



**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-03613250v1>**

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 &amp; 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 &amp; 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 &amp;  Respiratory Medicine, Royal Manchester Children's Hospital  Park, Hae-Sim; Ajou University School of Medicine, Allergy &amp; Clinical  Immunology;  Passalacqua, Giovanni; Allergy &amp; 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  
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

Dear Editor,

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

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

Editor's comments:

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

RESPONSE: We will contact Anna Głobińska just after having completed this submission

2. Convert the below part to a text box.

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.

RESPONSE: We followed your suggestion and converted the text into a text-box

3. Make an algorithm graph for molecular diagnosis.

RESPONSE: We thank the Editor for this suggestion, but we do believe that this is out of scope of our article 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 RESPONSE: We thank the Reviewer for his/her appreciation.  
18  
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 Cristoforo<sup>1</sup>, Al-Ahmad Mona<sup>2,3</sup>, Ansotegui Ignacio<sup>4</sup>, Arasi Stefania<sup>5</sup>, Bachert  
5 Claus<sup>6,7</sup>, Bos Catherine<sup>8</sup>, Bousquet Jean<sup>9</sup>, Bozek Andrzej<sup>10</sup>, Caimmi Davide<sup>11</sup>, Calderón  
6 Moises<sup>12</sup>, Casale Thomas<sup>13</sup>, Custovic Adnan<sup>14</sup>, De Blay Frédéric<sup>15</sup>, Demoly Pascal<sup>11,16</sup>,  
7 Devillier Philippe<sup>17</sup>, Didier Alain<sup>18</sup>, Fiocchi Alessandro<sup>5</sup>, Fox Adam<sup>19</sup>, Gevaert Philippe<sup>6</sup>,  
8 Gomez Maximiliano<sup>20</sup>, Heffler Enrico<sup>21,22</sup>, Iliina Natalia<sup>23</sup>, Irani Carla<sup>24</sup>, Jutel Marek<sup>25</sup>,  
9 Karagiannis Efstrathios<sup>8</sup>, Klimek Ludger<sup>26</sup>, Kuna Piotr<sup>27</sup>, O’Hehir Robin<sup>28</sup>, Kurbacheva  
10 Oxana<sup>29</sup>, Matricardi Paolo Maria<sup>30</sup>, Morais de Almeida Mario<sup>31,32</sup>, Mosges Ralph<sup>33,34</sup>,  
11 Novak Natalija<sup>35</sup>, Okamoto Yoshitaka<sup>36</sup>, Panzner Petr<sup>37</sup>, Papadopoulos Nikolaos<sup>38,39</sup>, Park  
12 Hae-Sim<sup>40</sup>, Passalacqua Giovanni<sup>41</sup>, Pawankar Ruby<sup>42</sup>, Pfaar Oliver<sup>43</sup>, Schmid-  
13 Grendelmeier Peter<sup>44</sup>, Scurati Silvia<sup>8</sup>, Tortajada-Girbés Miguel<sup>45,46</sup>, Vidal Carmen<sup>47</sup>,  
14 Virchow Christian<sup>48</sup>, Wahn Ulrich<sup>30</sup>, Worm Margitta<sup>30</sup>, Ziegelmayer Petra<sup>49</sup>, Canonica  
15 Giorgio Walter<sup>21,22</sup>.

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
- 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](mailto: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 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 breakthrough<sup>1</sup>, 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 phenotypes<sup>2</sup> 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 treatment<sup>3</sup>, but soon, with a significant boost from President Obama's announcement on  
20  
21 134 the great potential of personalized medicine<sup>4</sup>, 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 asthma<sup>5</sup>. 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 evidence<sup>6</sup> 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"<sup>7</sup>. 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 rhinitis<sup>8</sup>.  
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 scale<sup>9</sup>. 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 limited<sup>6</sup>. 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 1997<sup>10</sup>. 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 AIT<sup>11</sup>. 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 success<sup>12</sup>.

### 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<sup>13,14</sup>. 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 extracts<sup>13</sup>. 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 dose<sup>14</sup>. 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”<sup>15</sup>, molecular-based allergy diagnostics<sup>16</sup>, and molecular allergy diagnostics<sup>17</sup>. The updated WAO-ARIA- GA<sup>2</sup>LEN consensus document on molecular-based allergy proposed the unifying definition of “precision allergy molecular diagnostic applications” (PAMD@)<sup>18</sup>. 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*<sup>19</sup>). 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 testing<sup>20</sup>. 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 physician<sup>21</sup>, 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 sources<sup>22</sup>, 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 added<sup>23</sup>. The EUROLINE Southern European Pollen Profile [ESEP) was introduced to test pollen molecules of clinical relevance in Southern Europe<sup>24</sup>, while the Microarray Diagnostics (MADx) Allergen Explorer (ALEX) include 126 molecules from different allergen sources<sup>25</sup>. 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 result<sup>26</sup>. 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 found<sup>27</sup>.

