, Papadopoulos NG, Canonica GW; Respiratory Effectiveness Group
33 821 Collaborators. The importance of real-life research in respiratory medicine: manifesto of
34 822 the Respiratory Effectiveness Group: Endorsed by the International Primary Care
35 823 Respiratory Group and the World Allergy Organization. *Eur Respir J.* 2019 19;54(3)

36 822

37

38 823 76)Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, LaVange
39 824 L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue
40 825 LQ, Califf RM . Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J*
41 826 *Med.* 2016;375(23):2293-2297..

42 825

43

44 826 77)Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefit of allergen
45 827 immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy.* 2018;
46 828 74(3):594-604.

47 827

48

49 829 78)Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy
50 830 provides long-term relief in allergic rhinitis and reduces the risk of asthma: a
51 831 retrospective, real-world database analysis. *Allergy.* 2018;165-177.

52 831

53

54 832

55

56 833

57

58 834

59

60 835

60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 79)Hulsen T, Jamuar SS, Moody AR, Karnes JH, Varga O, Hedensted S, Spreafico R, Hafler DA, McKinney EF. From Big Data to Precision Medicine. Front Med (Lausanne). 2019;6:34. 2019.
- 80)Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010; 22; 363(4):301-4.
- 81)Calderon M, Demoly P, Gert van Wijk R, Bousquez J, Sheikh A, Frew A, Scadding G, Bachert c, et al. EAACI: a European declaration on immunotherapy. Designing the future of allergen specific immunotherapy. Clin Transl Allergy 2012 30;2(1):20.
- 82)Passalacqua G, Canonica GW. AIT (allergen immunotherapy): a model for the "precision medicine". Clin Mol Allergy. 2015; 8;13:24
- 83)Bachert C, Larché M, Bonini S, Canonica GW, Kündig T, Larenas-Linnemann D, Ledford D, Neffen H, Pawankar R, Passalacqua G. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. World Allergy Organ J. 2015;8(1):29.
- 84)Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M, Kleine-Tebbe J, Klimek L, Klysner S, Kopp MV, Kuna P, Larché M, Muraro A, Schmidt-Weber CB, Shamji MH, Simonsen K, Somoza C, Valovirta E, Ziegelmayer P, Zuberbier T, Wahn U; FASIT group. Perspectives in allergen immunotherapy: 2017 and beyond. Allergy. 2018;73 Suppl 104:5-23.
- 85)Jacobsen L, Wahn U, Bilo MB. Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: the effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy. Clin Transl Allergy. 2012 Apr 13;2:8.
- 86)Cox LS, Murphey A, Hankin C. The Cost effectiveness of allergen immunotherapy compared with pharmacotherapy for treatment of allergic rhinitis and asthma. Immunol Allergy Clin North Am. 2020;40(1):69-85.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

871 87) Krishna MT, Knibb RC, Huissoon AP. Is there a role for telemedicine in adult allergy
872 services?. Clin Exp Allergy. 2016;46(5):668-77.

873
874

875 88) Gómez RM, Ansotegui I, Canonica GW. Will precision medicine be available for all
876 patients in the near future? Curr Opin Allergy Clin Immunol. 2019;19(1):75-80.

