



Patient-centered digital biomarkers for allergic respiratory diseases and asthma: The ARIA-EAACI approach – ARIA-EAACI Task Force Report

Jean Bousquet^{1,2,3}  | Mohamed H. Shamji^{4,5}  | Josep M. Anto^{6,7,8} |
 Holger J. Schünemann⁹ | G. Walter Canonica^{10,11} | Marek Jutel^{12,13} |
 Stefano Del Giacco¹⁴  | Torsten Zuberbier^{1,3}  | Oliver Pfaar¹⁵  | Joao A. Fonseca^{16,17} |
 Bernardo Sousa-Pinto^{16,17} | Ludger Klimek^{18,19}  | Wiencyslawa Czarlewski^{20,21} |
 Anna Bedbrook^{21,22} | Rita Amaral^{16,17}  | Ignacio J. Ansotegui²³ |
 Sinthia Bosnic-Anticevich^{24,25,26} | Fulvio Braido^{27,28} | Claudia Chaves Loureiro²⁹  |
 Bilun Gemicioglu³⁰ | Tari Haahtela³¹  | Marek Kulus³² | Piotr Kuna³³ |
 Maciej Kupczyk³³ | Paolo M. Matricardi³⁴  | Frederico S. Regateiro^{35,36,37} |
 Boleslaw Samolinski³⁸ | Mikhail Sofiev³⁹ | Sanna Toppila-Salmi³¹  | Arunas Valiulis⁴⁰ |
 Maria Teresa Ventura^{41,42} | Cristina Barbara⁴³ | Karl C. Bergmann^{1,3} | Michael Bewick⁴⁴ |
 Hubert Blain⁴⁵ | Matteo Bonini^{4,46,47}  | Louis-Philippe Boulet⁴⁸  | Rodolphe Bourret⁴⁹ |
 Guy Brusselle⁵⁰ | Luisa Brussino^{51,52} | Roland Buhl⁵³ | Victoria Cardona^{54,55} |
 Thomas Casale⁵⁶ | Lorenzo Cecchi⁵⁷  | Denis Charpin⁵⁸ | Ivan Cherrez-Ojeda^{59,60}  |
 Derek K. Chu⁹ | Cemal Cingi⁶¹  | Elisio M. Costa⁶² | Alvaro A. Cruz⁶³  |
 Philippe Devillier⁶⁴ | Stephanie Dramburg⁶⁵ | Wytske J. Fokkens⁶⁶  | Maia Gotua⁶⁷ |
 Enrico Heffler^{10,11}  | Zhanat Ispayeva⁶⁸ | Juan Carlos Ivancevich⁶⁹ | Guy Joos⁵⁰ |
 Igor Kaidashev⁷⁰ | Helga Kraxner⁷¹ | Violeta Kvedariene^{72,73} |
 Désirée E. Larenas-Linnemann⁷⁴  | Daniel Laune⁷⁵ | Olga Lourenço⁷⁶  |
 Renaud Louis^{77,78} | Mika Makela³¹ | Michael Makris⁷⁹ | Marcus Maurer^{1,3}  |
 Erik Melén^{80,81} | Yann Micheli⁷⁵ | Mario Morais-Almeida⁸²  | Joaquim Mullet^{83,84} |
 Marek Niedozytko⁸⁵  | Robyn O'Hehir⁸⁶  | Yoshitaka Okamoto^{87,88} | Heidi Olze^{89,90} |
 Nikolaos G. Papadopoulos⁹¹  | Alberto Papi⁹²  | Vincenzo Patella^{93,94,95}  |
 Benoit Pétré⁹⁶ | Nhat Pham-Thi^{97,98,99} | Francesca Puggioni¹⁰⁰ | Santiago Quirce¹⁰¹ |

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AIT, Allergen immunotherapy; ARIA, Allergic Rhinitis and its Impact on Asthma; BEST, Biomarkers, Endpoints and other Tools; CARAT, Control of Allergic Rhinitis and Asthma Test; CDSS, Clinical Decision Support System; COSMIN, COnsensus-based Standards for the selection of health status Measurement INstruments; CSMS, ARIA-EAACI allergy Combined Symptom-Medication Score; EAACI, European Academy of Allergy and Clinical Immunology; e-DASTHMA, Electronic daily asthma control score; EQ-5D, European Quality of Life Five Dimension; FDA, Food and Drug Administration; Hb1ac, Glycated haemoglobin; MASK-air®, Mobile Airways Sentinel Network for airway diseases; PRO, Patient-reported outcome; PROM, Patient-reported outcome measure; RAPP, RhinAsthma Patient Perspective; SMS, Symptom-medication score; TF, Task Force; VAS, Visual analogue scale; WHO, World Health Organization; WPAI: AS, Work Productivity and Activity Impairment: Allergy Specific.

Jean Bousquet and Mohamed H Shamji participated equally in the Task Force.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

Nicolas Roche¹⁰² | Philip W. Rouadi^{103,104}  | Ana Sá-Sousa^{16,17} | Hironori Sagara¹⁰⁵ |
 Joaquin Sastre¹⁰⁶ | Nicola Scichilone¹⁰⁷ | Aziz Sheikh¹⁰⁸ | Milan Sova¹⁰⁹ |
 Charlotte Suppli Ulrik^{110,111} | Luis Taborda-Barata^{112,113} | Ana Todo-Bom¹¹⁴ |
 Maria J. Torres¹¹⁵  | Ioanna Tsiligianni^{116,117} | Omar S. Usmani^{4,118} | Erkka Valovirta¹¹⁹ |
 Tuula Vasankari^{120,121} | Rafael José Vieira^{16,17}  | Dana Wallace¹²² | Susan Wasserman¹²³ |
 Mihaela Zidarn^{124,125} | Arzu Yorgancioglu¹²⁶  | Luo Zhang¹²⁷  | Tomas Chivato¹²⁸ |
 Markus Ollert^{129,130} 

Correspondence

Jean Bousquet, Institute of Allergology, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. Email: jean.bousquet@orange.fr

Abstract

Biomarkers for the diagnosis, treatment and follow-up of patients with rhinitis and/or asthma are urgently needed. Although some biologic biomarkers exist in specialist care for asthma, they cannot be largely used in primary care. There are no validated biomarkers in rhinitis or allergen immunotherapy (AIT) that can be used in clinical practice. The digital transformation of health and health care (including mHealth) places the patient at the center of the health system and is likely to optimize the practice of allergy. Allergic Rhinitis and its Impact on Asthma (ARIA) and EAACI (European Academy of Allergy and Clinical Immunology) developed a Task Force aimed at proposing patient-reported outcome measures (PROMs) as digital biomarkers that can be easily used for different purposes in rhinitis and asthma. It first defined control digital biomarkers that should make a bridge between clinical practice, randomized controlled trials, observational real-life studies and allergen challenges. Using the MASK-air app as a model, a daily electronic combined symptom-medication score for allergic diseases (CSMS) or for asthma (e-DASTHMA), combined with a monthly control questionnaire, was embedded in a strategy similar to the diabetes approach for disease control. To mimic real-life, it secondly proposed quality-of-life digital biomarkers including daily EQ-5D visual analogue scales and the bi-weekly RhinAsthma Patient Perspective (RAAP). The potential implications for the management of allergic respiratory diseases were proposed.

KEYWORDS

apps, ARIA, digital health, EAACI, rhinitis

1 | INTRODUCTION

Asthma and allergy phenotyping and endotyping are constantly evolving.¹ The introduction of biologicals increases the need for biomarkers in patient selection, prediction of outcomes and monitoring. An adequate cost-effective choice of these costly and long-lasting therapies is thus available.^{2,3} Biomarkers for patients with asthma are urgently needed.^{4,5} Some exist in specialist care (e.g., FeNO⁶ or sputum eosinophils⁷), but, to date, there are no biologic or omics biomarkers that can be largely used in primary care.^{8,9} Blood eosinophils and serum total IgE are related to the treatment with anti-IL-5 or anti-IgE biologics. There are no validated biomarkers in rhinitis¹⁰ or allergen immunotherapy (AIT).¹¹

Digital health is an umbrella term which encompasses eHealth and benefits from areas such as advanced computer sciences (e.g., “big data” and artificial intelligence). eHealth, as defined by the World Health Organization (WHO),¹² comprises several components including electronic health records, telehealth and mobile health (mHealth). The latter has been defined as a “medical and public health practice supported by mobile devices, such as mobile phones.”¹³ It includes (i) equipment/connected medical devices, (ii) mHealth services, and (iii) mHealth apps.¹⁴

The digital transformation of health and health care (including mHealth) places the patient at the center of the health system and is likely to optimize the practice of medicine.^{15,16} Biomarkers associated with mHealth and clinical decision support systems (CDSSs)

BOX 1 Aims of the Task Force.

Since biologic or genetic biomarkers are not readily available for rhinitis and asthma, the TF aimed at proposing digital biomarkers that can be easily used for different purposes in rhinitis and asthma.

The first step was to define mHealth biomarkers that should make a bridge between:

- Clinical practice
- Randomized controlled trials
- Observational real-life studies
- Epidemiologic studies
- Challenges. More specifically, two sets of digital biomarkers have been proposed to mimic the diabetes approach^{33,106}
- Equivalent to glycemia: daily electronic combined symptom-medication score for rhinitis (combined symptom-medication score, ARIA-EAACI 2021 TF: Combined symptom-medication scores (CSMSs)^{42,107}) and asthma (Electronic daily asthma control score: e-DASTHMA)
- Equivalent to Hb1ac: monthly evaluation of rhinitis and asthma control (CARAT)¹⁰⁸
- Quality-of-life biomarkers include daily EQ-5D visual analogue scale (VAS) and bi-weekly RAPP

CARAT, Control of asthma and rhinitis test; CSMS, Combined symptom medication score; EAACI, European Academy of Allergy and Clinical Immunology; e-DASTHMA, Electronic daily symptom medication score in asthma; Hb1ac, glycated hemoglobin; RAPP, RhinAsthma Patient Perspective; TF, Task Force; VAS, visual analogue scale.

may change the scope of the practice of asthma and allergic diseases. They help to monitor disease control¹⁶ and enable: (i) shared decision-making, (ii) patient stratification, (iii) clinical trials and real-world evidence, (iv) monitoring of the efficacy and safety of targeted therapies (a critical process for identifying appropriate reimbursement), (v) implementation of stopping rules, and (vi) exchange of information between physicians and healthcare professionals.¹⁷

An ARIA-EAACI Task Force (TF) was set up to provide a state-of-the-art review to find out the applicability of mHealth biomarkers in allergic diseases and asthma (Box 1).

2 | BACKGROUND**2.1 | Digital biomarkers**

As defined in the Biomarkers, EndpointS and other Tools (BEST) glossary, developed by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health Biomarker Working

Group, a biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions"¹⁸ (e.g., blood pressure). Biomarkers include clinical signs identified by physical examination, biological assays, digital outcomes, genomic indices, and others that can be objectively measured and used as indicators of pathophysiological processes.¹⁹ Biomarkers can be used individually or in combination. However, to be used in clinical practice, biomarkers need to be validated.²⁰ Biomarker measurements have become an essential component in some fields of medicine such as oncology, particularly in this era of targeted therapies and precision medicine.²¹

"In line with the BEST definition and in a guidance document,²² the FDA defines a digital biomarker as a characteristic or set of characteristics, collected from digital health technologies, that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions." «Monitoring biomarker: A biomarker measured repeatedly for assessing the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent».²² The use of "characteristic or set of characteristics" in the definition of digital biomarkers stems from the ability to derive one or more biomarkers from one or more digital health technologies simultaneously.²³ With advancements in digitalization across health care, the ability to detect non-biological external factors (e.g., environmental features like pollen count or pollution) enables the identification of predictors and influences on health.²³

Digital biomarkers have the potential to improve diagnosis and to continually monitor patient health, accurately predict outcomes and rapidly assess exacerbations.²⁴ These huge technical advances have evolved regarding evidence, analysis and sharing data to optimally respond to patients' requirements as well as to physicians (shared decision-making), regulators and payers.²⁵ Moreover, physiological data may now be collected via portable, wearable, and implantable digital devices. However, there are limitations and risks with these advances that require the development of a structured and validated approach (Figure 1).²⁶

2.2 | Biomarkers in precision medicine of allergic diseases

Precision medicine aims to customize health care with medical decisions, practices and/or products tailored to the individual patient. While frequently associated with genomics, precision medicine goes well beyond that field, also referring to the tailoring of medical treatment to the clinical and social characteristics of each patient.²⁷ The stratification of patients into subpopulations is the basis of clinical decision-making for increased diagnostic and treatment efficacy in all disease areas including allergic diseases. It should optimally be patient centered.

