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

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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.
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9 COMMENTS FOR THE AUTHOR(S)

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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.
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18 RESPONSE: We thank the Reviewer for his/her appreciation.
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22 Best regards,

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24 Enrico Heffler (on behalf of all my co-Authors)
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1 **Personalized Medicine for allergy treatment: allergen immunotherapy** 2 **still a unique and unmatched model.**

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3 **Abstract**

4
5 100 The introduction of personalized medicine (PM) has been a milestone in the history of
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7 101 medical therapy, because it has revolutionized the previous approach of treating the
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9 102 disease with that of treating the patient. It is known today that diseases can occur in
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11 103 different genetic variants, making specific treatments of proven efficacy necessary for a
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13 104 given endotype. Allergic diseases are particularly suitable for PM, because they meet the
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15 105 therapeutic success requirements, including a known molecular mechanism of the
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17 106 disease, a diagnostic tool for such disease, and a treatment blocking the mechanism. The
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19 107 stakes of PM in allergic patients are molecular diagnostics, to detect specific IgE to single
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21 108 allergen molecules and to distinguish the causative molecules from those merely cross-
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23 109 reactive, pursuit of patient's treatable traits addressing genetic, phenotypic and
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25 110 psychosocial features, and omics, such as proteomics, epi-genomics, metabolomics and
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27 111 breathomics, to forecast patient's responsiveness to therapies, to detect biomarker and
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29 112 mediators, and verify the disease control. This new approach has already improved the
30
31 113 precision of allergy diagnosis and is likely to significantly increase, through the higher
32
33 114 performance achieved with the personalized treatment, the effectiveness of allergen
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35 115 immunotherapy by enhancing its already known and unique characteristics of treatment
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37 116 that acts on the causes.

38 **Key words:** allergen immunotherapy, personalized medicine, molecular diagnosis,
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40 120 treatable traits, omics.

41 **Short title:** Allergen immunotherapy: a model of personalized medicine.
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3 **124 Introduction**

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

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

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

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3 158 allergenic source directly from the doctor, was hugely lower than the allergen extracts
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5 159 used today, but the positive results obtained paved the way to an evolution finally resulting
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7 160 in high quality products. Another definition that underlines how the AIT was yet, but
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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
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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,
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17 166 namely all the allergens giving positive results to allergy testing, were frequently used,
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19 167 especially in the U.S.A, but they were found to be ineffective in a pivotal double-blind,
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21 168 placebo-controlled trial in 1997¹⁰. Nowadays, registered products, whose effectiveness
22 169 has been plainly demonstrated by controlled trials on large patient populations, are
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24 170 considered ideal for AIT¹¹. However, good quality NPPs with demonstration of efficacy by
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26 171 placebo-controlled trials, are still available to treat respiratory allergy with expectancy of
27 172 clinical success¹².

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

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31 174 The traditional diagnosis by skin tests relay on extracts, whose composition in minor and
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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
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36 177 testing and AIT. As to the latter, Larenas-Linneman et al. found a substantial variability in
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38 178 allergen extract potency as measured and reported worldwide^{13,14}. In particular, in Europe
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40 179 the potency of extracts for sublingual immunotherapy (SLIT) is based on comparison with
41 180 in-house references, making it difficult to translate the dose to US extracts¹³. Moreover,
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43 181 comparing SLIT maintenance solutions of grass pollen and *Dermatophagoides*
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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
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48 184 potency was around 10 times higher for US standardized extracts (to be diluted for SLIT)
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50 185 than for European SLIT maintenance dosage. The authors argued that, based on the
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52 186 efficacy demonstrations from controlled trials, SLIT efficacy is likely to depend on
53 187 additional factors apart from the extract dose¹⁴. Today, the pillars of AIT as a personalized
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55 188 therapy are represented by molecular diagnostics for achieving the highest possible
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57 189 precision, by the use of treatable traits, and by “omics”.