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 studies<sup>28-37</sup>. A vast literature is available, as  
16  
17 234 recently reviewed<sup>38-39</sup>, 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 allergy<sup>40</sup>,  
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 inhibition<sup>41</sup>, 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<sup>35,42</sup> and to have a lower cost<sup>43</sup> 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 basophils<sup>44</sup>. 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 ImmunoCAP<sup>45</sup> 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 BAT<sup>46</sup>. 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 challenge<sup>47</sup>.  
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 treatment<sup>48</sup>. 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 rhinitis<sup>49</sup>. 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 health<sup>50</sup>. 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

recent years<sup>51</sup>. 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 control<sup>52</sup>. 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 bronchiectasis<sup>53</sup>.

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 outcomes<sup>54</sup>. 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 phenotypes<sup>55</sup>.

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 patients<sup>56</sup>. Concerning AIT, treatable traits of clinical interest may consist of the treatment outcome, beyond the disease to be treated, on comorbidities<sup>57</sup>. 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 organism<sup>58</sup>, 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 metabolites<sup>59</sup>, breathomics (the multidimensional molecular analysis of  
32  
33 345 exhaled breath<sup>60</sup>, 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 biomarkers<sup>61</sup>. 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 life<sup>62</sup>.

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 practice<sup>63</sup>. 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 aspects<sup>64</sup>.

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 general<sup>65</sup>. 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 needs<sup>66-70</sup>. 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 needed<sup>71</sup>. 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 reactivity<sup>72</sup>.

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 Authorities<sup>73</sup>. 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 <sup>74</sup>. 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 research<sup>75</sup>. 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 al<sup>76</sup>. 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<sup>77,78</sup>.

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<sup>79,80</sup>. We previously pointed out AIT as a prototype of precision medicine<sup>7</sup> 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 <sup>81</sup>  
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 mechanism<sup>82</sup>. 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.  
20 440 The current and future tools to reach a AIT personalized prescription are summarized in  
21  
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  
39 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such  
40  
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 WAO<sup>83</sup> and EAACI<sup>84</sup> 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 rhinitis<sup>85</sup>, the identification of biomarkers predictive of treatment efficacy (still not known)<sup>57</sup> and cost-effectiveness compared to drug therapy, clearly demonstrated on the basis of the persistence over time of the control of symptoms after AIT withdrawal<sup>86</sup>, but further improvable by greater diagnostic precision. Further issues could concern the expansion of e-health systems<sup>7</sup> and the implementation of telemedicine<sup>87</sup>.

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 patients<sup>88</sup>.

#### 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,  
4 483 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,  
9 486 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  
12 488 meetings from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-  
13 489 Aventis, Takeda, Teva, Uriach (Advisory Board, consultant, meeting lectures fees),  
14 490 Kyomed (shares).

18 491 A. Bozek has nothing to disclose.

20 492 D. Caimmi has nothing to disclose.

22 493 M. Calderon has nothing to disclose.

24 494 T. Casale has nothing to disclose.

25 495 A. Custovic has nothing to disclose.

27 496 GW. Canonica declares he has received lecture fees and/or participation at expert board  
28 497 meetings BI, ALK, Stallergenes Greer (Grant/ research support), (Menarini, GSK, Sanofi,  
29 498 Teva, Hal, AZ, Novartis (honoraria or consultation fees).

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

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

43 504 P. Devillier declares he has received has received consultancy fees, honoraria for  
44 505 lectures, and/or research funding from ALKAbelló, Stallergenes Greer, AstraZeneca,  
45 506 Chiesi, Boehringer-Ingelheim, GlaxoSmithKline.

49 507 A. Didier declares he has received personal fees for consultancy services for ALK and  
50 508 grants for participation in clinical research projects with ALK.

52 509 A. Fiocchi has nothing to disclose.

54 510 A. Fox has nothing to disclose.