In allergic diseases, the role of precision medicine in selecting an AIT regimen was proposed by an expert meeting²⁸ and expanded

FIGURE 1 Benefits, limitations, and risks of digital biomarkers (from²⁶).

Strengths

- Patient empowerment
- Automation of data
- Standardised data collection
- Close monitoring
- Validation of tools
- Culturally acceptable
- Low cost
- Can be used globally

Weaknesses

- No long-term data
- Attrition
- Potential measurement bias
- Selection of patients prone to using mHealth
- Precise patient characterisation
- Information bias
- Unsupervised input of data

Threats

- Negative impact on the patient psychology
- Overinterpretation of the role of the patient
- Possible use of non-validated mHealth tools

Opportunities

- Reduction of work load
- Early detection of exacerbations
- Prevention of complications
- Optimal shared decision making
- mHealth tools for clinical trials and drug development

in the ARIA care pathways for AIT.^{11,29} Biologic biomarkers do not yet exist in routine clinical practice, and digital/mHealth biomarkers may be of great value, given the large volumes of data available from mobile app users in different countries.

In severe asthma, precision medicine is also of great importance since there are different biologics that are available and have different properties.^{30–32} Genetic or biologic biomarkers are not yet able to be used in routine clinical practice globally. Digital biomarkers may therefore be of interest for optimal shared decision-making in the stratification and follow-up of patients.

In diabetes, two types of biomarkers are defined to monitor the control of the disease.^{33,34}

- Daily control monitoring is assessed using glycemia measurement, and longer-term monitoring using glycosylated haemoglobin (Hb1ac) measurement. It is recommended that both tests are required to optimize diabetes treatment. By analogy with the diabetes approach, two types of patient-centered digital biomarkers can be defined in rhinitis or asthma
- Long-term monitoring using control scores (analogous to Hb1AC measurement): CARAT (Control of Allergic Rhinitis and Asthma Test)^{35–37} is proposed as it combines rhinitis and asthma control and there is a recall period of 4 weeks, whereas many other rhinitis (e.g., Allergic Rhinitis Control Test³⁸ and Rhinitis Control Assessment Test³⁹) or asthma (e.g., Asthma Control Questionnaire—ACQ⁴⁰) control questionnaires are based on a one-week recall period. The Asthma Control Test (ACT) was based on a 4-week recall.⁴¹

Validated questionnaires assess asthma or rhinitis control over the previous 1–4 weeks, but do not fully capture the control in patients with fluctuating symptoms, in particular those with severe asthma. Daily monitoring of the control (analogous to glycemia measurement) can be measured using the ARIA-EAACI allergy Combined

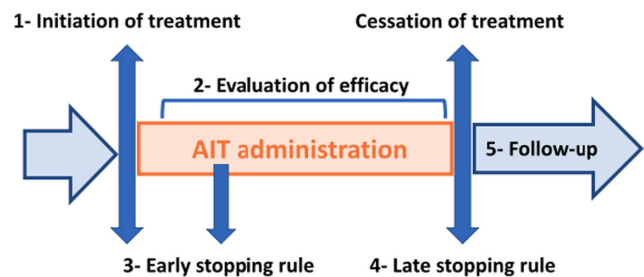


FIGURE 2 Care pathway for allergen immunotherapy (AIT) (from²⁹).

Symptom-Medication Score (CSMS)⁴² or the electronic daily asthma control score (e-DASTHMA, submitted).

3 | METHODS USED TO DEVELOP THE TASK FORCE

3.1 | Steps for the development of the Task Force

The TF was initiated following the concept proposed in ARIA care pathways on AIT (Figure 2).²⁹ It was then developed, revised, and submitted to the ARIA TF (Online supplement).

3.2 | Selection of the app

In rhinitis, an automatic market research was carried out.⁴³ Among the apps available on iOS and Android (>2000), less than 20 include clinical data. The only fully validated app is MASK-air.® However, in English and multi-languages, the Pollen Austria app^{44,45} (mainly focusing on pollen and unable to develop a CSMS) and AllergyMonitor®^{46,47} have features that can be used.

AllergyMonitor® studies are mainly carried out on children but a CSMS can be proposed in adults if the amount of data is sufficient.⁴⁸

In asthma, there are less than 10 apps (English and multi-languages) that include symptoms and also have over 10,000 users (in preparation). The Propeller Health app is the largest one studied and includes a monthly ACT as well as a connected inhaler system (cost around 80\$). However, it does not include daily symptoms.^{49–51} The other apps do not appear to be sufficiently validated, and/or data have not been published in peer-reviewed journals.⁴⁸

Thus, there is no broad spectrum of apps, and MASK-air appears to be the only current one to have been tested for CSMS, e-DASTHMA, and CARAT.⁵² The results of this TF can, however, be used by other apps to develop the ARIA-EAACI approach.

4 | THE ARIA-EAACI APPROACH USING THE MASK-AIR® APP IN ALLERGIC RHINITIS

4.1 | Limitations and strengths of MASK-air® (online ANNEX 1)

4.1.1 | Limitations

The limitations of MASK-air® studies are those of mobile technology real-world studies. They include potential measurement biases, selected users, lack of precise characterization of patients, unconfirmed diagnosis of rhinitis or asthma, and unsupervised input of data. Moreover, real-world studies can only be hypothesis-generating and findings should be confirmed by using appropriate study designs.

In MASK-air, we often use a cross-sectional approach, taking days as the unit of analysis instead of patients (although patients were used to cluster reporting days). This approach has been applied in many studies^{53–57} and has provided novel information. Cross-sectional studies cannot provide definite information about temporal relationships, let alone cause-and-effect relationships (causal inference). By contrast, longitudinal studies can establish sequences of events and allow the establishment of links or associations between variables. Longitudinal studies with MASK-air data have shown that results are consistent with previous cross-sectional data.⁵⁸

Although carried out in over 25,000 users in 29 countries, replication studies are not available.

4.1.2 | Strengths

Overall, MASK-air® has several strengths: (i) low cost, (ii) quickly available data, (iii) 50,000 users from 29 countries (20 languages) and (iv) inter-operable with a web-based physician's questionnaire⁵⁹ and an e-CDSS for AR.⁶⁰ (Figure 3).

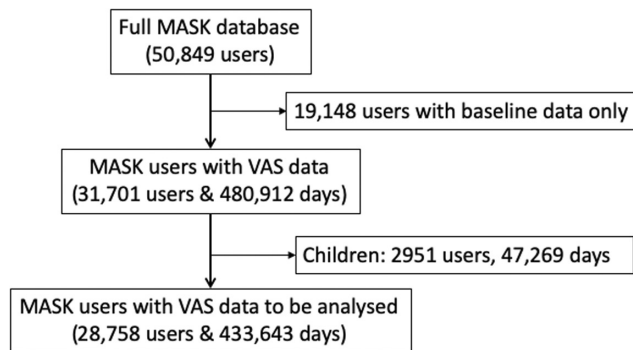


FIGURE 3 Repartition of MASK-air® users (December 2021).

The app is an MDR Class IIa. It is fully validated and includes pollen data and pollution (daily and predictive) based on the patients' geolocation.^{57,61} The database does not have any missing values due to the structure of the app.

It is a Best Practice of DG Santé for digitally-enabled, patient-centered care and a candidate Good Practice of OECD (Organization for Economic Co-operation and Development).

The rhinitis assessment is nearing completion in over 20,000 users (current paper), and the asthma assessment has been initiated in over 8000. In asthma, all categories of patients are included, and the database can be used to compare asthmatics of different severity grade.

4.1.3 | Economic evaluation

The economic evaluation is currently being assessed and several MASK-air® tools can be compared. These tools include cost of medications effectively used, cost of absenteeism and presenteeism (VAS Work, WPAI:AS), cost of health resource utilization (EQ-5D dimensions), and potential benefits of expensive treatments such as AIT and biologics. Combining the results of these tools, a monetary value will be ascribed to the allergy-CSMS and to e-DASTHMA.

4.2 | Development of patient-reported outcome measures (PROMs)

4.2.1 | Definitions of PROMs

There is an increased focus on placing patients at the center of health care and research to improve their experience and to ensure that research is robust and of maximum value for treatment or health services. A patient-reported outcome (PRO) is directly reported by the patient without interpretation of the patient's response by a clinician or anyone else. It pertains to the patient's health, quality of life, or functional status.⁶² Patient-reported outcome measures (PROMs) are tools and/or instruments used to report PROs. They may measure functional status, health-related quality of life, symptom and symptom burden, personal experience of care as well as

health-related behaviors such as anxiety and depression.⁶² PROMs provide important indicators of treatment efficacy not captured by objective markers or clinical assessments.⁶³ They may be used as indicators of acute symptoms and help to monitor response to treatment, especially if collected in real time. However, there are limitations of using PROMs in open trials.⁶³

4.2.2 | e-PROMs in MASK-air

A series of validated e-PROMs are available in MASK-air for rhinitis, global respiratory allergic diseases, and asthma (Table 1).

TABLE 1 e-PROMs in MASK-air.

1- Control digital biomarkers	
• Daily: validated CSMS (Allergy), e-DASTHMA, VAS nose, eye, asthma	
• Monthly: CARAT (A + R), ACT (A)	
2- QoL digital biomarkers	
• Daily: EQ-5D VAS	
• Bi-weekly: Rhinasthma (A + R)	
3- Impact digital biomarkers	
• VAS work	
• VAS school	
• VAS sleep	

Abbreviations: ACT, Asthma Control Test; CARAT, Control of Allergic Rhinitis and Asthma Test; CSMS, ARIA-EAACI allergy Combined Symptom-Medication Score; e-DASTHMA, Electronic daily asthma control score; EQ-5D, European Quality of Life Five Dimension; VAS, Visual analogue scale.

4.2.3 | Visual analogue scale for global allergy symptoms, nose, eye, and asthma

PROMs in MASK-air® include visual analogue scales (VASs) assessing daily global allergy symptoms, nose, eye or⁶⁴ asthma symptoms,⁶⁵ dyspnea as well as impact of allergy on work^{55,66} and sleep.

All PROMs are highly correlated (Figure 4),^{54,56,66-69} and these correlations are unlikely to be explained by a low quality of data arising from repeated VAS measures.⁵⁵ PROMs can be used in different aspects of allergic diseases including clinical trials, observational studies, and clinical practice.

In three different studies, VAS global, nose, eye, and asthma were correlated (Spearman rank test) with VAS work.

4.2.4 | Validation of the VAS scales

The methodologic validation of PROMs in MASK-air® has been achieved (Table 2).

4.2.5 | PROM cutoff values (online ANNEX 2)

In clinical and epidemiological studies, PROM cutoffs can be used to classify patients into groups of statistical and clinical relevance. The MASK-air® cutoffs for the different VASs have been arbitrarily defined according to the International Classification of Functioning, Disability and Health ICF grading.⁷⁰ Four cutoffs have been defined for all five VASs: 0/100 (full control), 1-19/100 (good control), 20-49/100 (partial control), and ≥50/100 (poor control).

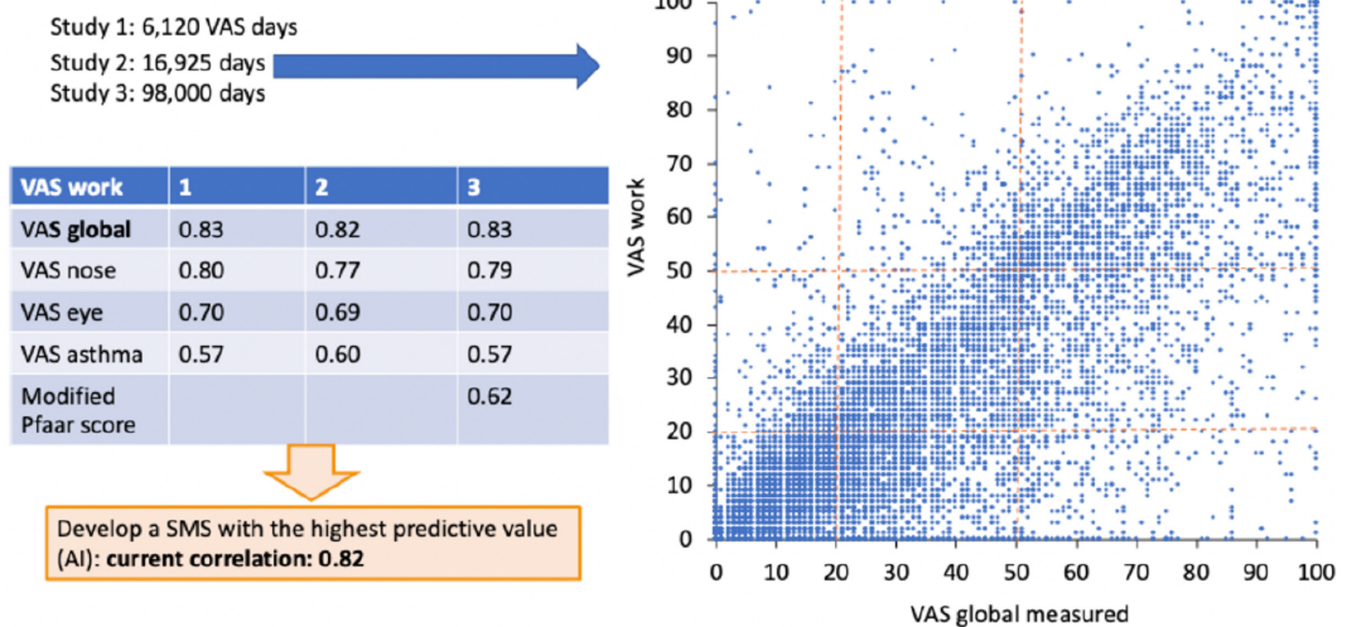


FIGURE 4 Correlation using the Spearman rank test between some of the MASK-air PROMs (from^{42,55,66,82}).