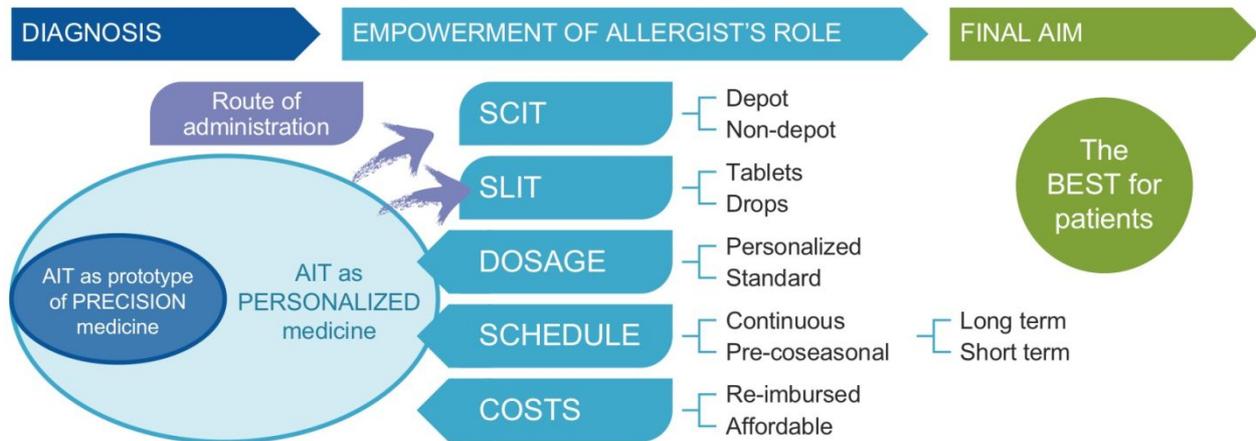
877
878

879

DRAFT REVIEW ARTICLE dated 11.11.2020
For Peer Review

880 **Figure 1** - Allergen Immunotherapy as personalized treatment

AIT AS PERSONALIZED TREATMENT



881
882
883 **Figure 2** - Tools for personalized Allergen Immunotherapy

Tools for personalized AIT

Validated tools for AIT

- Clinical history
- Skin tests with allergen extracts
- Serum-specific IgE
- Component-resolved diagnosis
- CAP-inhibition (*limited*)



Tools still to be validated for AIT

- Basophil activation test
- Nasal cytology
- Nasal challenge with the suspected allergen



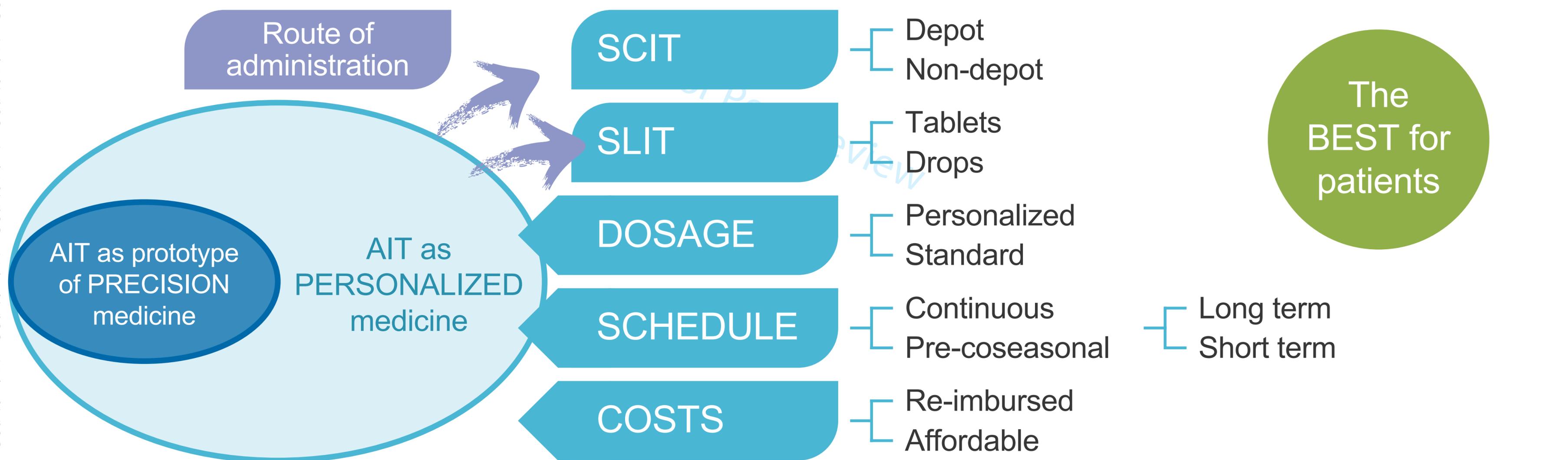
Tools of future applications

- **Treatable traits** (*genetic, phenotypic, psychosocial features*)
- **Omics** (*proteomics, epigenomics, metabolomics, breathomics*)



885

AIT AS PERSONALIZED TREATMENT



Tools for personalized AIT

Validated tools for AIT

- Clinical history
- Skin tests with allergen extracts
- Serum-specific IgE
- Component-resolved diagnosis
- CAP-inhibition (*limited*)



Tools still to be validated for AIT

- Basophil activation test
- Nasal cytology
- Nasal challenge with the suspected allergen



Tools of future applications

- **Treatable traits**
(*genetic, phenotypic, psychosocial features*)
- **Omics**
(*proteomics, epigenomics, metabolomics, breathomics*)



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15