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@IT2020: An innovative algorithm for allergen immunotherapy prescription in seasonal allergic rhinitis

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Abstract

Background: Allergen immunotherapy (AIT) is the only disease-modifying treatment in patients with seasonal allergic rhinoconjunctivitis (SAR). Its efficacy depends on the precise identification of the triggering allergen. However, diagnostics based on retrospective clinical history and sensitization to whole extracts (SWE) often leads to equivocal results.

Objectives: To assess the usability and impact of a recently established algorithm for a clinical decision support system (@IT2020-CDSS) for SAR and its diagnostic steps [anamnesis, SWE (skin prick test or serum IgE), component resolved diagnosis, CRD, and real-time digital symptom recording, eDiary] on doctor's AIT prescription decisions.

Methods: After educational training on the @IT2020-CDSS algorithm, 46 doctors (18 allergy specialists, AS, and 28 general practitioners, GP) expressed their hypothetical AIT prescription for 10 clinical index cases. Decisions were recorded repeatedly based on different steps of the algorithm. The usability and perceived impact of the algorithm were evaluated.

Results: The combined use of CRD and an eDiary increased the hypothetical AIT prescriptions, both among AS and GP ($p < .01$). AIT prescription for pollen and *Alternaria* allergy based on anamnesis and SWE was heterogeneous but converged towards a consensus by integrating CRD and eDiary information. Doctors considered the algorithm useful and recognized its potential in enhancing traditional diagnostics.

Conclusions and clinical implications: The implementation of CRD and eDiary in the @IT2020-CDSS algorithm improved consensus on AIT prescription for SAR among AS and GP. The potential usefulness of a CDSS for aetiological diagnosis of SAR and AIT prescription in real-world clinical practice deserves further investigation.

KEYWORDS
allergen-specific immunotherapy, clinical decision support system, component resolved diagnostics, mobile health, seasonal allergic rhinitis

1 | INTRODUCTION

Seasonal rhinoconjunctivitis due to pollen allergy (SAR) affects millions of people around the globe and is particularly prevalent among children.[1] Symptom-relieving drugs can control the disease, but the only disease-modifying treatment with long-term effects is an allergen-specific immunotherapy (AIT).[2,3] The efficacy of AIT depends on the precise identification of the eliciting allergen inducing IgE sensitization and triggering the patient's symptoms.[4-6] Unfortunately, pinning down the causing allergen is often difficult, especially in Southern European countries, as patients are frequently sensitized to multiple, often cross-reactive, pollens with overlapping exposure seasons.[7]

Component resolved diagnostics (CRD) helps identifying the allergens eliciting symptoms and thereby choosing those for AIT. Algorithms on the molecular diagnosis of allergies have been published but infrequently used[8-10] and a traditional diagnosis, based exclusively on anamnesis, skin prick tests (SPT) or IgE tests with whole allergen extracts, is still the most frequently used worldwide.[3] Expert systems and software solutions may facilitate the adoption of diagnostic algorithms for CRD[11] but, to our knowledge, are not yet available. In contrast, a great variety of mobile phone applications—most of which not yet validated—has flooded the market, aiming at an improved disease control and quality of life for allergic patients. However, electronic clinical diaries (eDiaries) are useful for real-time prospective symptom monitoring[12-16] and enable doctors to evaluate individual symptoms and the need for medication. With the help of software systems, clinical scores can be automatically generated, graphically matching patients´ combined symptom and medication score (CSMS) trajectories with those of the local allergen counts.[16,17]

Mobile Health (mHealth) technology is used also as part of clinical decision support systems (CDSS) assisting patients, clinicians and pharmacists at the point of care.[18-22] In preparation of a CDSS for the precise prescription of AIT, we developed @IT2020, a diagnostic algorithm based on CRD and eDiaries. We aimed this study at assessing usability and impact of this algorithm when used by allergy specialists (AS) and general practitioners or non-allergy specialists (GP) examining SAR patients sensitized to pollen and/or *Alternaria*.