Study name	Ref.	Type of study	N users	N days	N countries
COSMIN guidelines	[101]	Obs, CS-L	2497	14,612	15
Test-retest, intra-class coefficient	[102]	Obs, CS-L	17,780	317,176	25
Quality of data (intra-individual response variability)	[103]	Obs, CS	14,189	205,904	23
Independence of data	[102]	Obs, CS	1136	5889	18
EQ-5D	[82,104]	Obs, CS	1288	NA	18
WPAI:AS	[82,104]	Obs, CS	1288	NA	18
CARAT	[52]	Obs, CS	1086	2042	22

Abbreviations: CARAT, Control of Allergic Rhinitis and Asthma Test; COSMIN, COnsensus-based Standards for the selection of health status Measurement Instruments guidelines; CS, cross sectional; EQ-5D, European Quality of Life Five Dimension; L, longitudinal; NA, not applicable; Obs, observational; WPAI:AS, Work Productivity and Activity Impairment:Allergy Specific.

TABLE 3 Allergy-CSMS tested in the study.⁴²

- 1- A hypothesis-driven score (m-CSMS), built without knowing real-life data, moderately correlated with the 4 outcomes (Spearman rank correlation with VAS work: $Rho=0.61$, $N=120,959$)
- 2- A mixed data- and hypothesis-driven score (MIXED score), built based on real-life data obtained in MASK, highly correlated with the 4 outcomes (Spearman rank correlation with VAS work: $Rho=0.81$, $N=118,275$)
- 3- Six data-driven cluster-based CSMSs, built from clusters based on VAS work and EQ-5D (3 CSMS) and CARAT and WPAI:AS (3 CSMS), highly correlated with the 4 outcomes (Spearman rank correlation with VAS work: $Rho=0.73-0.83$, $N=57,527-123,123$)
- 4- One regression-based MIXED-CSMS, built from MASK-air data, correlated with the 4 outcomes (Spearman rank correlation with VAS work: $Rho=0.81$, $N=94,399-128,123$)
- 5- A factorial analysis method (1 score) had a poor correlation with the 4 outcomes (Spearman rank correlation with VAS work: $Rho=0.42$, $N=59,378$)

Abbreviations: CARAT, Control of asthma and rhinitis test; CSMS, ARIA-EAACI allergy Combined Symptom-Medication Score; EQ-5D, European Quality of Life Five Dimension; VAS, visual analogue scale; WPAI:AS, Work Productivity and Activity Impairment:Allergy Specific.

There are two statistical approaches for determining a cutoff value: percentile-oriented (i.e., "PROM distribution-oriented") and outcome-oriented.⁷¹ In a cross-sectional study design of 395,223 days from 23,201 MASK-air® participants, cutoffs for VAS global, nasal, ocular, and asthma symptoms were assessed using outcome-oriented approaches. The proposed cutoff differentiating "controlled" and "partly-controlled" patients was similar to the arbitrary cutoff value (20/100).⁶⁴ However, a lower cutoff was obtained to differentiate between "partly-controlled" and "uncontrolled" patients (35/100 versus the arbitrarily value of 50/100) for VAS global, nose, eye, and asthma.

4.2.6 | Quality-of-life biomarkers

In MASK-air, the EQ-5D VAS is answered daily. The EQ-5D full questionnaire is optional.

TABLE 2 Methodologic validation of PROMs.

RhinAsthma Patient Perspective (RAPP) is a simple eight-question questionnaire with good measurement properties and sensitivity to health changes. It provides a valid, reliable, and standardized HRQoL measurement in patients with asthma and comorbid allergic rhinitis in the clinical practice.⁷²⁻⁸⁰ RAPP discriminates between patients with different disease severity levels. It is also sensitive to individual changes and reliable in stable patients. Moreover, it is simple to complete and to score, and its interpretation is immediate, both for the physician and for the patient. A validated adult version of RAPP is available in Italian, Spanish, Portuguese, English (Philippines), and Polish. A validated children's version of RAPP is available in Italian.

4.3 | ARIA-EAACI-allergy-CSMS (Combined Symptom-Medication Score) (Online ANNEX 3)

Validated combined symptom-medication scores (CSMSs) are needed to investigate the effects of allergic rhinitis treatments.^{42,81}

MASK-air® data assessed the concurrent validity, test-retest reliability, and responsiveness of several hypotheses and/or data-driven CSMSs. These allergy-CSMSs were compared with scales measuring (i) the impact of rhinitis on work productivity (VAS work of MASK-air®,^{55,66} Work Productivity and Activity Impairment: Allergy Specific [WPAI:AS]),⁸² (ii) quality-of-life (EQ-5D VAS),^{83,84} and (iii) control of allergic diseases (CARAT).⁴²

317,176 days of MASK-air® use were assessed from 17,780 users in 25 countries.⁴² (Table 3 and Figure 5). Among data-driven CSMSs, a better performance was observed for cluster analyses-based CSMSs.

There was a consistent pattern of allergy-CSMS in different countries, indicating that this biomarker can be used globally in different languages and cultures (Figure 6).

Three observational cross-sectional studies have assessed the allergy-CSMS and confirmed that this tool can be used in allergy and AIT.^{85,86} The allergy-CSMS provided a better discrimination between treatments than VAS global or VAS nose.

FIGURE 5 Allergy-CSMS.

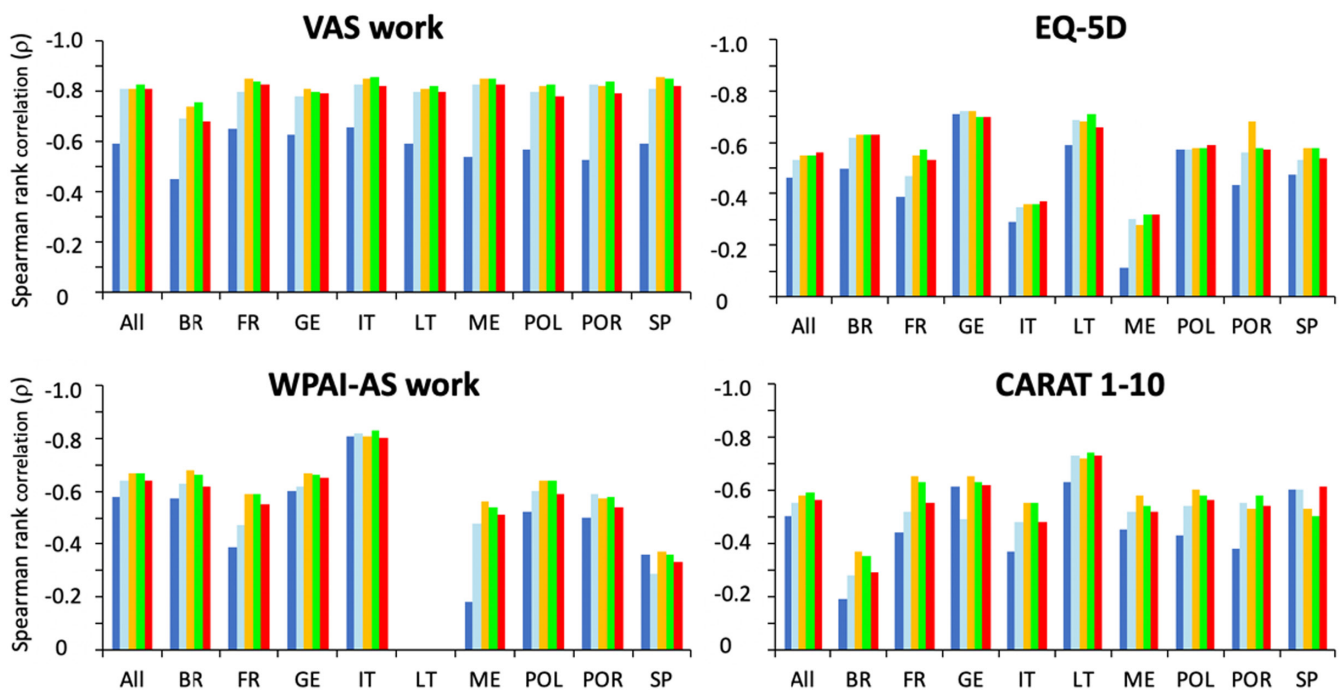
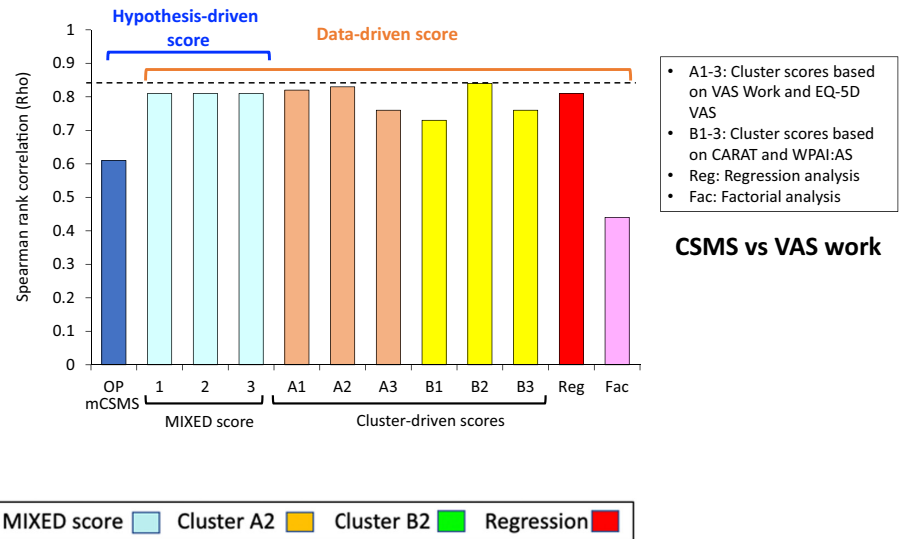


FIGURE 6 Allergy-CSMS validation in different countries.

4.4 | Potential impact of the ARIA-EAACI allergy-CSMS in allergic diseases

4.4.1 | Overall impact

The allergy-CSMS is a **daily, validated, real-life, digitally-enabled, patient-centered biomarker for any allergic treatment including AIT**. The allergy-CSMS bridges clinical practice, randomized controlled trials (RCTs), observational studies, chamber studies, and real-world data (RWD) (Table 4):

Importantly, the allergy-CSMS is centered around the patient (with its inputs including VAS on respiratory allergic symptoms). It includes quality-of-life measures (VAS EQ-5D, now included daily in

MASK-air®) and the assessment of the impact of work (VAS work was found to be a reliable end point^{55,66,82}).

4.4.2 | Implication in allergen immunotherapy (AIT)

In AIT, the allergy-CSMS can be used to (i) stratify patients (uncontrolled days during the allergen exposure, for example, pollen season, despite guideline-based treatment in patients adherent to treatment), (ii) propose an early stopping rule, (iii) follow the patient during the treatment, and (iv) follow the patient during the after-cessation follow-up (Figure 7). However, a dual approach can be proposed combining the daily allergy-CSMS with

a control test for allergic diseases assessing at least 1 month of survey.

5 | THE ARIA-EAACI APPROACH USING THE MASK-AIR® APP IN ASTHMA

5.1 | PROMs

5.1.1 | Visual analogue scales for asthma

PROMs for asthma have also been evaluated.^{52,65} Correlations between VAS asthma and other MASK-air® daily reported PROMs were studied in severe asthmatic patients (reporting long-acting muscarinic agonists and/or omalizumab) with nasal symptoms. Strong correlations were found between VAS asthma and other measures (Table 5).

TABLE 4 Potential implications of the allergy-CSMS.