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1) Molecular diagnostics and other *in vitro* tests

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

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

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

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

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

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

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
42 282 challenge, a pivotal role being currently acknowledged only in diagnosis of occupational
43
44 283 rhinitis and local allergic rhinitis⁴⁹. If future studies will achieve standardization of the
45
46 284 method, the nasal challenge could be used, alike BAT, as a test toward precision medicine.
47
48 285

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
54 289 based on finding genetic, phenotypic and psychosocial features which are associated with
55
56 290 therapies able to improve respiratory health⁵⁰. The field of application considered as most
57
58 291 appropriate for the use of treatable traits is represented by chronic respiratory diseases
59 292 and in particular by asthma and chronic obstructive pulmonary disease (COPD), which
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293 share various clinical aspects but whose drug therapy has significantly differentiated in

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

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

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

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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
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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
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17 336 AIT, once ceased the contraindication, can induce the long-term immunological changes.
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19 337 Studies to investigate whether such synergy is achievable are warranted.

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22 339 **4.Omics**

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

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

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5 363 Impact of personalized medicine on AIT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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41 383 ensured in terms of quality product and standardization.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 400 In this context, the evaluation of the Real-World Evidences (RWE), should be properly
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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
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16 403 registration by Regulatory Authorities⁷³. In fact, distinction is made between the final
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18 404 outcome of DBPCT efficacy and the one in RWE. Nonetheless, a correct evaluation of
19
20 405 these RWE has to be methodologically performed. To this purpose an ongoing European
21
22 406 Academy of Allergy and Clinical Immunology (EAACI) initiative is designed to ascertain the
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24 407 validity of the existing RWE concerning AIT, applying the recent tools proposed by
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26 408 Respiratory Effectiveness Group (REG)/EAACI from one side (Relevant) and Grading of
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28 409 Recommendations, Assessment, Development and Evaluation (GRADE) on the other side
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30 410 ⁷⁴. Through this initiative we will be able define the real validity of the existing AIT RWEs.
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32 411 This action has been also stated and promoted by the recent Real-Life Research
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34 412 Manifesto, where it is pointed out the need to consider RWE in the complex scenario of
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36 413 scientific clinical research⁷⁵. This document supported the use of tools, such as the ones
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38 414 mentioned previously, to analyze RWE properly. Finally, the Manifesto also underlined the
39
40 415 major differences existing between retrospective and prospective RWE: where prospective
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42 416 approach, whose typical example is a Disease or intervention's Registry, is the most
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44 417 credible, as also stated by Sherman et al⁷⁶. In fact, it should be underlined that several AIT
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46 418 RWE reports were retrospectively collected, combining different methodologies, thus
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48 419 decreasing the validity of the final outcomes/conclusions. However, recent, well conducted
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50 420 real-life studies, derived from a well-designed and set up database and including very
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52 421 large patient populations, were of relevant importance, because they contributed to
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54 422 increase the knowledge on the effectiveness of AIT in patients seen in daily clinical
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56 423 practice, possibly not meeting the strict criteria to be included in a trial^{77,78}.

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

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55 426 All the above is in line with the current view that collecting Big Data can lead to precision
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57 427 medicine^{79,80}. We previously pointed out AIT as a prototype of precision medicine⁷ and
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59 428 now we would propose AIT as one of the best example of Personalized and Participatory
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61 429 Medicine, aimed to satisfy the needs and preferences of patients and to strengthen the

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3 430 cooperation patient/doctor in jointly choosing the best therapeutic option. AIT is the only
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5 431 medical treatment that has the capacity to change the natural history of allergic diseases ⁸¹
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7 432 and responds perfectly to the three major needs to be met in personalized medicine, which
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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
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12 435 blocking the mechanism⁸². In Figure 1 we summarized all the possible aspects of the
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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
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19 439 deciding the subsequent investigations in accordance with the individual characteristics.
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21 440 The current and future tools to reach a AIT personalized prescription are summarized in
22 441 Figure 2 . Their variable characteristics suggest that personalized care is valuable in this
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24 442 setting and may be also be preventive (by focusing on quality of life), predictive (by
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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
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29 445 medicine treatment (especially with high quality NPP) that enable the physician to identify
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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
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36 449 number of SLIT drops up dosing regimens and maintenance treatment were shown to be
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38 450 safe and effective. This means that SLIT liquid allergen extract formulations are extremely
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40 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such
41 452 parameters can be fine-tuned to suit the patient's day-to-day treatment response and
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43 453 intercurrent events. Depending on the sensitization profile and the clinical signs, the
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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
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48 456 makes it possible to adapt the dose and regimen during the up dosing and/or the
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50 457 maintenance phase to target optimal effectiveness.
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The clinician should then evaluate:

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

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

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

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

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3 565 **Table 1 Studies that have assessed the benefits of attaining with PAMD a more**
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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.