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

601

602

603

**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

31 618 17)Kespohl S, Raulf M. Mould allergens: Where do we stand with molecular allergy  
32 619 diagnostics?: Part 13 of the series Molecular Allergology. Allergo J Int. 2014;23(4):120-  
33 620 125.  
34 620  
35 621

36 621 18)A WAO - ARIA - GA<sup>2</sup>LEN 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.  
40 624  
41 625

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.  
45 626

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.  
48 628  
49 629

50 629 21)Garib V, Rigler E, Gastager F, et al. Determination of IgE and IgG reactivity to more  
51 630 than 170 allergen molecules in paper dried blood spots. J Allergy Clin Immunol.  
52 631 2019;143:437-440.  
53 631  
54 632

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.  
58 634 2015;24:320-332.  
59 635  
60 635

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 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  
21 715 tolerance in venom immunotherapy: a long-term sting challenge study. *Allergy.* 2012  
22 716 Jun;67(6):822-30.

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  
28 719 immunotherapy in grass pollen-allergic patients. *Allergy.* 2020 Mar 7. [Epub ahead of  
29 720 print].

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  
36 724 CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ,  
37 725 Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M,  
38 726 Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU,  
39 727 Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson  
40 728 HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L,  
41 729 Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL,  
42 730 Tantilipikorn P, Tversky JR, Veling MC, Wang Y, Westman M, Wickman M, Zacharek  
43 731 M. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int*  
44 732 *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  
55 735 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 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.

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.

877

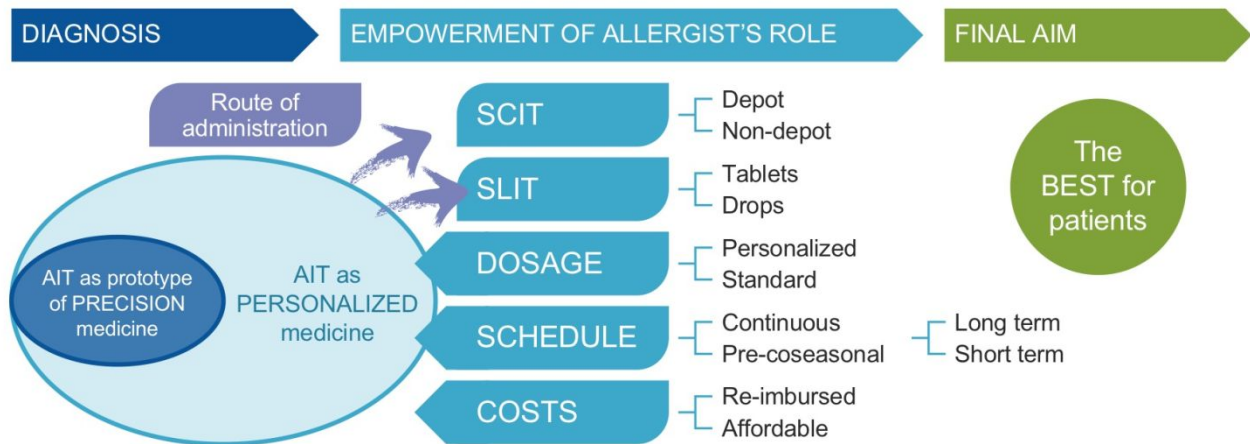
878

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

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 Cristoforo<sup>1</sup>, Al-Ahmad Mona<sup>2,3</sup>, Ansotegui Ignacio<sup>4</sup>, Arasi Stefania<sup>5</sup>, Bachert  
5 Claus<sup>6,7</sup>, Bos Catherine<sup>8</sup>, Bousquet Jean<sup>9</sup>, Bozek Andrzej<sup>10</sup>, Caimmi Davide<sup>11</sup>, Calderón  
6 Moises<sup>12</sup>, Casale Thomas<sup>13</sup>, Custovic Adnan<sup>14</sup>, De Blay Frédéric<sup>15</sup>, Demoly Pascal<sup>11,16</sup>,  
7 Devillier Philippe<sup>17</sup>, Didier Alain<sup>18</sup>, Fiocchi Alessandro<sup>5</sup>, Fox Adam<sup>19</sup>, Gevaert Philippe<sup>6</sup>,  
8 Gomez Maximiliano<sup>20</sup>, Heffler Enrico<sup>21,22</sup>, Iliina Natalia<sup>23</sup>, Irani Carla<sup>24</sup>, Jutel Marek<sup>25</sup>,  
9 Karagiannis Efstrathios<sup>8</sup>, Klimek Ludger<sup>26</sup>, Kuna Piotr<sup>27</sup>, O’Hehir Robin<sup>28</sup>, Kurbacheva  
10 Oxana<sup>29</sup>, Matricardi Paolo Maria<sup>30</sup>, Morais de Almeida Mario<sup>31,32</sup>, Mosges Ralph<sup>33,34</sup>,  
11 Novak Natalija<sup>35</sup>, Okamoto Yoshitaka<sup>36</sup>, Panzner Petr<sup>37</sup>, Papadopoulos Nikolaos<sup>38,39</sup>, Park  
12 Hae-Sim<sup>40</sup>, Passalacqua Giovanni<sup>41</sup>, Pawankar Ruby<sup>42</sup>, Pfaar Oliver<sup>43</sup>, Schmid-  
13 Grendelmeier Peter<sup>44</sup>, Scurati Silvia<sup>8</sup>, Tortajada-Girbés Miguel<sup>45,46</sup>, Vidal Carmen<sup>47</sup>,  
14 Virchow Christian<sup>48</sup>, Wahn Ulrich<sup>30</sup>, Worm Margitta<sup>30</sup>, Ziegelmayer Petra<sup>49</sup>, Canonica  
15 Giorgio Walter<sup>21,22</sup>.