1. Clinical practice
• Indication of a treatment in stratified patients
• Follow-up of a treatment and early stopping rule
• Follow-up of a treatment and regular review of efficacy
• Follow-up of the patient when the treatment is stopped
• Re-introduction and follow-up of the treatment in patients who relapsed
2. RCTs: mHealth biomarkers are currently exploratory end points but may become primary end points mimicking real life after validation
3. Observational studies can triangulate RCTs and make a link with clinical practice
4. Real-world data are the data relating to patient health status and/or to the delivery of health care. They are routinely collected from a variety of sources including apps. They enable large simple trials and pragmatic clinical trials to be performed
5. Epidemiologic studies will use the same approach to better relate RCTs and clinical practice
6. Allergen challenge can triangulate RCTs and make a link with clinical practice

Abbreviations: CSMS, ARIA-EAACI allergy Combined Symptom-Medication Score; RCT, Randomized Controlled Trials.

The cutoff values for VAS asthma are 0/100 (fully-controlled asthma), 1–19/100 (partly-controlled asthma), 20–35/100 (partly-uncontrolled asthma), and $\geq 36/100$ (uncontrolled asthma).

5.1.2 | Correlation between VAS asthma and Asthma Control Test (ACT)

A random observational trial evaluated the usefulness of the MASK-air® app in improving rhinitis control in 262 patients with AR.⁸⁷ There was a significant correlation between VAS asthma and the ACT score (Pearson -0.79132 , $p < 0.0001$).

5.1.3 | CARAT

CARAT, a PROM developed for assessing the control of asthma and AR at a 4-week interval, has been evaluated in several studies. A systematic review has aimed to evaluate the measurement properties of CARAT.^{35–37,52,88–92} A total of 16 studies were included. CARAT was found to have sufficient content validity and to have a bifactorial structure with good consistency (meta-analytical Cronbach alpha=0.83; 95% CI=0.80–0.86; $I^2=62.6\%$). The CARAT meta-analytical intra-class correlation coefficient was 0.91; 95% CI=0.64–0.98; $I^2=93.7\%$. It presented good construct validity—especially for correlations with PROMs assessing asthma (range of absolute Spearman correlation coefficients: 0.68 to 0.73; moderate quality of evidence)—as well as good responsiveness. Its minimal important difference was 3.5 (out of 30). CARAT can be used to assess the control of asthma and AR.

5.2 | Development and validation of the daily electronic asthma control score (e-DASTHMA) (online ANNEX 4)

5.2.1 | Selection of the digital tool

An automatic market research investigated the asthma apps that can be used to develop an e-DASTHMA. MASK-air® appears to be the

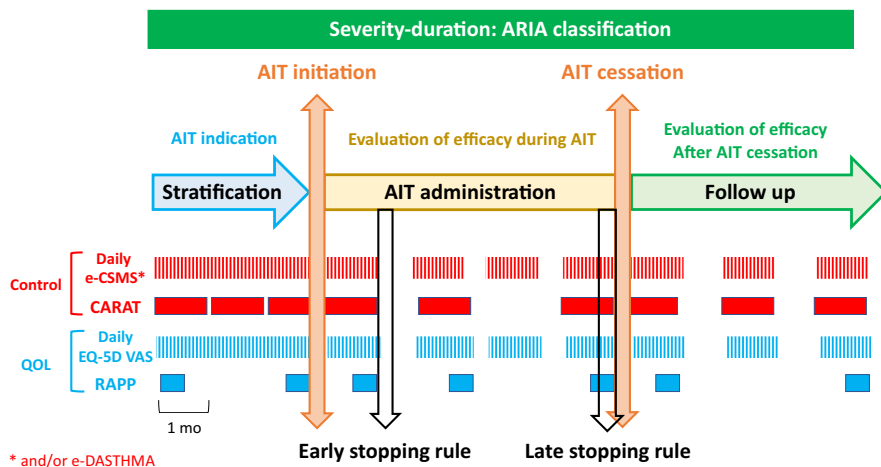


FIGURE 7 Applicability of digital biomarkers in AIT for allergic rhinitis.

TABLE 5 Correlation coefficients between different PROMs in severe asthma (from⁶⁵).

	N observations	Spearman correlation coefficient (95% CI)	Repeated measures correlation coefficient (95% CI) ¹⁰⁵
VAS asthma vs. VAS dyspnea	1862	0.898 (0.879; 0.915)	0.713 (0.690; 0.735)
VAS asthma vs. VAS global	4822	0.767 (0.750; 0.784)	0.544 (0.524; 0.564)
VAS asthma vs. VAS nose	4822	0.755 (0.738; 0.771)	0.465 (0.443; 0.487)
VAS asthma vs. VAS eyes	4822	0.640 (0.620; 0.661)	0.378 (0.354; 0.402)
VAS asthma vs. VAS work	1840	0.768 (0.739; 0.793)	0.658 (0.631; 0.683)
VAS asthma vs. VAS sleep	4168	0.637 (0.613; 0.658)	0.339 (0.312; 0.366)
VAS asthma vs. CSMS	4822	0.875 (0.865; 0.884)	0.747 (0.734; 0.759)

Abbreviations: CSMS, ARIA-EAACI allergy Combined Symptom-Medication Score; VAS, Visual analogue scale.

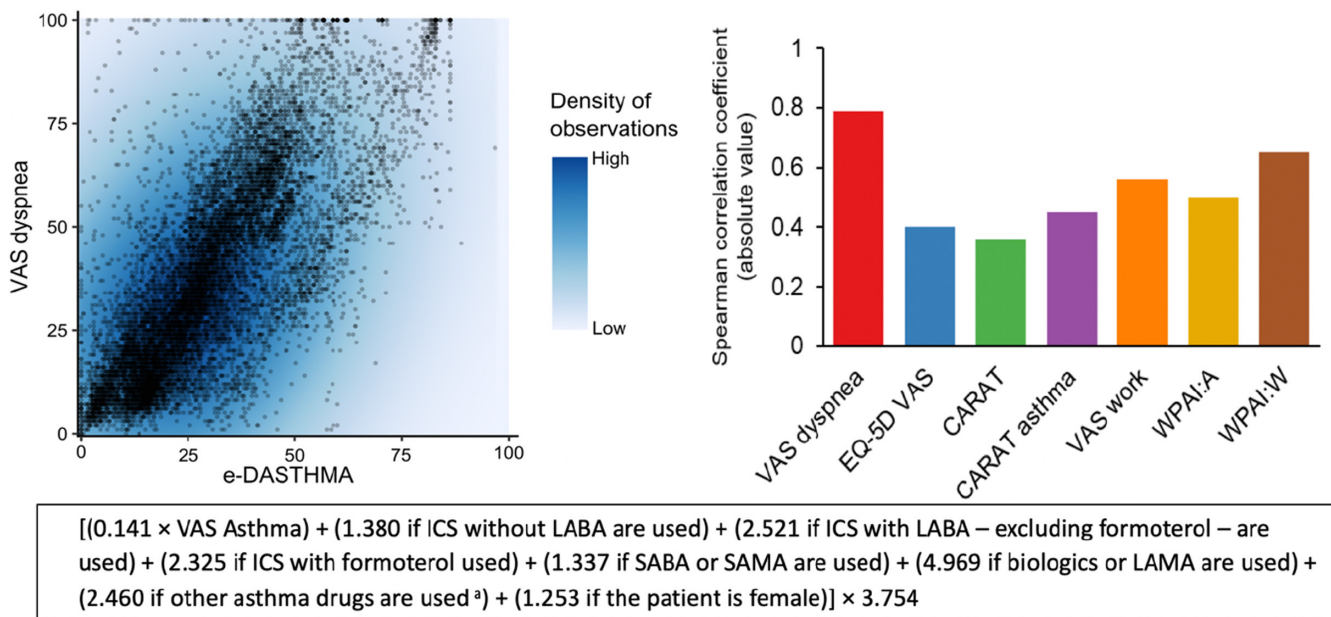


FIGURE 8 Correlations between e-DASTHMA and comparators.

only one that can be used, and the database of MASK-air included more patients than other apps.

5.2.2 | Development of e-DASTHMA

Data-driven control scores were developed based on (i) asthma symptoms reported by a VAS and (ii) reported asthma medication use. For each score, construct validity, test-retest reliability, and responsiveness were assessed. VASs on dyspnea and work, EQ-5D VAS, CARAT, CARAT-asthma and WPAI:AS were used as comparators.

A total of 135,635 days of MASK-air® data were studied from 1662 users. Cluster- and linear regression-based scales were strongly correlated with VAS dyspnea (Spearman correlation Rho range=0.57 to 0.99) and moderately correlated with work- and quality-of-life-related

comparators (Rho range=0.33–0.68). They displayed high test-retest reliability and moderate-to-high responsiveness (Figure 8).

5.2.3 | Validation of the asthma-CSMS in an external cohort (INSPIRERS)

An external validation of eDASTHMA was performed—using a cohort of patients with physician-diagnosed asthma (INSPIRERS)—in 69 patients and 425 days.⁹³ The daily activity scores of INSPIRERS were correlated with e-DASTHMA scores (Rho=0.70; 95% CI=0.61;0.78). In addition, the areas under ROC curves (AUC-ROC) compared the performance of e-DASTHMA scores to the GINA classification of patients (assessed at medical evaluation) with uncontrolled/partly-controlled versus controlled asthma. The best-performing score displayed good accuracy for the identification

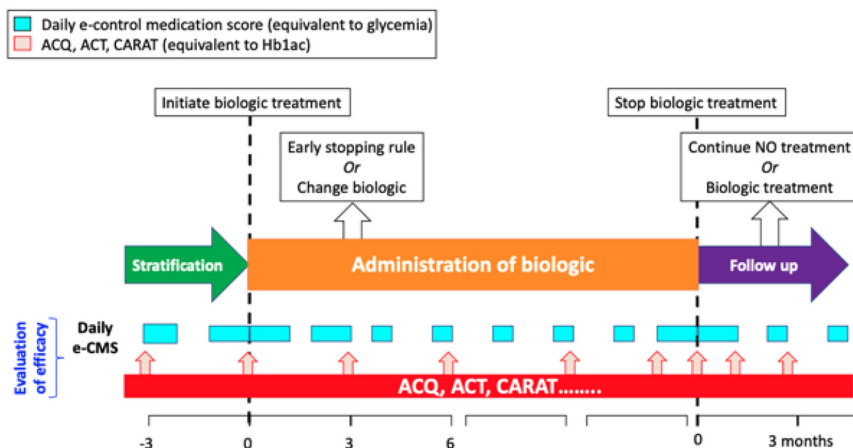


FIGURE 9 Applicability of digital biomarkers in severe asthma using the diabetes approach.

of patients with uncontrolled/partially-controlled asthma (AUC-ROC=0.74; 95% CI=0.68;0.78).

5.3 | Application to the biologic treatment of severe asthma

Currently, a major criterion to initiate or stop a biologic in asthma is the frequency of exacerbations. In MASK-air®, exacerbations can be defined by the occurrence of uncontrolled VAS using the cutoffs calculated ($VAS \geq 36/100$) and/or the use of oral corticosteroids. With the available data on file, MASK-air® researchers are assessing whether the change in e-DASTHMA could be associated with an exacerbation. Moreover, in future studies, with the new development of MASK-air® (MDR Class IIa), e-DASTHMA values will be refined (Figure 9).

5.4 | Application to the treatment of mild/moderate asthma

Among other possible studies, one is of particular importance. In mild to moderate asthma, PRN (Pro re nata, as needed) treatment with formoterol/ICS (inhaled corticosteroids) combination is favored to short-acting β -agonists (LABAs).⁹⁴ However, this recommendation is not accepted widely as the costs incurred by Formoterol/ICS are higher than those of generic SABAs, and Formoterol/ICS is not available globally. One of the studies in MASK-air® (unpublished) suggests that combination therapy is more effective than SABAs and might also be cost-effective.

The MASK-air® diabetes approach may be applied (i) to confirm the importance of the new strategy for payers, (ii) to improve the global use of this strategy by optimizing the WHO essential list of drugs,⁹⁵ (iii) to follow-up patients in clinical practice, (iv) to propose novel algorithms based on RWD, and (v) to develop next-generation guidelines based on RWD and evidence-based medicine.⁹⁶

6 | DIGITAL BIOMARKERS IN OCCUPATIONAL ALLERGY AND ASTHMA

The diagnosis and management of occupational allergic diseases and asthma are often difficult. The relative role of nasal, ocular, and bronchial symptoms may be complicated,⁹⁷ and they often overlap.⁶⁷ MASK-air® can assess days with exposure to work. It can also easily compare the different symptoms during and outside exposure as well as the control of allergy and asthma. When validated, digital biomarkers may prove to be an easy and simple tool for the diagnosis of occupational asthma.