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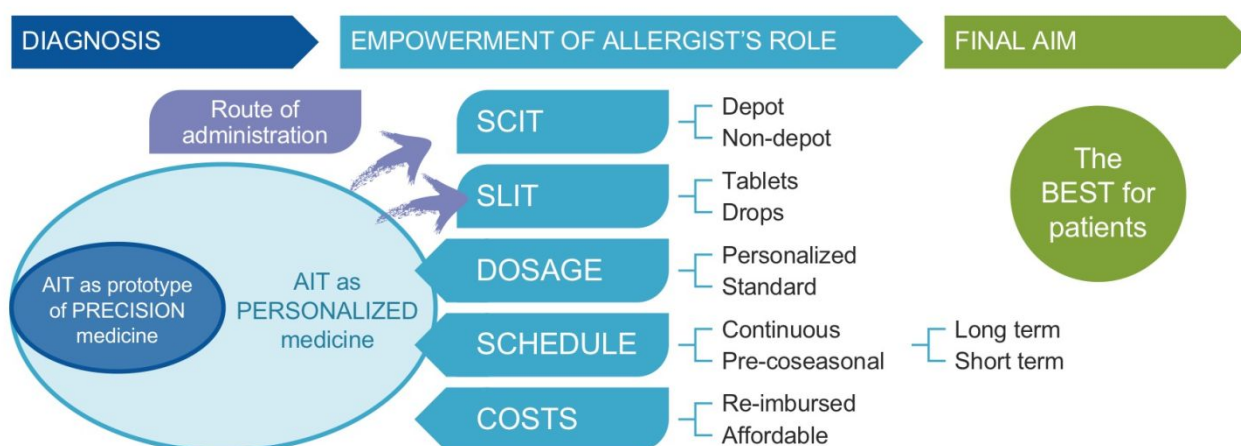
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880 **Figure 1** - Allergen Immunotherapy as personalized treatment

AIT AS PERSONALIZED TREATMENT



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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*)



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

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3 99 **Abstract**

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5 100 The introduction of personalized medicine (PM) has been a milestone in the history of
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7 101 medical therapy, because it has revolutionized the previous approach of treating the
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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
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12 104 given endotype. Allergic diseases are particularly suitable for PM, because they meet the
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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
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17 107 stakes of PM in allergic patients are molecular diagnostics, to detect specific IgE to single
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19 108 allergen molecules and to distinguish the causative molecules from those merely cross-
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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
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24 111 breathomics, to forecast patient's responsiveness to therapies, to detect biomarker and
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26 112 mediators, and verify the disease control. This new approach has already improved the
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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
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31 115 immunotherapy by enhancing its already known and unique characteristics of treatment
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33 116 that acts on the causes.

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

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41 121 **Short title:** Allergen immunotherapy: a model of personalized medicine.
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1 2 3 124 **Introduction**

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

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

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50 151 As hinted above, AIT was introduced more than one hundred years ago, when the
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52 152 knowledge on allergic disease was very limited⁶. Still, the different role of AIT compared
53 153 with the drug therapy available at the time was apparent, because drugs were aimed at
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55 154 treating the symptoms of allergic rhinitis, while AIT was aimed at treating the specific
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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
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60 157 that the quality of the products in that time, which consisted of extracts obtained from the

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3 158 allergenic source directly from the doctor, was hugely lower than the allergen extracts
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5 159 used today, but the positive results obtained paved the way to an evolution finally resulting
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7 160 in high quality products. Another definition that underlines how the AIT was yet, but
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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.
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12 163 Nevertheless, NPPs were not a guarantee of clinical efficacy, because alongside products
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14 164 with evidence of efficacy proven by placebo-controlled trials, others without such evidence
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17 166 namely all the allergens giving positive results to allergy testing, were frequently used,
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19 167 especially in the U.S.A, but they were found to be ineffective in a pivotal double-blind,
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21 168 placebo-controlled trial in 1997¹⁰. Nowadays, registered products, whose effectiveness
22 169 has been plainly demonstrated by controlled trials on large patient populations, are
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24 170 considered ideal for AIT¹¹. However, good quality NPPs with demonstration of efficacy by
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26 171 placebo-controlled trials, are still available to treat respiratory allergy with expectancy of
27 172 clinical success¹².