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](mailto: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 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 breakthrough<sup>1</sup>, 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 phenotypes<sup>2</sup> 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 treatment<sup>3</sup>, but soon, with a significant boost from President Obama's announcement on  
20  
21 134 the great potential of personalized medicine<sup>4</sup>, 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 asthma<sup>5</sup>. 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 evidence<sup>6</sup> 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"<sup>7</sup>. 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 rhinitis<sup>8</sup>.  
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 scale<sup>9</sup>. 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 limited<sup>6</sup>. 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 1997<sup>10</sup>. 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 AIT<sup>11</sup>. 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 success<sup>12</sup>.

### 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<sup>13,14</sup>. 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 extracts<sup>13</sup>. 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 dose<sup>14</sup>. 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”<sup>15</sup>, molecular-based allergy diagnostics<sup>16</sup>, and molecular allergy diagnostics<sup>17</sup>. The updated WAO-ARIA- GA<sup>2</sup>LEN consensus document on molecular-based allergy proposed the unifying definition of “precision allergy molecular diagnostic applications” (PAMD@)<sup>18</sup>. 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*<sup>19</sup>). 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 testing<sup>20</sup>. 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 physician<sup>21</sup>, 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 sources<sup>22</sup>, 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 added<sup>23</sup>. The EUROLINE Southern European Pollen Profile [ESEP) was introduced to test pollen molecules of clinical relevance in Southern Europe<sup>24</sup>, while the Microarray Diagnostics (MADx) Allergen Explorer (ALEX) include 126 molecules from different allergen sources<sup>25</sup>. 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 result<sup>26</sup>. 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 found<sup>27</sup>.

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 studies<sup>28-37</sup>. A vast literature is available, as  
16  
17 234 recently reviewed<sup>38-39</sup>, 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 allergy<sup>40</sup>,  
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 inhibition<sup>41</sup>, 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<sup>35,42</sup> and to have a lower cost<sup>43</sup> 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 basophils<sup>44</sup>. 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 ImmunoCAP<sup>45</sup> 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 BAT<sup>46</sup>. 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 challenge<sup>47</sup>.  
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 treatment<sup>48</sup>. 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 rhinitis<sup>49</sup>. 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 health<sup>50</sup>. 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

recent years<sup>51</sup>. 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 control<sup>52</sup>. 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 bronchiectasis<sup>53</sup>.

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 outcomes<sup>54</sup>. 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 phenotypes<sup>55</sup>.

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 patients<sup>56</sup>. Concerning AIT, treatable traits of clinical interest may consist of the treatment outcome, beyond the disease to be treated, on comorbidities<sup>57</sup>. 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  
21 338

#### 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 organism<sup>58</sup>, 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 metabolites<sup>59</sup>, breathomics (the multidimensional molecular analysis of  
32  
33 345 exhaled breath<sup>60</sup>, 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 biomarkers<sup>61</sup>. 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 life<sup>62</sup>.

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 practice<sup>63</sup>. 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 aspects<sup>64</sup>.

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 general<sup>65</sup>. 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 needs<sup>66-70</sup>. 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 needed<sup>71</sup>. 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 reactivity<sup>72</sup>.