2 | MATERIALS AND METHODS

2.1 | Study design and population

A workshop ('AIT prescription workshop', AIT-WS) was organised with 10 GP +11 AS at 'Ospedale S. Pertini' (Rome, Italy) and with 18 GP +7 AS at 'Ospedale S. Maria degli Angeli' (Pordenone, Italy). The study design and procedures were approved by the ethic committees 'Comitato Etico Indipendente Lazio 2' (Study 10–16, Protocol number 9871—01/02/2016) and 'Comitato Etico Regionale Unico (Friuli Venezia Giulia)' (Protocol number 22/2016/Os—08/03/2016). The participants were recruited among those physicians collaborating with each centre on a regular basis. Each workshop consisted of the following three phases: (a) educational training; (b) decision making on clinical cases; and (c) feedback survey.

2.2 | Educational training

During the first part of the AIT-WS, the target, nature and methodology of the diagnostic tools (ie questionnaires; SPT, and/or sIgE to allergen extracts; CRD; and eDiary) were presented in comprehensive lectures. In detail, three lectures explained the general concepts, specific methodologies and clinical interpretation of the diagnostic tools. A fourth lecture was focused on the procedures for the following workshop module involving clinical cases.

2.3 | Algorithm for a potential clinical decision support system (CDSS) for seasonal allergic rhinitis

The @IT2020-CDSS tools are based on clinical data progressively considered in three steps: 1) step 1—clinical history and sensitization to whole extracts (SWE) [ie skin prick tests (SPT) and/or serum sIgE to a panel of allergens including timothy grass, cypress, birch, olive trees, ragweed, mugwort, pellitory, *Alternaria*]; 2) step 2—addition of IgE assays to molecular allergenic components (component resolved diagnostics, CRD); 3) step 3—addition of electronic clinical diary (eDiary).[19] In the first step, a list of potentially relevant allergens is selected considering the period of allergic symptoms reported by the patient (clinical history, seasonality of SAR symptoms) and the sensitization profile against whole allergen extracts (ie 'traditional' diagnosis). In the second step, the list of allergens previously selected is restricted to those confirmed by IgE sensitization to their respective major allergenic proteins (Cup a 1 for cypress, Phl p 1 and/or Phl p 5 for grass, Bet v 1 for birch, Ole e 1 for Olive, Amb a 1 for ragweed, Art v 1 for mugwort, and Alt a 1 for *Alternaria alternata*). Finally, in the third step, the list of allergens considered in step 2 is furtherly restricted to those whose pollination period matched with the symptoms prospectively registered by the patient with the eDiary. The three steps of the algorithm form a 'pyramid' for each of the eight allergens (Figure 1A) generating a precision 'target' or dartboard when combined (Figure 1B). Herein, we used the words 'pollen', 'pollinosis' and 'pollination' throughout the manuscript for ease of expression in reference to the whole group pollens-*Alternaria*.

2.4 | Clinical cases

The @IT2020 pilot study population (n = 200) has been described elsewhere.[17,23] From this population, twenty clinical index cases (10 per center) were selected to reproduce the local epidemiological scenario[6] and to provide the widest spectrum of allergen(s) causing moderate-to-severe SAR (Table E1). @IT2020-pilot study population (n = 200) and the respective diagnostic work-up have been reported in detail elsewhere[17,23] and in the electronic repository (see section