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

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31 174 The traditional diagnosis by skin tests relay on extracts, whose composition in minor and
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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
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36 177 testing and AIT. As to the latter, Larenas-Linneman et al. found a substantial variability in
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38 178 allergen extract potency as measured and reported worldwide^{13,14}. In particular, in Europe
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40 179 the potency of extracts for sublingual immunotherapy (SLIT) is based on comparison with
41 180 in-house references, making it difficult to translate the dose to US extracts¹³. Moreover,
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43 181 comparing SLIT maintenance solutions of grass pollen and *Dermatophagoides*
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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
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48 184 potency was around 10 times higher for US standardized extracts (to be diluted for SLIT)
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50 185 than for European SLIT maintenance dosage. The authors argued that, based on the
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52 186 efficacy demonstrations from controlled trials, SLIT efficacy is likely to depend on
53 187 additional factors apart from the extract dose¹⁴. Today, the pillars of AIT as a personalized
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55 188 therapy are represented by molecular diagnostics for achieving the highest possible
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57 189 precision, by the use of treatable traits, and by “omics”.

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1) Molecular diagnostics and other *in vitro* tests

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

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

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

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26 239 As far as the identification of the really causative allergen in polysensitized patients is
27 240 concerned, the first *in vitro* test was the RAST inhibition⁴¹, which then evolved into CAP
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29 241 inhibition assay. The latter has been shown to be comparable to PAMD@ in the ability to
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31 242 identify the causative allergen^{35,42} and to have a lower cost⁴³ in patients with multiple
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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
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36 245 respiratory allergens, involving a much higher number of molecules.

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38 246 The basophil activation test (BAT), which measures basophil degranulation by flow
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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
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43 249 has a similar meaning to the *in vivo* provocation test with specific allergens, without
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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
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48 252 patients with allergic conditions including respiratory, food and *Hymenoptera* venom
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50 253 allergy who show multiple allergen reactivity, distinguishing the allergens as causative or
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52 254 not based on the response of the basophils⁴⁴. As mentioned above, our review is focused
53 255 on the effects of personalized diagnosis on the outcomes of AIT. As for CAP inhibition, the
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55 256 first studies concerned *Hymenoptera* venom allergy, demonstrating that BAT
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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
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60 259 anaphylactic reactions to wasp stings over IgE detection by Enzyme-Linked

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

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33 277 **2 In vivo tests**

35 278 Theoretically, inducing allergic symptoms by a challenge with the suspected allergen in the
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37 279 target organs can be a valuable in vivo test. However, as stated in the International
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39 280 Consensus Statement on allergic rhinitis, the contrasting findings from different studies
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41 281 and the absence thus far of a standardized technique limit the diagnostic utility of nasal
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43 282 challenge, a pivotal role being currently acknowledged only in diagnosis of occupational
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45 283 rhinitis and local allergic rhinitis⁴⁹. If future studies will achieve standardization of the
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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
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53 288 medicine methodology of diagnosis and treatment of chronic disorders of the airways
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55 289 based on finding genetic, phenotypic and psychosocial features which are associated with
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57 290 therapies able to improve respiratory health⁵⁰. The field of application considered as most
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59 291 appropriate for the use of treatable traits is represented by chronic respiratory diseases
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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

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

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

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

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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
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7 330 5) or their receptors (IL 5 rec. or IL4/IL13 rec.). Nonetheless, we should consider that the
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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
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12 333 mild/moderate asthma while severe asthma is a contraindication. Based on the
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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
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17 336 AIT, once ceased the contraindication, can induce the long-term immunological changes.
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19 337 Studies to investigate whether such synergy is achievable are warranted.

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22 339 **4.Omics**

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

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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
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48 354 that omics-based investigation are used increasingly to distinguish subtypes of
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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
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53 357 concluded that omics testing in this field for are not yet a standard of care, and that key
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55 358 factors need to be recognized before such technologies can be used successfully in
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57 359 common clinical practice⁶³. On the other hand, according to Fitzgerald et al., the promise
58 360 of new technology must leave room to an humanomics perspective, i.e. the
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60 361 acknowledgement of patient’s behavioral aspects⁶⁴.