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 Authorities<sup>73</sup>. 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  
20 406 Academy of Allergy and Clinical Immunology (EAACI) initiative is designed to ascertain the  
21  
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 <sup>74</sup>. 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 research<sup>75</sup>. 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  
39 417 credible, as also stated by Sherman et al<sup>76</sup>. In fact, it should be underlined that several AIT  
40  
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<sup>77,78</sup>.

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<sup>79,80</sup>. We previously pointed out AIT as a prototype of precision medicine<sup>7</sup> and  
58 428 now we would propose AIT as one of the best example of Personalized and Participatory  
59  
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 <sup>81</sup>  
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 mechanism<sup>82</sup>. 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.  
20 440 The current and future tools to reach a AIT personalized prescription are summarized in  
21  
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  
39 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such  
40  
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 WAO<sup>83</sup> and EAACI<sup>84</sup> 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 rhinitis<sup>85</sup>, the identification of biomarkers predictive of treatment efficacy (still not known)<sup>57</sup> and cost-effectiveness compared to drug therapy, clearly demonstrated on the basis of the persistence over time of the control of symptoms after AIT withdrawal<sup>86</sup>, but further improvable by greater diagnostic precision. Further issues could concern the expansion of e-health systems<sup>7</sup> and the implementation of telemedicine<sup>87</sup>.

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 patients<sup>88</sup>.

#### **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
- 31 618 17)Kespohl S, Raulf M. Mould allergens: Where do we stand with molecular allergy  
32 619 diagnostics?: Part 13 of the series Molecular Allergology. *Allergo J Int.* 2014;23(4):120-  
33 620 125.  
34 620  
35 621
- 36 621 18)A WAO - ARIA - GA<sup>2</sup>LEN 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.  
40 624  
41 625
- 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.  
45 626
- 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.  
48 628  
49 629
- 50 629 21)Garib V, Rigler E, Gastager F, et al. Determination of IgE and IgG reactivity to more  
51 630 than 170 allergen molecules in paper dried blood spots. *J Allergy Clin Immunol.*  
52 631 2019;143:437-440.  
53 631  
54 632
- 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.*  
58 634 2015;24:320-332.  
59 635  
60 635

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  
26 650 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.  
28 652
- 31 653 28) Mittermann I, Zidarn M, Silar M, Markovic-Housley Z, Aberer W, Korosec P, Kosnik M,  
32 654 Valenta R. Recombinant allergen-based IgE testing to distinguish bee and wasp  
33 655 allergy. *J Allergy Clin Immunol*. 2010 Jun;125(6):1300-1307.  
34 656
- 36 657 29) Sastre J, Landivar ME, Ruiz-García M, Andregnette-Rosigno MV, Mahillo I.  
37 658 How molecular diagnosis can change allergen-specific immunotherapy prescription in a  
38 659 complex pollen area. *Allergy*. 2012 May;67(5):709-11.  
39 660
- 41 661 30) Moreno C, Justicia JL, Quiralte J, Moreno-Ancillo A, Iglesias-Cadarso A, Torrecillas M,  
42 662 Labarta N, García MA, Dávila I. Olive, grass or both? Molecular diagnosis for  
43 663 the allergen immunotherapy selection in polysensitized pollinic patients. *Allergy*. 2014  
44 664 Oct;69(10):1357-63.  
45 665
- 48 666 31) Popescu FD. Molecular biomarkers for grass pollen immunotherapy. *World J Methodol*.  
49 667 2014 Mar 26;4(1):26-45.  
50 668
- 51 669 32) Vidal C, Enrique E, Gonzalo A, Moreno C, Tabar AI; Expert Clinical Participants.  
52 670 Diagnosis and allergen immunotherapy treatment of polysensitized patients with  
53 671 respiratory allergy in Spain: an Allergists' Consensus. *Clin Transl Allergy*. 2014 Nov  
54 672 7;4:36.  
55 673
- 58 674 33) Saltabayeva U, Garib V, Morenko M, Rosenson R, Ispayeva Z, Gatauova M, Zulus L,  
59 675 Karaulov A, Gastager F, Valenta R. Greater Real-Life Diagnostic Efficacy  
60 676

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.

60 703



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, Halken 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.

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.