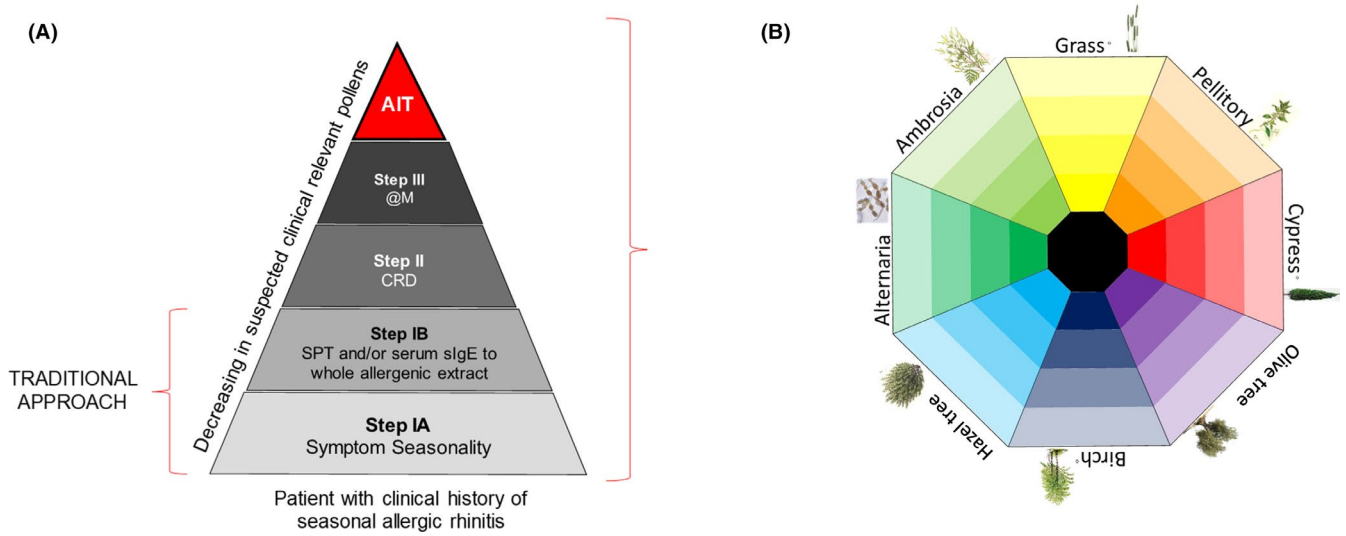

FIGURE 1 Algorithm for a potential Clinical Decision Support System (CDSS) for seasonal allergy. A, «Pyramid model». The successive steps of the diagnostic algorithm of @IT2020-CDSS develop vertically as a 'pyramid'. In most clinical cases, excluding step by step more and more seasonal allergens, the 'pyramid' algorithm proceeds from a large basis towards a narrow top, allowing the recognition of the only one or a few relevant allergen(s) among the many putative considered by the traditional diagnostic approach. Modified from Matricardi PM et al.[19] B, The octagonal 'dartboard'. Each of the 8 pyramids referred to one of the main local airborne allergenic sources is graphically represented as one of the 8 regular triangles constituting the octagonal 'dartboard'. As in a dartboard, the algorithm aims to hit the target, that is identifying the clinically relevant allergen(s). Step by step, the algorithm proceeds from the basis up to the top of each pyramid, which is also from the outer edge towards the core of the dartboard. Allergens excluded are turned off and only the selected allergen remains coloured with a more intense tone in the same colour gamma. At the end, the target will take the colour of the only relevant allergen(s). AIT, allergen immunotherapy; eDiary, electronic clinical diary; CRD, component-resolved diagnosis; sIgE, serum specific immunoglobulin E; SPT, skin prick tests

'Material and methods'). Briefly, 101 children ('Ospedale Sandro Pertini', Rome), and 99 adults ('Ospedale S. Maria degli Angeli', Pordenone) underwent a complete diagnostic allergy work-up, including a detailed assessment of the retrospective clinical history, skin prick testing (SPT, Stallergenes, Anthony, France), blood drawing for IgE determination (ESEP, Euroimmun, Luebeck, Germany) against a pre-defined panel of allergenic extracts and molecules[23] (Figure E1), and a prospective collection of clinical data via mobile phone application (AllergyMonitor, TPS) (Figure E2).

2.5 | Therapeutic decision making

During the second part of AIT-WS, doctors were asked to express their therapeutic decision concerning their respective 10 clinical index cases. Each participating doctor filled a questionnaire reporting their own decision on AIT prescription, on the basis of the primary data progressively added at each of the three steps of the @IT2020-CDSS.