Moreover, severe occupational asthma⁹⁸ may be assessed combining e-DASTHMA and CARAT.

7 | EMBEDDING MACHINE LEARNING IN DIGITAL BIOMARKERS

Individuals with allergic respiratory diseases often suffer from a combination of asthma, conjunctivitis, and rhinitis. Because of its complexity, this allergic multimorbidity is not well understood from a research perspective. Furthermore, it is difficult to manage from a clinical viewpoint. Data analytics offer a promising way of addressing these challenges. For instance, by enabling (i) the rigorous identification of disease phenotypes⁹⁹ and (ii) improved estimates of the likelihood that an individual responds to a treatment.

Response to treatment has been studied using machine learning. A clinical review found that, in the past 5 years, 22 studies have successfully applied machine learning to asthma mHealth data. However, most have been developed on small datasets with internal validation. Small sample sizes and lack of external validation limit the generalizability of these studies.¹⁰⁰ Future research should collect data that are more representative of the wider asthma population and focus on validating the derived algorithms and technologies in a real-world setting.

These approaches will enable us to fully benefit from the wealth of data made available by MASK-air. The ultimate goal will be that of raising novel hypotheses concerning the response to the treatment of patients with allergic multimorbidity (asthma, conjunctivitis, rhinitis). Other studies will assess treatment algorithms and the prediction of exacerbations.

FUNDING INFORMATION

MASK-air® has been supported by Charité Universitätsmedizin Berlin, EU grants (EU Structural and Development Funds Languedoc Roussillon and Region PACA; POLLAR: EIT Health; Twinning: EIP on AHA; Twinning DHE: H2020; Catalyse: Horizon Europe) and educational grants from Mylan-Viatrix, ALK, GSK, Novartis, Stallergènes-Greer and Uriach.

AUTHOR CONTRIBUTIONS

OP, LK, and JB proposed the study. JB wrote the paper. MHS, JMA, JAF, BS-P, and WC proposed the asthma flow chart for biomarkers. HJS and TZ are working on how to integrate the results of the TF in care pathways. GWC and FB added the quality-of-life proposal. The text was then submitted to AB, RA, IJA, SB-A, CCL, BG, TH, MK, PK, MK, MO, FSR, BS, MS, ST-S, and AV. After their helpful comments, the text was sent to ARIA and EAACI members.

AFFILIATIONS

¹Institute of Allergology, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

²University Hospital Montpellier, Montpellier, France

³Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

⁴National Heart and Lung Institute (NHLI), Imperial College London, London, UK

⁵NIHR Imperial Biomedical Research Centre, London, UK

⁶ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain

⁷Universitat Pompeu Fabra (UPF), Barcelona, Spain

⁸CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

⁹Department of Health Research Methods, Evidence, and Impact, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

¹⁰Department of Biomedical Sciences, Humanitas University, Milan, Italy

¹¹Personalized Medicine, Asthma & Allergy, IRCCS Humanitas Research Center, Milan, Italy

¹²Department of Clinical Immunology, Wrocław Medical University, Wrocław, Poland

¹³ALL-MED Medical Research Institute, Wrocław, Poland

¹⁴Department of Medical Sciences and Public Health and Unit of Allergy and Clinical Immunology, University Hospital "Dulio Casula," University of Cagliari, Cagliari, Italy

¹⁵Section of Rhinology and Allergy, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

¹⁶MEDCIDS - Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal

¹⁷CINTESIS@RISE- Health Research Network, Faculty of Medicine, University of Porto, Porto, Portugal

¹⁸Department of Otolaryngology, Head and Neck Surgery,

Universitätsmedizin Mainz, Mainz, Germany

¹⁹Center for Rhinology and Allergology, Wiesbaden, Germany

²⁰Medical Consulting Czarlewski, Levallois, France

²¹MASK-air, Montpellier, France

²²ARIA, Montpellier, France

²³Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain

²⁴Quality Use of Respiratory Medicines Group, Woolcock Institute of Medical Research, Sydney, New South Wales, Australia

²⁵Sydney Local Health District, Sydney, New South Wales, Australia

²⁶Sydney Pharmacy School, The University of Sydney, Sydney, New South Wales, Australia

²⁷Respiratory Clinic, Department of Internal Medicine, University of Genoa, Genoa, Italy

²⁸IRCCS Ospedale Policlinico San Martino, Genoa, Italy

²⁹Pneumology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

³⁰Department of Pulmonary Diseases, Istanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Istanbul, Turkey

³¹Skin and Allergy Hospital, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

³²Department of Pediatric Respiratory Diseases and Allergology, Medical University of Warsaw, Warsaw, Poland

³³Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Lodz, Poland

³⁴Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany

³⁵Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

³⁶Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (ICBR), University of Coimbra, Coimbra, Portugal

³⁷Faculty of Medicine, Institute of Immunology, University of Coimbra, Coimbra, Portugal

³⁸Department of Prevention of Environmental Hazards, Allergology and Immunology, Medical University of Warsaw, Warsaw, Poland

³⁹Finnish Meteorological Institute (FMI), Helsinki, Finland

⁴⁰Institute of Clinical Medicine and Institute of Health Sciences, Medical Faculty of Vilnius University, Vilnius, Lithuania

⁴¹Unit of Geriatric Immunoallergology, University of Bari Medical School, Bari, Italy

⁴²Institute of Sciences of Food Production, National Research Council (ISPA-CNR), Bari, Italy

⁴³Portuguese National Programme for Respiratory Diseases, Direção -Geral da Saúde, Faculdade de Medicina de Lisboa, Instituto de Saúde Ambiental, Lisbon, Portugal

⁴⁴University of Central Lancashire Medical School, Preston, UK

⁴⁵Department of Geriatrics, Montpellier University Hospital, MUSE, Montpellier, France

⁴⁶Department of Cardiovascular and Respiratory Sciences, Università Cattolica del Sacro Cuore, Rome, Italy

⁴⁷Department of Neurological, ENT and Thoracic Sciences, Fondazione Policlinico Universitario A Gemelli - IRCCS, Rome, Italy

⁴⁸Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada

⁴⁹University Hospital of Nice, Nice, France

⁵⁰Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

⁵¹Department of Medical Sciences, University of Torino, Torino, Italy

- ⁵²Allergy and Clinical Immunology Unit, Mauriziano Hospital, Torino, Italy
- ⁵³Department of Pulmonary Medicine, Mainz University Hospital, Mainz, Germany
- ⁵⁴Allergy Section, Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain
- ⁵⁵ARADyAL Research Network, Barcelona, Spain
- ⁵⁶Division of Allergy/Immunology, University of South Florida, Tampa, Florida, USA
- ⁵⁷SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy
- ⁵⁸Clinique des Bronches, Allergie et Sommeil, Hôpital Nord, Marseille, France
- ⁵⁹Universidad Espíritu Santo, Samborondón, Ecuador
- ⁶⁰Respiralab Research Group, Guayas, Ecuador
- ⁶¹ENT Department, Medical Faculty, Eskisehir Osmangazi University, Eskisehir, Turkey
- ⁶²UCIBIO, REQUINTE, Faculty of Pharmacy and Competence Center on Active and Healthy Ageing, University of Porto (Porto4Ageing), Porto, Portugal
- ⁶³Fundação ProAR, Federal University of Bahia and GARD/WHO Planning Group, Salvador, Brazil
- ⁶⁴VIM Suresnes, UMR 0892, Pôle des Maladies des Voies Respiratoires, Hôpital Foch, Université Paris-Saclay, Suresnes, France
- ⁶⁵Department of Pediatric Pneumology, Immunology and Intensive Care Medicine, Charité Medical University, Berlin, Germany
- ⁶⁶Department of Otorhinolaryngology, Amsterdam University Medical Centres, Amsterdam, The Netherlands
- ⁶⁷Center of Allergy and Immunology, David Tvildiani Medical University, Tbilisi, Georgia
- ⁶⁸Kazakhstan Association of Allergology and Clinical Immunology, Department of Allergology and Clinical Immunology of the Kazakh National Medical University, Almaty, Kazakhstan
- ⁶⁹Servicio de Alergia e Immunologia, Clinica Santa Isabel, Buenos Aires, Argentina
- ⁷⁰Poltava State Medical University, Poltava, Ukraine
- ⁷¹Department of Otorhinolaryngology, Head and Neck Surgery, Semmelweis University, Budapest, Hungary
- ⁷²Faculty of Medicine, Institute of Clinical Medicine, Clinic of Chest Diseases and Allergology, Vilnius University, Vilnius, Lithuania
- ⁷³Department of Pathology, Faculty of Medicine, Institute of Biomedical Sciences, Vilnius University, Vilnius, Lithuania
- ⁷⁴Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico
- ⁷⁵KYomed INNOV, Montpellier, France
- ⁷⁶Faculty of Health Sciences and CICS - UBI, Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
- ⁷⁷Department of Pulmonary Medicine, CHU Liège, Liège, Belgium
- ⁷⁸GIGA I3 Research Group, University of Liège, Liège, Belgium
- ⁷⁹Allergy Unit "D Kalogeromitros," 2nd Department of Dermatology and Venereology, National & Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece
- ⁸⁰Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
- ⁸¹Sach's Children and Youth Hospital, Stockholm, Sweden
- ⁸²Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
- ⁸³Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic, Barcelona, Spain
- ⁸⁴Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Barcelona, Spain
- ⁸⁵Department of Allergology, Medical University of Gdansk, Gdansk, Poland
- ⁸⁶Allergy, Asthma and Clinical Immunology, Alfred Health and Department of Immunology, Central Clinical School, Monash University, Melbourne, Victoria, Australia
- ⁸⁷Chiba Rosai Hospital, Chiba, Japan
- ⁸⁸Chiba University Hospital, Chiba, Japan
- ⁸⁹Department of Otorhinolaryngology, Charité-Universitätsmedizin Berlin, Berlin, Germany
- ⁹⁰Berlin Institute of Health, Berlin, Germany
- ⁹¹Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece
- ⁹²Respiratory Medicine, Department of Translational Medicine, University of Ferrara, Ferrara, Italy
- ⁹³Division of Allergy and Clinical Immunology, Department of Medicine, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy
- ⁹⁴Agency of Health ASL, Salerno, Italy
- ⁹⁵Postgraduate Programme in Allergy and Clinical Immunology, University of Naples Federico II, Naples, Italy
- ⁹⁶Department of Public Health, University of Liège, Liège, Belgium
- ⁹⁷Ecole Polytechnique de Palaiseau, Palaiseau, France
- ⁹⁸IRBA (Institut de Recherche Bio-Médicale des Armées), Brétigny sur Orge, France
- ⁹⁹Université Paris Cité, Paris, France
- ¹⁰⁰Personalized Medicine, Asthma & Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy
- ¹⁰¹Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain
- ¹⁰²Pneumologie, AP-HP Centre Université de Paris Cité, Hôpital Cochin, et UMR 1016, Institut Cochin, Paris, France
- ¹⁰³Department of Otolaryngology, Head and Neck Surgery, Eye and Ear, University Hospital, Beirut, Lebanon
- ¹⁰⁴Department of Otolaryngology, Head and Neck Surgery, Dar Al Shifa Hospital - Salmiya, Hawally, Kuwait
- ¹⁰⁵Department of Medicine, Division of Respiratory Medicine and Allergology, Showa University School of Medicine, Tokyo, Japan
- ¹⁰⁶Allergy Service, Fundacion Jimenez Diaz, Autonoma University of Madrid, CIBERES-ISCIII, Madrid, Spain
- ¹⁰⁷PROMISE Department, University of Palermo, Palermo, Italy
- ¹⁰⁸Usher Institute, The University of Edinburgh, Edinburgh, UK
- ¹⁰⁹Department of Respiratory Medicine and Tuberculosis, University Hospital Brno, Lískovec, Czech Republic
- ¹¹⁰Department of Respiratory Medicine, Copenhagen University Hospital-Hvidovre, Copenhagen, Denmark
- ¹¹¹Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
- ¹¹²Department of Immunoallergology, Cova da Beira University Hospital Centre, Covilhã, Portugal
- ¹¹³UBIAir - Clinical & Experimental Lung Centre and CICS-UBI Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
- ¹¹⁴Imunoalergologia, Faculty of Medicine, Centro Hospitalar Universitário de Coimbra, University of Coimbra, Coimbra, Portugal
- ¹¹⁵Allergy Unit, Málaga Regional University Hospital-IBIMA, Málaga, Spain
- ¹¹⁶International Primary Care Respiratory Group (IPCRG), Aberdeen, UK
- ¹¹⁷Health Planning Unit, Department of Social Medicine, Faculty of Medicine, University of Crete, Heraklion, Greece
- ¹¹⁸Royal Brompton Hospital, Airways Disease Section, London, UK
- ¹¹⁹Department of Lung Diseases and Clinical Immunology, University of Turku, Turku, Finland
- ¹²⁰FIHLA, Finnish Lung Health Association, Helsinki, Finland
- ¹²¹Department of Clinical Medicine, Pulmonary Diseases and Clinical Allergology, University of Turku, Turku, Finland