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5 363 Impact of personalized medicine on AIT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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41 383 ensured in terms of quality product and standardization.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 400 In this context, the evaluation of the Real-World Evidences (RWE), should be properly
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12 401 reappraised, since patients in clinical practice often do not meet the same criteria of the
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14 402 subjects enrolled in the double-blind placebo-controlled trials (DBPCRT) leading to
15 403 registration by Regulatory Authorities⁷³. In fact, distinction is made between the final
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17 404 outcome of DBPCT efficacy and the one in RWE. Nonetheless, a correct evaluation of
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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
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22 407 validity of the existing RWE concerning AIT, applying the recent tools proposed by
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24 408 Respiratory Effectiveness Group (REG)/EAACI from one side (Relevant) and Grading of
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26 409 Recommendations, Assessment, Development and Evaluation (GRADE) on the other side
27 410 ⁷⁴. Through this initiative we will be able define the real validity of the existing AIT RWEs.
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29 411 This action has been also stated and promoted by the recent Real-Life Research
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31 412 Manifesto, where it is pointed out the need to consider RWE in the complex scenario of
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33 413 scientific clinical research⁷⁵. This document supported the use of tools, such as the ones
34 414 mentioned previously, to analyze RWE properly. Finally, the Manifesto also underlined the
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36 415 major differences existing between retrospective and prospective RWE: where prospective
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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 al⁷⁶. In fact, it should be underlined that several AIT
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41 418 RWE reports were retrospectively collected, combining different methodologies, thus
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43 419 decreasing the validity of the final outcomes/conclusions. However, recent, well conducted
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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
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48 422 increase the knowledge on the effectiveness of AIT in patients seen in daily clinical
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50 423 practice, possibly not meeting the strict criteria to be included in a trial^{77,78}.

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

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

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3 430 cooperation patient/doctor in jointly choosing the best therapeutic option. AIT is the only
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5 431 medical treatment that has the capacity to change the natural history of allergic diseases ⁸¹
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7 432 and responds perfectly to the three major needs to be met in personalized medicine, which
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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
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12 435 blocking the mechanism⁸². In Figure 1 we summarized all the possible aspects of the
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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
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17 438 must be kept in mind that the medical history collected by a skilled doctor is the basis for
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19 439 deciding the subsequent investigations in accordance with the individual characteristics.
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21 440 The current and future tools to reach a AIT personalized prescription are summarized in
22 441 Figure 2 . Their variable characteristics suggest that personalized care is valuable in this
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24 442 setting and may be also be preventive (by focusing on quality of life), predictive (by
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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
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29 445 medicine treatment (especially with high quality NPP) that enable the physician to identify
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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
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36 449 number of SLIT drops up dosing regimens and maintenance treatment were shown to be
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38 450 safe and effective. This means that SLIT liquid allergen extract formulations are extremely
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40 451 flexible in terms of frequency of dosing and number of allergen doses delivered. Such
41 452 parameters can be fine-tuned to suit the patient's day-to-day treatment response and
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43 453 intercurrent events. Depending on the sensitization profile and the clinical signs, the
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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
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48 456 makes it possible to adapt the dose and regimen during the up dosing and/or the
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50 457 maintenance phase to target optimal effectiveness.
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The clinician should then evaluate:

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

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

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

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

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3 565 **Table 1 Studies that have assessed the benefits of attaining with PAMD a more**
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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.