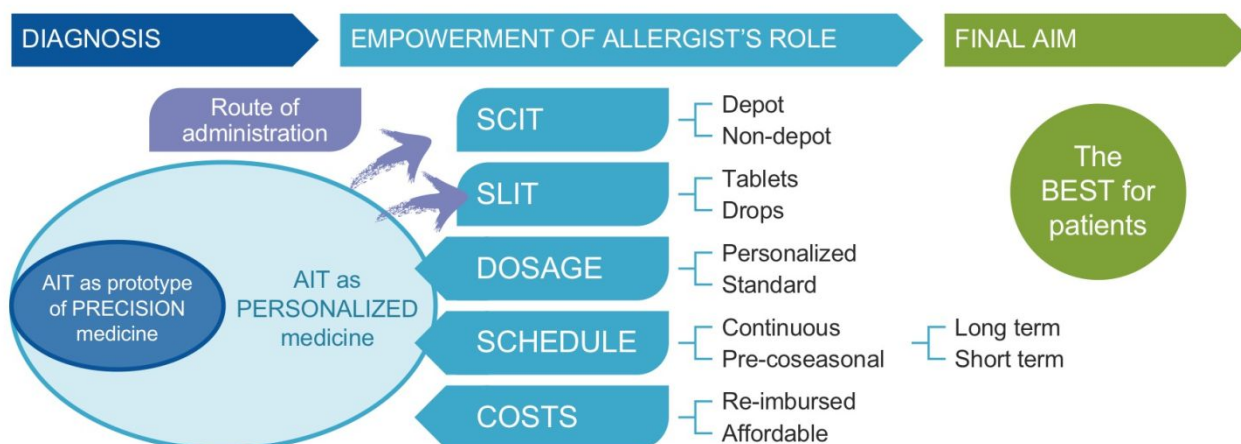
877  
878

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

886

887

888

889

890

891

892

893

894

895

896

897

898

899

900

901

902

903

904

905

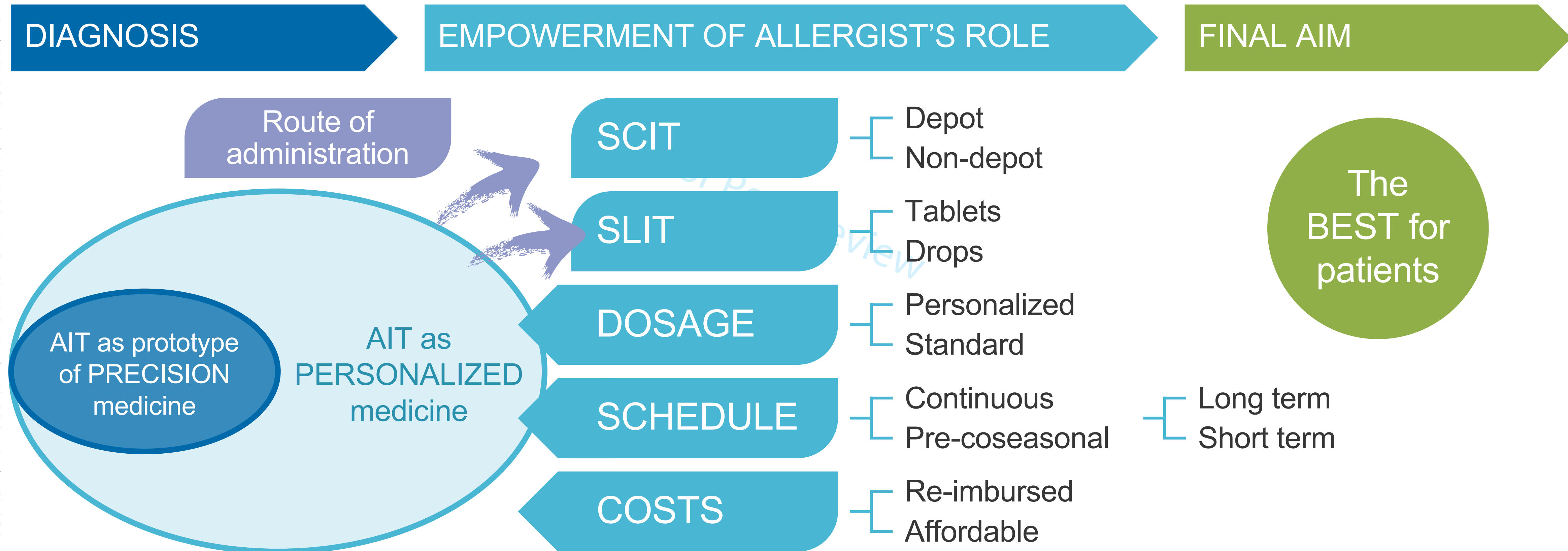
906

907

908



# 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