¹²²Nova Southeastern University, College of Allopathic Medicine, Fort Lauderdale, Florida, USA

¹²³Department of Medicine, Clinical Immunology and Allergy, McMaster University, Hamilton, Ontario, Canada

¹²⁴University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

¹²⁵Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

¹²⁶Department of Pulmonary Diseases, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

¹²⁷Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital and Beijing Institute of Otolaryngology, Beijing, China

¹²⁸School of Medicine, University CEU San Pablo, Madrid, Spain

¹²⁹Department of Infection and Immunity, Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg

¹³⁰Department of Dermatology and Allergy Centre, Odense University Hospital, Odense Research Center for Anaphylaxis (ORCA), Odense, Denmark

ACKNOWLEDGMENTS

The authors thank Ms Véronique Pretschner for submitting the paper. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from Mask-air-SAS, outside the submitted work. VC reports personal fees from ALK, personal fees from Allergopharma, personal fees from GSK, grants from Thermofisher, outside the submitted work. MK reports personal fees from Astra Zeneca, personal fees from GSK, personal fees from Adamed, personal fees from Polpharma, personal fees from Celon Pharma, personal fees from Berlin Chemie Menarini, personal fees from Novartis, personal fees from Nexter Allergopharma, personal fees from Teva, personal fees from Chiesi, personal fees from Zentiva, personal fees from Sanofi Aventis, personal fees from Pfizer, personal fees from Abbvie, personal fees from Lekam, outside the submitted work. JS reports grants and personal fees from SANOFI, personal fees from GSK, personal fees from NOVARTIS, personal fees from ASTRA ZENECA, personal fees from MUNDIPHARMA, personal fees from FAES FARMA, outside the submitted work. LPB reports grants from Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Sanofi-Regeneron, personal fees from Astra Zeneca, Novartis, GlaxoSmithKline, Merck, Sanofi-Regeneron, personal fees from AstraZeneca, Covis, GlaxoSmithKline, Novartis, Merck, Sanofi, outside the submitted work. NR reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, grants and personal fees from GSK, personal fees from AstraZeneca, personal fees from Chiesi, grants and personal fees from Pfizer, personal fees from Sanofi, personal fees from Zambon, personal fees from MSD, personal fees from Austral, outside the submitted work. LC reports personal fees from Thermofisher, personal fees from Sanofi, personal fees from Astra Zeneca, personal fees from Novartis, outside the submitted work. BS reports personal fees from Polpharma, personal fees from Viatrix, grants and personal fees from AstraZeneca, personal fees from TEVA, personal fees from patient

ombudsman, personal fees from Polish Allergology Society, grants from GSK, outside the submitted work. LTB reports personal fees from AstraZeneca, personal fees from Diater, outside the submitted work. JCI reports personal fees from Laboratorios Casasco, personal fees from Bago Bolivia, personal fees from Abbott Ecuador, personal fees from Faes Farma, outside the submitted work. SBA reports grants from TEVA, personal fees from TEVA, personal fees from TEVA, personal fees from AstraZeneca, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Sanofi, personal fees from Mylan, outside the submitted work. GB reports personal fees from Astra Zeneca, personal fees from Boehringer-Ingelheim, personal fees from Chiesi, personal fees from GSK, personal fees from Novartis, personal fees from Sanofi, grants from MSD, outside the submitted work. TH reports personal fees from Orion Pharma, outside the submitted work. RB reports grants from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche, personal fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Novartis, Roche, Sanofi, Teva, outside the submitted work. JM reports personal fees and other from SANOFI-GENZYME & REGENERON, personal fees and other from NOVARTIS, grants and personal fees from VIATRIS, grants and personal fees from URIACH Group, personal fees from Mitsubishi-Tanabe, personal fees from Menarini, personal fees from UCB, personal fees from AstraZeneca, grants and personal fees from GSK, personal fees from MSD, outside the submitted work. PK reports personal fees from Adamed, personal fees from Berlin Chemie Menarini, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Celon Pharma, personal fees from Polpharma, personal fees from Teva, personal fees from Novartis, personal fees from Glenmark, personal fees from Zentiva, outside the submitted work. DC reports AAAAI Foundation Faculty Development Awardee. SQ reports personal fees and non-financial support from GSK, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Novartis, personal fees and non-financial support from Mundipharma, personal fees and non-financial support from Teva, personal fees and non-financial support from Allergy Therapeutics, outside the submitted work. HK reports personal fees from Mylan/Viatrix, personal fees from Sanofi, outside the submitted work. PD reports personal fees from ALK Abello, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Chiesi, personal fees and non-financial support from Astra Zeneca, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees from Novartis, personal fees and non-financial support from Stallergenes, personal fees from Sanofi, outside the submitted work. AC reports personal fees from AstraZeneca, personal fees from Chiesi, personal fees from GSK, personal fees from SANOFI, personal fees from Novartis, personal fees from Boehringer Ingelheim, personal fees from Glenmark, personal fees from Eurofarma, personal fees from Abdi Ibrahim, personal fees from CROSSJECT, outside the submitted work. TZ reports grants and personal fees from Novartis, grants

and personal fees from Henkel, personal fees from Bayer, personal fees from FAES, personal fees from Astra Zeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from Hal, personal fees from Leti, personal fees from Mesa, personal fees from Menarini, personal fees from Merck, personal fees from MSD, personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, personal fees from Henkel, personal fees from Kryolan, personal fees from L'Oreal, outside the submitted work; and Organizational affiliations: Committee member: WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA), Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI), Head: European Centre for Allergy Research Foundation (ECARF), President: Global Allergy and Asthma European Network (GA2LEN), Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). DLL reports personal fees from Abbvie, ALK, Allakos, Amstrong, Astrazeneca national and global, Chiesi, DBV Technologies, Grunenthal, Grin, GSK national and global, Viatrix, Menarini, MSD, Novartis, Pfizer, Sanofi, UCB, Carnot, grants from Abbvie, Bayer, Lilly, Sanofi, Astrazeneca, Lilly, Pfizer, Novartis, Circassia, UCB, GSK, Purina institute, outside the submitted work. IT reports grants from GSK Hellas, Astra Zeneca Hellas, Boehringer Ingelheim, personal fees from Novartis, Johnson and Johnson, Boehringer Ingelheim, Chiesi, Astra Zeneca, outside the submitted work. YO reports personal fees from Torii pharmaceutical CO., LTD., personal fees from Tanabe-Mitsubishi Pharmaceutical CO., LTD., personal fees from Kirin Holdings CO., LTD., personal fees from Novartis CO., LTD., personal fees from Allergologisk Laboratorium København, personal fees from Shionogi CO., LTD., outside the submitted work. OP reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Immunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Regeneron Pharmaceuticals Inc., personal fees from RG Aertzefortbildung, personal fees from Institut für Disease

Management, personal fees from Springer GmbH, grants and personal fees from AstraZeneca, personal fees from IQVIA Commercial, personal fees from Ingress Health, personal fees from Wort&Bild Verlag, personal fees from Verlag ME, personal fees from Procter&Gamble, outside the submitted work. VK reports other from NORAMEDA, outside the submitted work. MZ reports personal fees from TAKEDA, outside the submitted work. LK reports grants and personal fees from Allergopharma, grants and personal fees from Viatrix, personal fees from HAL Allergie, personal fees from ALK Abelló, grants and personal fees from LETI Pharma, grants and personal fees from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut, grants from AstraZeneca, grants and personal fees from GSK, grants from Immunotek, personal fees from Cassella med, personal fees from Novartis, personal fees from Regeneron Pharmaceuticals, personal fees from ROXALL Medizin GmbH, outside the submitted work; and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV, GPA, EAACI. NGP reports personal fees from NOVARTIS, personal fees from NUTRICIA, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI/REGENERON, personal fees from MYLAN/MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT BIOTECH, personal fees from Boehringer Ingelheim, grants from CAPRICARE, grants from Gerolymatos Int, grants from NUTRICIA, personal fees from MEDCARE, personal fees from ALK, personal fees from OM PHARMA, from ABBOTT, outside the submitted work. SDG reports grants from AstraZeneca, grants from GSK, grants from Novartis, grants from Sanofi, outside the submitted work. CSU reports grants and personal fees from AZ, grants and personal fees from GSK, personal fees from Chiesi, personal fees from Orion Pharma, grants and personal fees from Sanofi, personal fees from TEVA, personal fees from Pfizer, grants and personal fees from BI, personal fees from Novartis, outside the submitted work. MJ reports personal fees from ALK-Abello, personal fees from Allergopharma, personal fees from Stallergenes, personal fees from Anergis, personal fees from Allergy Therapeutics, personal fees from Leti, personal fees from HAL, during the conduct of the study; personal fees from GSK, personal fees from Novartis, personal fees from Teva, personal fees from Takeda, personal fees from Chiesi, outside the submitted work. RL reports Grants from GSK, Chiesi and AZ and adboard and lecture fees from AZ, GSK, Chiesi. AP reports grants and personal fees from CHIESI, grants and personal fees from ASTRAZENECA, grants and personal fees from GSK, grants and personal fees from SANOFI, grants from AIFA, personal fees from MSD, personal fees from NOVARTIS, personal fees from IQVIA, personal fees from AVILLION, personal fees from ELPEN PHARMACEUTICALS, personal fees from MENARINI, personal fees from ZAMBON, personal fees from MUNDIPHARMA, personal fees from EDMOND PHARMA, outside the submitted work. JAF reports being co-founder of an SME that develops mHealth technologies, such as digital biomarkers and has the copyright of the CARAT and a

CARATkids PROM. ATB reports grants and personal fees from Novartis, personal fees from Astra Zeneca, grants and personal fees from GSK, grants and personal fees from Sanofi, grants and personal fees from AbbVie, personal fees from Mylan, grants and personal fees from Leti, personal fees from Bial, outside the submitted work. STS reports personal fees from Sanofi, personal fees from ALK-Abello, personal fees from ERT, personal fees from GSK, personal fees from AstraZeneca, grants from GSK, outside the submitted work. AS reports other from GINA, outside the submitted work. GJ reports personal fees and non-financial support from AstraZeneca, personal fees from GlaxoSmithKline, personal fees from Chiesi, personal fees from Lapharcon, personal fees from Novartis, personal fees from Eureka vzw, outside the submitted work. SD reports personal fees from OMRON Healthcare CO. LTD., personal fees from Allergopharma, personal fees from Bencard Allergie, outside the submitted work. HS reports personal lecture fees from GSK, AstraZeneca, Sanofi, Novartis, and Boehringer Ingelheim. IJA reports personal fees from Roxall, personal fees from UCB, personal fees from Faes Farma, personal fees from Sanofi, personal fees from Bial, personal fees from Abbott, personal fees from Bayer, personal fees from Menarini, outside the submitted work. HS reports and developed guidelines on Allergic Rhinitis in Asthma (ARIA) and his academic institution received research funding for it. MO reports personal fees from Hycor Diagnostics, outside the submitted work; and Scientific Co-Founder, ToleroGenics SARL, Luxembourg. The other authors have no COIs to disclose, outside the submitted work.