2.6 | Feedback survey

Finally, the doctors filled a questionnaire on the relative impact and benefits of each diagnostic tool (clinical history, SWE, CRD, eDiary) and of the whole algorithm. Doctors expressed also their satisfaction level on the entire AIT-WS (tutorial, clinical cases and feedback survey) in terms of content and general organization (Figure E3).

2.7 | Statistics

Data were summarized as numbers (*n*) and frequencies (%) if they were categorical and as mean and standard deviation (SD) if quantitative. Percentages of correct hypothetical AIT prescription at each step and for each medical category were computed, taking as comparison reference, for each examined case, the most frequent AIT hypothetical prescription of allergen immunotherapy among allergy specialists at the final stage of CDSS (gold standard). Chi-squared test, when conditions were respected, or Fisher's exact test were used to evaluate the association of categorical data between AS and GP groups. McNemar's test was used to compare difference of frequency within each group. A p-value <.05 was considered statistically significant. Statistical analyses were performed with R Core Team (2014), version 3.2.3.

3 | RESULTS

3.1 | Study population

The study included 46 physicians attending the AIT-WS in Rome (n = 21; 11 AS and 10 GP) and Pordenone 25 (n = 25; 7 AS and 18 GP) (Table 1). All participants completed the full set of surveys and provided informed written consent. No relevant differences were detected for age, professional experience and other major characteristic among AS and among GP, respectively, between the two

clinical centres. Most of the AS (94%) and a minority of the GP (36%) were familiar with the concept of CRD; and similarly, 83% of the AS and 14% of the GP, had used CRD as a diagnostic tool in SAR. Furthermore, 12 of 18 (67%) AS and 15 of 28 (54%) GP had previous knowledge about electronic clinical diaries. However, only part of them have already used an eDiary in their own clinical practice: most of the physicians with previous experience being AS (44%, *n* = 8) and only a few GP (21%, *n* = 6). A minority of doctors declared previous knowledge of CDSS (AS 28%; GP 14%) but none indicated any experience in their use in the management of SAR patients (Table 1).

TABLE 1 Characteristics of the respondents

	Allergy specialists (*n* = 18)		General practitioners (*n* = 28)	
	n	%	*n*	%
Male	5	28	15	54
Age (year) (mean, SD)	47.4	9.3	51.9	7.4
Workplace				
Hospital	13	72	2	7
Private practice	5	28	20	71
Local health service	0	0	6	21
Specialty				
ENT	0	0	1	4
Internal medicine	1	6	0	0
Allergology	14	78	0	0
Immunology	8	44	0	0
Paediatrics	7	39	10	36
General medicine	0	0	18	64
Work experience (year) (mean ± SD)	15.4	8	22.5	8.6
2	1	6	0	0
3–5	1	6	2	7
6–10	3	17	2	7
≥11	13	72	24	86
Previous knowledge				
Component resolved diagnosis	17	94	10	36
Mobile Health technologies	12	67	15	54
Clinical decision support system	5	28	4	14
Previous experience				
Component resolved diagnosis	15	83	4	14
Mobile Health technologies	8	44	6	21
Clinical decision support system	0	0	0	0

Data are summarized as numbers (*n*) and frequencies (%) if they are categorical and as mean and SD if quantitative.

3.2 | Cases' presentation: clinically relevant pollen(s) and hypothetical AIT prescription

The pollen(s) considered clinically relevant at each step through the potential CDSS tools and those selected for AIT prescription (if any) by the clinicians (all coauthors of this paper) in Rome (ST, VV, IS) and Pordenone (DV, SP, PM) are shown in Table E2. In eight patients (two in Rome and six in Pordenone), only one pollen was considered clinically relevant after the three diagnostic steps and was, therefore, the one selected for AIT prescription (Table E2). In six patients, the algorithm led to identify two allergens, but the clinicians prescribed AIT towards only one of them in five of the six cases. In the case of no (*n* = 2) or ≥4 (*n* = 4) clinically relevant allergens, no AIT has been prescribed, with one exception (case 4, Rome) (Table E2).