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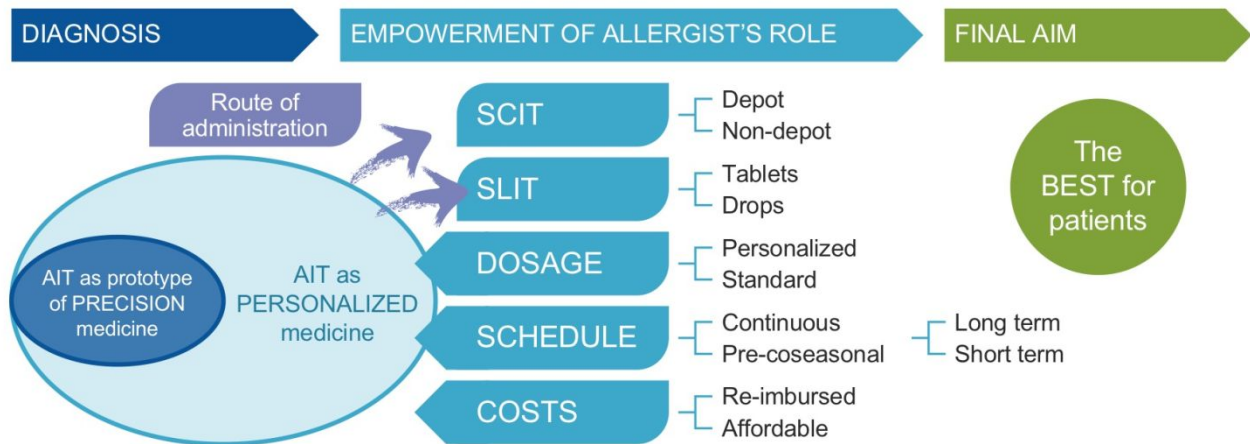
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DRAFT REVIEW ARTICLE dated 11.11.2020
For Peer Review

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

AIT AS PERSONALIZED TREATMENT



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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



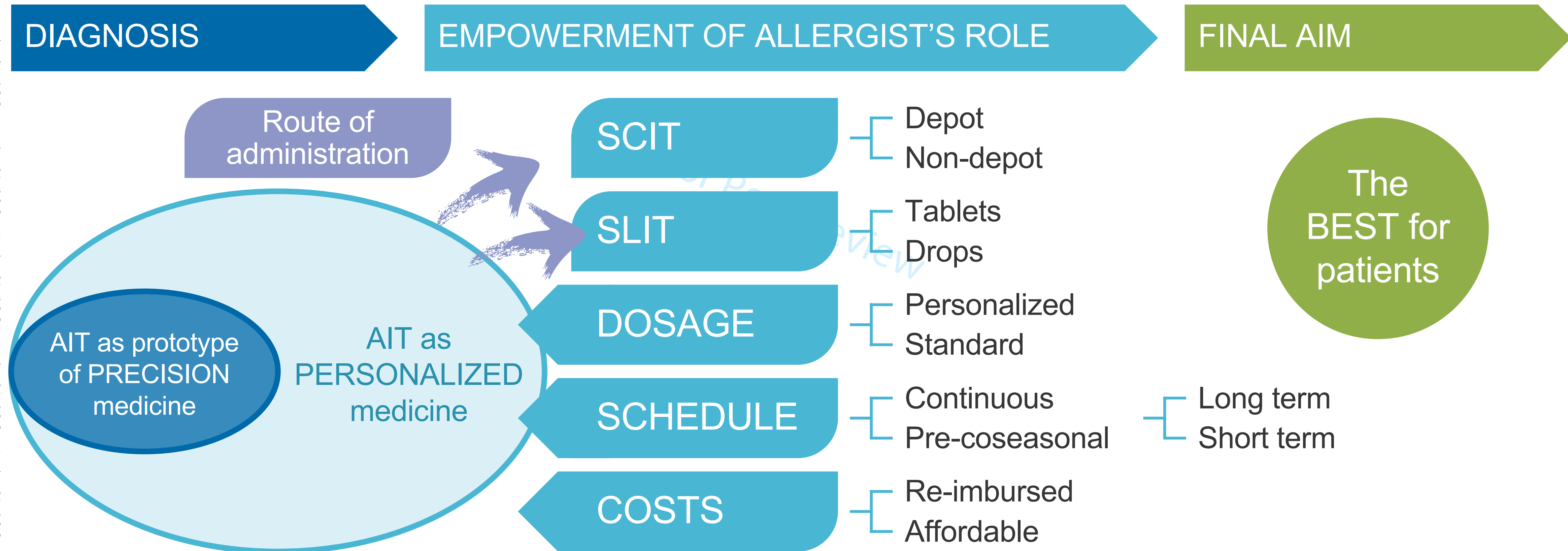
Tools of future applications

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



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AIT AS PERSONALIZED TREATMENT



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Tools for personalized AIT

Validated tools for AIT

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



Tools still to be validated for AIT

- Basophil activation test
- Nasal cytology
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Tools of future applications

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(*genetic, phenotypic, psychosocial features*)
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(*proteomics, epigenomics, metabolomics, breathomics*)



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