ORCID

Jean Bousquet  <https://orcid.org/0000-0002-4061-4766>
 Mohamed H. Shamji  <https://orcid.org/0000-0003-3425-3463>
 Stefano Del Giacco  <https://orcid.org/0000-0002-4517-1749>
 Torsten Zuberbier  <https://orcid.org/0000-0002-1466-8875>
 Oliver Pfaar  <https://orcid.org/0000-0003-4374-9639>
 Ludger Klimek  <https://orcid.org/0000-0002-2455-0192>
 Rita Amaral  <https://orcid.org/0000-0002-0233-830X>
 Claudia Chaves Loureiro  <https://orcid.org/0000-0003-0438-6126>
 Tari Haahtela  <https://orcid.org/0000-0003-4757-2156>
 Paolo M. Matricardi  <https://orcid.org/0000-0001-5485-0324>
 Sanna Toppila-Salmi  <https://orcid.org/0000-0003-0890-6686>
 Matteo Bonini  <https://orcid.org/0000-0002-3042-0765>
 Louis-Philippe Boulet  <https://orcid.org/0000-0003-3485-9393>
 Lorenzo Cecchi  <https://orcid.org/0000-0002-0658-2449>
 Ivan Cherrez-Ojeda  <https://orcid.org/0000-0002-1610-239X>
 Cemal Cingi  <https://orcid.org/0000-0003-3934-5092>
 Alvaro A. Cruz  <https://orcid.org/0000-0002-7403-3871>
 Wytse J. Fokkens  <https://orcid.org/0000-0003-4852-229X>
 Enrico Heffler  <https://orcid.org/0000-0002-0492-5663>
 Désirée E. Larenas-Linnemann  <https://orcid.org/0000-0002-5713-5331>
 Olga Lourenço  <https://orcid.org/0000-0002-8401-5976>
 Marcus Maurer  <https://orcid.org/0000-0002-4121-481X>
 Mario Morais-Almeida  <https://orcid.org/0000-0003-1837-2980>

Marek Niedoszytko  <https://orcid.org/0000-0003-1089-1911>
 Robyn O'Hehir  <https://orcid.org/0000-0002-3489-7595>
 Nikolaos G. Papadopoulos  <https://orcid.org/0000-0002-4448-3468>
 Alberto Papi  <https://orcid.org/0000-0002-6924-4500>
 Vincenzo Patella  <https://orcid.org/0000-0001-5640-6446>
 Philip W. Rouadi  <https://orcid.org/0000-0002-5365-9568>
 Maria J. Torres  <https://orcid.org/0000-0003-2988-6055>
 Rafael José Vieira  <https://orcid.org/0000-0003-1834-3055>
 Arzu Yorgancioglu  <https://orcid.org/0000-0002-4032-0944>
 Luo Zhang  <https://orcid.org/0000-0002-0910-9884>
 Markus Ollert  <https://orcid.org/0000-0002-8055-0103>

REFERENCES

1. Agache I. Severe asthma phenotypes and endotypes. *Semin Immunol.* 2019;46:101301. doi:10.1016/j.smim.2019.101301
2. Breiteneder H, Peng YQ, Agache I, et al. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. *Allergy.* 2020;75(12):3039-3068. doi:10.1111/all.14582
3. Porpodis K, Tsiouprou I, Apostolopoulos A, et al. Eosinophilic asthma, phenotypes-Endotypes and current biomarkers of choice. *J Pers Med.* 2022;12(7):1093. doi:10.3390/jpm12071093
4. Diamant Z, Vijverberg S, Alving K, et al. Toward clinically applicable biomarkers for asthma: an EAACI position paper. *Allergy.* 2019;74(10):1835-1851. doi:10.1111/all.13806
5. Radzikowska U, Baerenfaller K, Cornejo-Garcia JA, et al. Omics technologies in allergy and asthma research: an EAACI position paper. *Allergy.* 2022;77(10):2888-2908. doi:10.1111/all.15412
6. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir Med.* 2021;9(10):1165-1173. doi:10.1016/S2213-2600(21)00124-7
7. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med.* 2017;195(3):302-313. doi:10.1164/rccm.201602-0419OC
8. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev.* 2020;29(156):190137. doi:10.1183/16000617.0137-2019
9. Landry V, Coburn P, Kost K, Liu X, Li-Jessen NYK. Diagnostic accuracy of liquid biomarkers in airway diseases: toward point-of-care applications. *Front Med (Lausanne).* 2022;9:855250. doi:10.3389/fmed.2022.855250
10. Ogulur I, Pat Y, Ardicli O, et al. Advances and highlights in biomarkers of allergic diseases. *Allergy.* 2021;76(12):3659-3686. doi:10.1111/all.15089
11. Bousquet J, Pfaar O, Agache I, et al. ARIA-EAACI care pathways for allergen immunotherapy in respiratory allergy. *Clin Transl Allergy.* 2021;11(4):e12014. doi:10.1002/ctt2.12014
12. eHealth at WHO. 2021. <https://www.who.int/ehealth/about/en/>
13. mHealth. New horizons for health through mobile technologies. *Global Observatory for eHealth Series.* Vol 3. WHO Library Cataloguing-in-Publication Data; 2011. http://www.who.int/goe/publications/goe_mhealth_web.pdf
14. Anto A, Sousa-Pinto B, Bousquet J. Anaphylaxis and digital medicine. *Curr Opin Allergy Clin Immunol.* 2021;21(5):448-454. doi:10.1097/ACI.0000000000000764
15. Bousquet J, Ansotegui IJ, Anto JM, et al. Mobile Technology in Allergic Rhinitis: evolution in management or revolution in health

- and care? *J Allergy Clin Immunol Pract.* 2019;7(8):2511-2523. doi:10.1016/j.jaip.2019.07.044
16. Bousquet J, Hellings PW, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) phase 4 (2018): change management in allergic rhinitis and asthma multimorbidity using mobile technology. *J Allergy Clin Immunol.* 2019;143(3):864-879. doi:10.1016/j.jaci.2018.08.049
 17. Bousquet J, Jutel M, Pfaar O, et al. The role of mobile health technologies in stratifying patients for AIT and its cessation. The ARIA-EAACI perspective. *J Allergy Clin Immunol Pract.* 2021;9(5):1805-1812. doi:10.1016/j.jaip.2021.02.035
 18. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, Endpoint S, and Other Tools) Resource.* FDA-NIH Biomarker Working Group; 2016.
 19. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69(3):89-95.
 20. Goldsack JC, Coravos A, Bakker JP, et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for biometric monitoring technologies (BioMeTs). *NPJ Digit Med.* 2020;3:55. doi:10.1038/s41746-020-0260-4
 21. Hodgson DR, Whittaker RD, Herath A, Amakye D, Clack G. Biomarkers in oncology drug development. *Mol Oncol.* 2009;3(1):24-32. doi:10.1016/j.molonc.2008.12.002
 22. U.S. Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Final guidance document. <https://www.fda.gov/media/139088/download> 2020.
 23. Vasudevan S, Saha A, Tarver ME, Patel B. Digital biomarkers: convergence of digital health technologies and biomarkers. *NPJ Digit Med.* 2022;5(1):36. doi:10.1038/s41746-022-00583-z
 24. Pepin JL, Degano B, Tamiés R, Viglino D. Remote monitoring for prediction and Management of Acute Exacerbations in chronic obstructive pulmonary disease (AECOPD). *Life (Basel).* 2022;12(4):499. doi:10.3390/life12040499
 25. Ku JP, Sim I. Mobile health: making the leap to research and clinics. *NPJ Digit Med.* 2021;4(1):83. doi:10.1038/s41746-021-00454-z
 26. Sim I. Mobile Devices and Health. *N Engl J Med.* 2019;381(10):956-968. doi:10.1056/NEJMra1806949
 27. Paving the way for personalized medicine, FDA's role in a new era of medical product development. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421pdf> 2013.
 28. Canonica GW, Bachert C, Hellings P, et al. Allergen immunotherapy (AIT): a prototype of precision medicine. *World Allergy Organ J.* 2015;8(1):31. doi:10.1186/s40413-015-0079-7
 29. Bousquet J, Pfaar O, Togias A, et al. 2019 ARIA Care pathways for allergen immunotherapy. *Allergy.* 2019;74(11):2087-2102. doi:10.1111/all.13805
 30. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol.* 2019;144(1):1-12. doi:10.1016/j.jaci.2019.05.031
 31. Louis R, Bureau F, Desmet CJ. Advances toward precision medicine for asthma. *Biochem Pharmacol.* 2020;179:114081. doi:10.1016/j.bcp.2020.114081
 32. Salter B, Lacy P, Mukherjee M. Biologics in asthma: a molecular perspective to precision medicine. *Front Pharmacol.* 2021;12:793409. doi:10.3389/fphar.2021.793409
 33. Type 2 diabetes in adults: management. NICE Diabetes Guidance. <https://www.guidelinesco.uk/diabetes/nice-type-2-diabetes-guide/line/252691article>. 2022.
 34. American Diabetes Association. 6. Glycemic targets: standards of medical care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S61-S70. doi:10.2337/dc19-S006
 35. van der Leeuw S, van der Molen T, Dekhuijzen PN, et al. The minimal clinically important difference of the control of allergic rhinitis and asthma test (CARAT): cross-cultural validation and relation with pollen counts. *NPJ Prim Care Respir Med.* 2015;25:14107. doi:10.1038/nppjpcrm.2014.107
 36. Linhares DV, da Fonseca JA, Borrego LM, et al. Validation of control of allergic rhinitis and asthma test for children (CARATKids)—a prospective multicenter study. *Pediatr Allergy Immunol.* 2014;25(2):173-179. doi:10.1111/pai.12218
 37. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy.* 2010;65(8):1042-1048. doi:10.1111/j.1398-9995.2009.02310.x
 38. Wang Y, Chen H, Zhu R, et al. Allergic rhinitis control test questionnaire-driven stepwise strategy to improve allergic rhinitis control: a prospective study. *Allergy.* 2016;71(11):1612-1619. doi:10.1111/all.12963
 39. Nathan RA, Dalal AA, Stanford RH, et al. Qualitative development of the rhinitis control assessment test (RCAT), an instrument for evaluating rhinitis symptom control. *Patient.* 2010;3(2):91-99. doi:10.2165/11318410-000000000-00000
 40. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999;14(4):902-907. doi:10.1034/j.1399-3003.1999.14d29.x
 41. Schatz M, Sorkness CA, Li JT, et al. Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol.* 2006;117(3):549-556. doi:10.1016/j.jaci.2006.01.011
 42. Sousa-Pinto B, Azevedo LF, Jutel M, et al. Development and validation of combined symptom-medication scores for allergic rhinitis. *Allergy.* 2022;77(7):2147-2162. doi:10.1111/all.15199
 43. Anto A, Sousa-Pinto B, Czarlewski W, et al. Automatic market research of mobile health apps for the self-management of allergic rhinitis. *Clin Exp Allergy.* 2022;52(10):1195-1207. doi:10.1111/cea.14135
 44. Bastl K, Berger U, Kmenta M. Evaluation of pollen apps forecasts: the need for quality control in an eHealth service. *J Med Internet Res.* 2017;19(5):e152. doi:10.2196/jmir.7426
 45. Bastl M, Bastl K, Dirr L, Berger M, Berger U. Variability of grass pollen allergy symptoms throughout the season: comparing symptom data profiles from the Patient's Hayfever diary from 2014 to 2016 in Vienna (Austria). *World Allergy Organ J.* 2021;14(3):100518. doi:10.1016/j.waojou.2021.100518
 46. Dramburg S, Perna S, Di Fraia M, et al. Heterogeneous validity of daily data on symptoms of seasonal allergic rhinitis recorded by patients using the e-diary AllergyMonitor(R). *Clin Transl Allergy.* 2021;11(10):e12084. doi:10.1002/ct2.12084
 47. Tripodi S, Giannone A, Sfika I, et al. Digital technologies for an improved management of respiratory allergic diseases: 10 years of clinical studies using an online platform for patients and physicians. *Ital J Pediatr.* 2020;46(1):105. doi:10.1186/s13052-020-00870-z
 48. Sousa-Pinto B, Anto A, Berger M, et al. Real-world data using mHealth apps in rhinitis, rhinosinusitis and their multimorbidities. *Clin Transl Allergy.* 2022;12(11):e12208. doi:10.1002/ct2.12208
 49. Moore A, Preece A, Sharma R, et al. A randomised controlled trial of the effect of a connected inhaler system on medication adherence in uncontrolled asthmatic patients. *Eur Respir J.* 2021;57(6):2003103. doi:10.1183/13993003.03103-2020
 50. Mosnaim GS, Stempel DA, Gonzalez C, et al. The impact of patient self-monitoring via electronic medication monitor and Mobile app plus remote clinician feedback on adherence to inhaled corticosteroids: a randomized controlled trial. *J Allergy Clin Immunol Pract.* 2021;9(4):1586-1594. doi:10.1016/j.jaip.2020.10.064