3.3 | Trend and concordance between AS and GP in AIT prescription

For each step of the algorithm and each medical category (ie AS and GP), the hypothetical AIT prescription was compared per individual case to the most frequent AIT prescription decided by AS at the final step. This prescription has been chosen as the 'gold standard'. In both groups (AS and GP), the hypothetical prescription of AIT changed significantly through the three diagnostic steps proposed in our 'pyramid' model ($p < .01$) (Figure 2). Through this evolution, the AIT decisions harmonized within the AS groups and GP groups ($p < .01$) (Figure 2). In particular, taking into account the total amount of available choices (*n* = 110 and *n* = 70 for Rome and Pordenone, respectively), only 54% (Rome) and 59% (Pordenone) of AITs prescribed by AS at the first step of CDSS corresponded to the gold standard choice of AIT. These percentages increased to 66% (Rome) and 83% (Pordenone) in the second step, and furtherly to 86% (Rome) and 87% (Pordenone) in the third step. Similarly, the percentages of correct prescriptions of AIT by GP increased from 37% to 57% and 79% in the second and third steps in Rome and from 39% to 63% and 83% in Pordenone. Interestingly, the concordance of the GP's AIT prescription with the gold standard became step by step consistently closer to the one obtained by the AS until no statistically significant differences were observed anymore in AIT prescription between GP and AS after the last step of the diagnostic procedure (Figure E4).

3.4 | CRD and eDiary impact on AIT prescription by participating doctors

At *group* level, the frequency of AIT prescriptions increased from the first to the third diagnostic step. This general trend was observed among both, GP (Rome, 25%-->56-->63%; Pordenone, 29-->59-->72%) and AS (Rome, 49-->71-->65%; Pordenone, 53-->77-->87%) (Figure 3 and Table E3). At *individual* level, a declining trend in the frequency of AIT prescription was observed only in

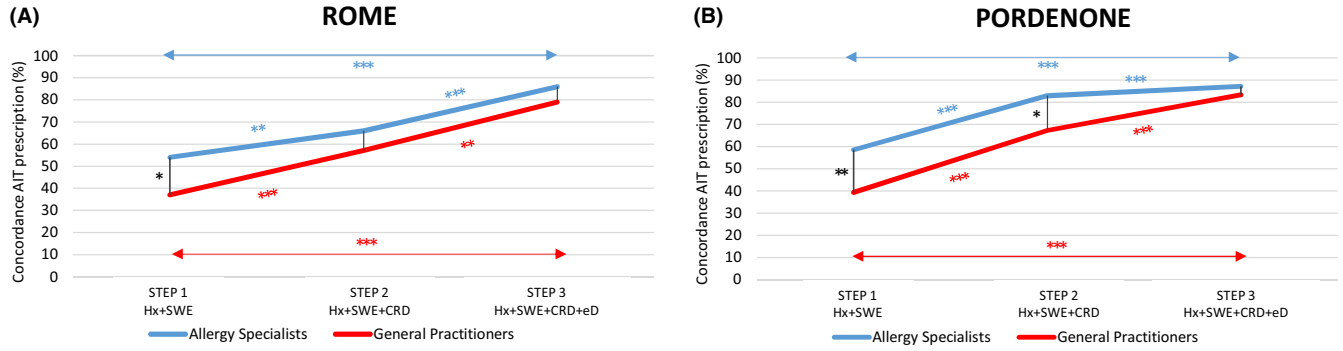

FIGURE 2 Concordance (%) of the 'hypothetical' prescription of allergen immunotherapy with the most prevalent final decision among allergy specialists for each medical category (allergy specialists and general practitioners) at each of the three diagnostic steps proposed in our 'pyramid' model in Rome (A) and Pordenone (B). CRD, component resolved diagnostics; eDiary, electronic clinical diary; Hx, clinical history; SWE, sensitization to whole extract. *$p < .05$, **$p < .01$, ***$p < .001$

2/10 cases in Rome (1 AS, 1 GP) and 2/10 cases in Pordenone (2 GP) (Table E3).

3.5 | Feedback survey on doctors' perception regarding diagnostic tools

Doctors filled a questionnaire on the impact of each diagnostic step in their own AIT-prescription (Table E4). Additionally, their opinion on the algorithm proposed for our innovative CDSS was assessed. All physicians considered the application of a CDSS useful and recognized its potential in improving the traditional diagnostic procedures (Figure 4). There was agreement also concerning the role of molecular diagnostics in improving the accuracy of AIT prescription (100%). The reliability of the retrospective assessment of clinical histories was considered as lacking (70–100%) and optimizable by an electronic clinical diary (82–100%). In addition, all respondents judged an eDiary as easier in compilation (patients) and interpretation (doctor) if compared to a traditional clinical diary on paper. Furthermore, the majority of doctors agreed on a potential role of an electronic diary in the diagnostics of other allergic diseases (eg asthma and food allergy). Participants were overall satisfied by the workshop (tutorial, clinical cases and feedback survey) in terms of content and general organization (Figure 4).

4 | DISCUSSION

In the AIT-WS involving 46 doctors dealing with patients seeking care for seasonal allergic rhinitis, we found that the measurement of serum specific IgE to the major allergenic molecules of pollen (CRD) and the use of an eDiary significantly improved the homogeneity of AIT prescription, not only among AS, but also among GP. In fact, when AS combined the 'traditional approach' (anamnesis and SWE) with these diagnostic tools (CRD and eDiary), they frequently modified and harmonized their AIT decision. The same trend was observed in the group of GP, who changed their clinical decision up to reproducing the standards of AS.

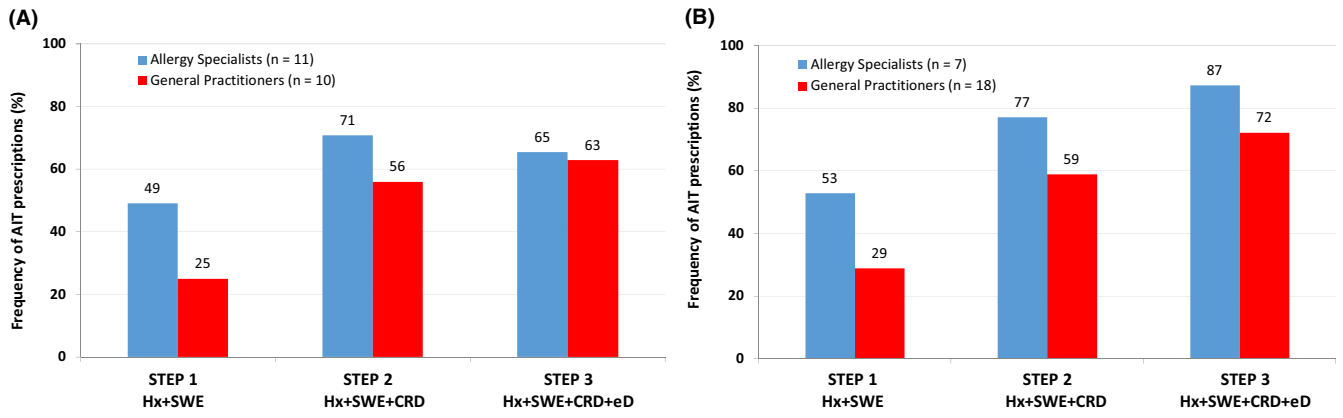

FIGURE 3 Frequency of hypothetical AIT prescriptions decided by allergists or general practitioners at each diagnostic step proposed in our 'pyramid' model in (A) Rome and (B) Pordenone study centres. CRD, component resolved diagnostics; eDiary, electronic clinical diary; Hx, clinical history; SWE, sensitization to whole extract. Percentages are calculated on total amount of 110 cases for allergy specialists and 100 cases for general practitioners in Rome (A) and 70 and 180 cases in Pordenone (B)