51. Mosnaim GS, Stempel DA, Gonzalez C, et al. Electronic medication monitoring versus self-reported use of inhaled corticosteroids and short-acting beta2-agonists in uncontrolled asthma. *J Asthma*. 2022;59(10):2024-2027. doi:10.1080/02770903.2021.1996600
52. Sousa-Pinto B, Sa-Sousa A, Amaral R, et al. Assessment of the control of allergic rhinitis and asthma test (CARAT) using MASK-air. *J Allergy Clin Immunol Pract*. 2022;10(1):343-345.e2. doi:10.1016/j.jaip.2021.09.012
53. Bousquet J, Devillier P, Anto JM, et al. Daily allergic multimorbidity in rhinitis using mobile technology: a novel concept of the MASK study. *Allergy*. 2018;73(8):1622-1631. doi:10.1111/all.13448
54. Bousquet J, Devillier P, Arnavielhe S, et al. Treatment of allergic rhinitis using mobile technology with real-world data: the MASK observational pilot study. *Allergy*. 2018;73(9):1763-1774. doi:10.1111/all.13406
55. Bedard A, Anto JM, Fonseca JA, et al. Correlation between work impairment, scores of rhinitis severity and asthma using the MASK-air(R) app. *Allergy*. 2020;75(7):1672-1688. doi:10.1111/all.14204
56. Bedard A, Basagana X, Anto JM, et al. Treatment of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study. *Clin Transl Allergy*. 2020;10(1):62. doi:10.1186/s13601-020-00342-x
57. Bedard A, Sofiev M, Arnavielhe S, et al. Interactions between air pollution and pollen season for rhinitis using Mobile technology: a MASK-POLLAR study. *J Allergy Clin Immunol Pract*. 2020;8(3):1063-1073.e4. doi:10.1016/j.jaip.2019.11.022
58. Sousa-Pinto B, Schunemann HJ, Sa-Sousa A, et al. Consistent trajectories of rhinitis control and treatment in 16,177 weeks: the MASK-air(R) longitudinal study. *Allergy*. 2022;78:968-983. doi:10.1111/all.15574
59. Bousquet J, Agache I, Aliberti MR, et al. Transfer of innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA) - EIP on AHA Twinning Reference Site (GARD research demonstration project). *Allergy*. 2017;73(1):77-92. doi:10.1111/all.13218
60. Courbis AL, Murray RB, Arnavielhe S, et al. Electronic clinical decision support system for allergic rhinitis management: MASK e-CDSS. *Clin Exp Allergy*. 2018;48(12):1640-1653. doi:10.1111/cea.13230
61. Sofiev M, Palamarchuk Y, Bedard A, et al. A demonstration project of global Alliance against chronic respiratory diseases: prediction of interactions between air pollution and allergen exposure-the Mobile airways sentinel Network-impact of air POLLution on asthma and rhinitis approach. *Chin Med J (Engl)*. 2020;133(13):1561-1567. doi:10.1097/CM9.0000000000000916
62. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights*. 2013;6:61-68. doi:10.4137/HSI.S11093
63. Kluzek S, Dean B, Wartolowska KA. Patient-reported outcome measures (PROMs) as proof of treatment efficacy. *BMJ Evid Based Med*. 2022;27(3):153-155. doi:10.1136/bmjebm-2020-111573
64. Bousquet J, Arnavielhe S, Bedbrook A, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. *Clin Transl Allergy*. 2018;8:45. doi:10.1186/s13601-018-0227-6
65. Sousa-Pinto B, Fonseca JA, Gemicoglu B, et al. Patient-reported outcome measures (PROMs) using the MASK-air(R) app in severe asthma. *Allergy*. 2022;77(5):1600-1602. doi:10.1111/all.15248
66. Bousquet J, Bewick M, Arnavielhe S, et al. Work productivity in rhinitis using cell phones: the MASK pilot study. *Allergy*. 2017;72(10):1475-1484. doi:10.1111/all.13177
67. Vandenplas O, Suarathana E, Riffart C, Lemiere C, Le Moual N, Bousquet J. The impact of work-related rhinitis on quality of life and work productivity: a general workforce-based survey. *J Allergy Clin Immunol Pract*. 2020;8:1583-1591.e5. doi:10.1016/j.jaip.2019.12.033
68. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: the MASK study. *J Allergy Clin Immunol*. 2019;144(1):135-143.e6. doi:10.1016/j.jaci.2019.01.053
69. Sousa-Pinto B, Filipe Azevedo L, Jutel M, et al. Development and validation of combined symptom-medication scores for allergic rhinitis. *Allergy*. 2021;77:2147-2162. doi:10.1111/all.15199
70. International Classification of Functioning, Disability and Health (ICF). <https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health>. World Health Organization; 2011.
71. Woo S, Kim S. Determination of cutoff values for biomarkers in clinical studies. *Precis Future Med*. 2020;4(1):2-8.
72. Baiardini I, Pasquali M, Giardini A, et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy*. 2003;58(4):289-294. doi:10.1034/j.1398-9995.2003.00079.x
73. Baiardini I, Fasola S, La Grutta S, Trucco E, Canonica GW, Braidò F. Rhinitis and asthma patient perspective (RAPP): clinical utility and predictive value. *J Allergy Clin Immunol Pract*. 2022;10(3):846-852.e1. doi:10.1016/j.jaip.2021.10.025
74. Ansotegui IJ, Braidò F, Molinengo G, et al. Cross-cultural adaptation and validation of the RhinAsthma patient perspective (RAPP) in Spanish. *Allergol Immunopathol (Madr)*. 2020;48(2):165-169. doi:10.1016/j.aller.2019.07.006
75. Todo-Bom A, Braidò F, Molinengo G, Loureiro C, Canonica GW, Baiardini I. The Portuguese version of rhinitis and asthma Patient's perspective (RAPP): validation and assessment. *Pulmonology*. 2020;26(2):73-77. doi:10.1016/j.pulmoe.2018.10.009
76. Lim MC, Baiardini I, Molinengo G, Navarro-Locsin CG, Canonica GW, Braidò F. The cross-cultural validation of the English version of RhinAsthma patient's perspective (RAPP). *J Asthma*. 2020;57(6):680-686. doi:10.1080/02770903.2019.1590595
77. Kupczyk M, Baiardini I, Molinengo G, et al. Cross-cultural adaptation and validation of the RhinAsthma patient perspective (RAPP) in the polish population. *Postepy Dermatol Alergol*. 2020;37(1):97-102. doi:10.5114/ada.2020.93387
78. Fasola S, Montalbano L, Ferrante G, et al. RAPP-children: a new tool for assessing quality of life in patients with asthma and rhinitis. *Clin Exp Allergy*. 2020;50(6):662-671. doi:10.1111/cea.13599
79. Molinengo G, Baiardini I, Braidò F, Loera B. RhinAsthma patient perspective: a Rasch validation study. *J Asthma*. 2018;55(2):119-123. doi:10.1080/02770903.2017.1316391
80. Braidò F, Baiardini I, Stagi E, et al. RhinAsthma patient perspective: a short daily asthma and rhinitis QoL assessment. *Allergy*. 2012;67(11):1443-1450. doi:10.1111/all.12014
81. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mosges R, Kleine-Tebbe J. Clinical trials in allergen immunotherapy: current concepts and future needs. *Allergy*. 2018;73(9):1775-1783. doi:10.1111/all.13429
82. Bousquet J, VandenPlas O, Bewick M, et al. The work productivity and activity impairment allergic specific (WPAI-AS) questionnaire using Mobile technology: the MASK study. *J Invest Allergol Clin Immunol*. 2018;28(1):42-44. doi:10.18176/jiaci.0197
83. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. *Appl Health Econ Health Policy*. 2017;15(2):127-137. doi:10.1007/s40258-017-0310-5
84. Remenschneider AK, Scangas G, Meier JC, et al. EQ-5D-derived health utility values in patients undergoing surgery for chronic rhinosinusitis. *Laryngoscope*. 2015;125(5):1056-1061. doi:10.1002/lary.25054
85. Sousa-Pinto B, Azevedo LF, Sa-Sousa A, et al. Allergen immunotherapy in MASK-air users in real-life: results of a Bayesian mixed-effects model. *Clin Transl Allergy*. 2022;12(3):e12128. doi:10.1002/ct2.12128
86. Sousa-Pinto B, Schunemann HJ, Sa-Sousa A, et al. Comparison of rhinitis treatments using MASK-air(R) data and considering

- the minimal important difference. *Allergy*. 2022;77:3002-3014. doi:10.1111/all.15371
87. Sastre J, Del Cuvillo A, Colas C, et al. Validation of the MASK-air app for assessment of allergic rhinitis. *Allergy*. 2020;75(11):2958-2961. doi:10.1111/all.14415
 88. Vieira R, Sousa-Pinto B, Cardoso-Fernandes A, et al. The control of allergic rhinitis and asthma test (CARAT): a systematic review of its measurement properties and COSMIN analysis. *Clin Transl Allergy*. 2022;12:e12194.
 89. Azevedo P, Correia de Sousa J, Bousquet J, et al. control of allergic rhinitis and asthma test (CARAT): dissemination and applications in primary care. *Prim Care Respir J*. 2013;22(1):112-116. doi:10.4104/pcrj.2013.00012
 90. Domingues M, Amaral R, Fonseca JA, Azevedo P, Correia-de-Sousa J. Assessment of asthma control using CARAT in patients with and without allergic rhinitis: a pilot study in primary care. *Rev Port Pneumol*. 2016;22(3):163-166. doi:10.1016/j.rppnen.2015.10.014
 91. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Control of allergic rhinitis and asthma test (CARAT) can be used to assess individual patients over time. *Clin Transl Allergy*. 2012;2(1):16. doi:10.1186/2045-7022-2-16
 92. Jacome C, Pereira R, Almeida R, et al. Validation of app and phone versions of the control of allergic rhinitis and asthma test (CARAT). *J Investig Allergol Clin Immunol*. 2021;31(3):270-273. doi:10.18176/jiaci.0640
 93. Amaral R, Jacome C, Almeida R, et al. Profiling persistent asthma phenotypes in adolescents: a longitudinal diagnostic evaluation from the INSPIRERS studies. *Int J Environ Res Public Health*. 2021;18(3):1015. doi:10.3390/ijerph18031015
 94. Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021: executive summary and rationale for key changes. *Eur Respir J*. 2022;59(1):2102730. doi:10.1183/13993003.02730-2021
 95. Bissell K, Ellwood P, Ellwood E, et al. Essential medicines at the National Level: the global asthma Network's essential asthma medicines survey 2014. *Int J Environ Res Public Health*. 2019;16(4):605. doi:10.3390/ijerph16040605
 96. Bousquet JJ, Schunemann HJ, Togias A, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. *Clin Transl Allergy*. 2019;9:44. doi:10.1186/s13601-019-0279-2
 97. Quirce S, Sastre J. Occupational asthma: clinical phenotypes, biomarkers, and management. *Curr Opin Pulm Med*. 2019;25(1):59-63. doi:10.1097/MCP.0000000000000535
 98. Vandenplas O, Godet J, Hurdubaea L, et al. Severe occupational asthma: insights from a multicenter European cohort. *J Allergy Clin Immunol Pract*. 2019;7(7):2309-2318.e4. doi:10.1016/j.jaip.2019.03.017
 99. Kwon JH, Wi CI, Seol HY, et al. Risk, mechanisms and implications of asthma-associated infectious and inflammatory multimorbidities (AIMs) among individuals with asthma: a systematic review and a case study. *Allergy Asthma Immunol Res*. 2021;13(5):697-718. doi:10.4168/aaair.2021.13.5.697
 100. Tsang KCH, Pinnock H, Wilson AM, Shah SA. Application of machine learning algorithms for asthma management with mHealth: a clinical review. *J Asthma Allergy*. 2022;15:855-873. doi:10.2147/JAA.S285742
 101. Caimmi D, Baiz N, Tanno LK, et al. Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control. *Clin Exp Allergy*. 2017;47(12):1526-1533. doi:10.1111/cea.13025
 102. Sousa-Pinto B, Eklund P, Pfaar O, et al. Validity, reliability, and responsiveness of daily monitoring visual analog scales in MASK-air(R). *Clin Transl Allergy*. 2021;11(7):e12062. doi:10.1002/ctt2.12062
 103. Dunn A, Heggstad E, Shanock L, Theilgard N. Intra-individual response variability as an indicator of insufficient effort responding: comparison to other indicators and relationships with individual differences. *J Business Psychol*. 2018;33(1):105-121.
 104. Bousquet J, Arnavielhe S, Bedbrook A, et al. The allergic rhinitis and its impact on asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: the MASK study. *Allergy*. 2018;73(2):505-510. doi:10.1111/all.13307
 105. Bakdash JZ, Marusich LR. Repeated measures correlation. *Front Psychol*. 2017;8:456. doi:10.3389/fpsyg.2017.00456
 106. Type 2 diabetes in adults: management. NICE guideline [NG28]. <https://www.nice.org.uk/guidance/ng28/chapter/Recommendations>
 107. Vieira RJ, Pham-Thi N, Anto JM, et al. Academic productivity of Young people with allergic rhinitis: a MASK-air study. *J Allergy Clin Immunol Pract*. 2022;10(11):3008-3017.e4. doi:10.1016/j.jaip.2022.08.015
 108. Vieira RJ, Sousa-Pinto B, Cardoso-Fernandes A, et al. Control of allergic rhinitis and asthma test: a systematic review of measurement properties and COSMIN analysis. *Clin Transl Allergy*. 2022;12(9):e12194. doi:10.1002/ctt2.12194

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bousquet J, Shamji MH, Anto JM, et al. Patient-centered digital biomarkers for allergic respiratory diseases and asthma: The ARIA-EAACI approach – ARIA-EAACI Task Force Report. *Allergy*. 2023;78:1758-1776. doi:10.1111/all.15740