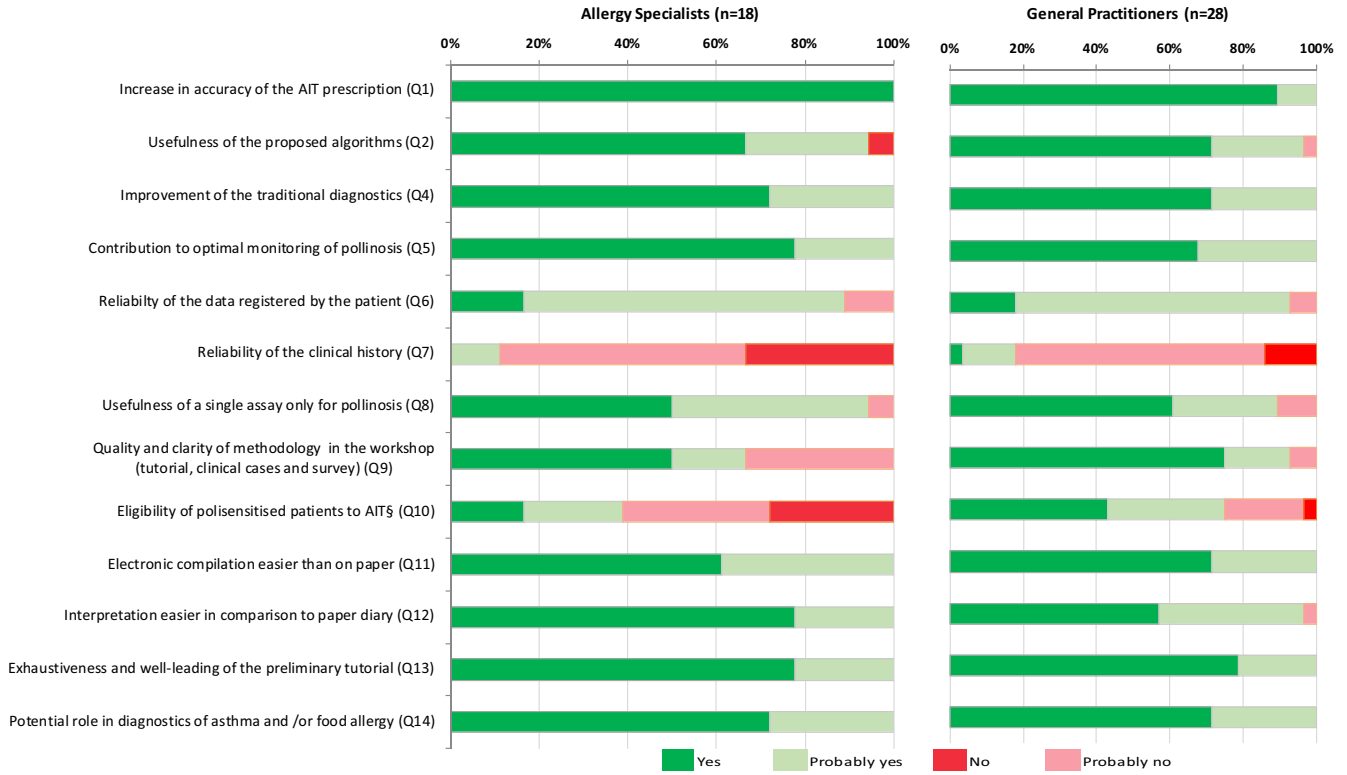

FIGURE 4 Answers to the 'feedback survey' among allergy specialists and general practitioners for each clinical centre in the context of the diagnostics of seasonal allergic rhinitis. §Sensitization to more than four aeroallergens. CDSS, clinical decision support system; CRD, component resolved diagnostics; eDiary, electronic clinical diary

We have previously reported[6] in another cohort of patients with SAR (n = 651), that the inclusion of CRD in the diagnostic algorithm led to a change in AIT prescription for 44% of the patients. This was explained by the presence of highly cross-reactive molecules from unrelated allergenic sources (eg profilins, polcalcins and LTPs), which contributed to a confounding SPT-reactivity to extracts. Once this interference is ruled out by CRD, the clinical decision making is simplified, especially for patients with various sensitization to whole extracts. Hence, it should be tested in the future the hypothesis that CRD may even substitute SWE and not only integrate it. Still, the clinical significance of individual sensitization profiles remains to be proven before prescribing the correct treatment. In order to overcome the inaccuracy of a retrospective symptom monitoring, the present study successfully assessed the use of digital symptom and medication prospective recording. The access to this real-time clinical information increased the diagnostic precision of the GP and AS significantly.

In general, it is estimated that only a restricted minority (2–6%) of eligible patients currently receives AIT.[24] One reason for this condition may be the fact that most patients with seasonal allergic rhinoconjunctivitis are polysensitized.[25] The choice of the correct allergen for immunotherapy appears then often difficult, which may be the cause for clinicians to refrain from this therapeutic option. Yet, the differentiation between a false polysensitization in mono-allergic patients and a real polysensitization in poly-allergic subjects is fundamental, as an AIT prescription for the former is clearly recommended.[2] We found that also allergy specialists were more inclined to prescribe AIT when CRD and eDiary information were added to clinical history and SPT data. Therefore, more patients could benefit of AIT, which is currently the only disease-modifying treatment for SAR.

Our study may have several implications for the clinical practice. Even though CRD and the use of prospective digital symptom and medication diary have been available for more than one decade, guidelines for AIT have not yet adopted these diagnostic approaches. Our findings suggest that a more precise description of the patient's sensitization profile before an AIT prescription should be taken into account. There is a need of controlled studies comparing the efficacy of AIT in patients in whom the therapeutic decision was based on SWE results vs SWE and CRD vs SWE, CRD and eDiary. It should be stressed that a more precise, prospective observation of patient´s symptoms with eDiary implies postponing a decision on AIT for many months to allow symptom recording during the following pollen season. Cost-benefit studies should also evaluate whether the immediate additional costs, implied by molecular analysis, are justified in the long-term period. Further, it is important to underline that the aim of CDSS should never be to replace a healthcare professional, but to enhance clinical routine by facilitating basic decisions and proper patient allocation at a primary care level.

We have to acknowledge some limitations of our study. First, the number of index cases used in the study is low and may be not representative of the whole patient population in Rome and Pordenone.

Second, our conclusions apply to settings with high pollen exposure for prolonged seasonal periods, such as those of Mediterranean countries. Therefore, the study should be repeated in other geographic areas on larger scale. Third, the forms filled by doctors were anonymous, so no sub-group analyses could be performed.

In conclusion, our findings suggest that in countries with high and prolonged exposure to various allergenic pollen sources, a clinical decision support system including CRD and eDiary can significantly improve the diagnostic accuracy and standardization in the clinical routine and increase the precision of AIT prescriptions. Moreover, the use of a CDSS can reinforce the crucial link between GP and AS in the treatment of the patients with SAR, facilitating a proper referral to allergy specialists. This conclusion might be useful to update national and international guidelines on the prescription of AIT in SAR. The hypothesis, that the precise identification of the proper allergen for AIT also improves its clinical efficacy, as well as cost-effectiveness, deserves to be tested.

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CONFLICTS OF INTEREST

Dr. Matricardi reports grants and personal fees from Euroimmun AG, during the conduct of the study; grants and personal fees from Thermo Fisher Scientific, personal fees from Hycor Biomedical Inc, outside the submitted work. Salvatore Tripodi is cofounder of TPS Production. All other Authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

PMM and SA conceived the study. SA designed the manuscript. AT, MAB and PLV performed and supervised the collection of aerobiological data in the study. SP and ST provided the technical infrastructure for symptom monitoring. SA performed the data management. SA and SP performed statistical analyses. SA, SC, MDF, DV, ST, MC, PM, IS, VV and PMM participated in the clinical coordination, patients' recruitment/monitoring and doctors' recruitment. SA wrote the first draft of the paper. PMM, SD and SP reviewed and provided feedback. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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