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Patient-centred digital biomarkers for allergic respiratory diseases and asthma: the ARIA-EAACI approach

ARIA-EAACI Task Force Report

Short title: Digital biomarkers in rhinitis and asthma

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Summary

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 centre of the health system and is likely to optimise the practice of allergy. ARIA (Allergic Rhinitis and its Impact on Asthma) 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, randomised 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, were 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.

Key words: ARIA, EAACI, digital health, apps, rhinitis, asthma

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
COA: Clinical outcome assessment
CSMS: ARIA-EAACI allergy Combined Symptom-Medication Score
COSMIN: CONsensus-based Standards for the selection of health status Measurement INSTRuments
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
mCSMS: Modified CSMS
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO: Patient-reported outcome
PROM: Patient-reported outcome measure
RAPP: RhinAsthma Patient Perspective
SMS: Symptom-medication score
TF: Task Force

VAS: Visual analogue scale

WPAI:AS: Work Productivity and Activity Impairment: Allergy Specific

WHO: World Health Organization

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 centre of the health system and is likely to optimise the practice of medicine.^{15,16} Biomarkers associated with mHealth and clinical decision support systems (CDSS) 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).

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
- Randomised controlled trials
- Observational real-life studies
- Epidemiologic studies
- Challenges

More specifically, two sets of digital biomarkers have been proposed to mimic the diabetes approach^{18,19}

- Equivalent to glycemia: daily electronic combined symptom-medication score for rhinitis (combined symptom-medication score, ARIA-EAACI 2021 TF: Combined-medication scores (CSMS) ^{20,21}) and asthma (Electronic daily asthma control score: e-DASTHMA)
- Equivalent to Hb1ac: monthly evaluation of rhinitis and asthma control (CARAT) ²²
- 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, e-DASTHMA: Electronic daily symptom medication score in asthma, Hb1ac: glycated haemoglobin, RAPP: RhinAsthma Patient Perspective, TF: Task Force, VAS: visual analogue scale

1. Background

1.1. 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” ²³ (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. ²⁴ Biomarkers can be used individually or in combination. However, to be used in clinical practice, biomarkers need to be validated. ²⁵ 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. ²⁶

“In line with the BEST definition and in a guidance document, ²⁷ 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 ». ²⁷ 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. ²⁸ With advancements in digitalisation 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.

28

Digital biomarkers have the potential to improve diagnosis as well as to continually monitor patient health, accurately predict outcomes and rapidly assess exacerbations. ²⁹ 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. ³⁰ 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).³¹

1.2. Biomarkers in precision medicine of allergic diseases

Precision medicine aims to customise 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.³² 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 centred.

In allergic diseases, the role of precision medicine in selecting an allergen immunotherapy (AIT) regimen was proposed by an expert meeting³³ and expanded in the ARIA care pathways for AIT.^{11,34} 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.³⁵⁻³⁷ 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.^{19,38}

- Daily control monitoring is assessed using glycemia measurement, and longer-term monitoring using glycated haemoglobin (Hb1ac) measurement. It is recommended that both tests are required to optimise diabetes treatment. By analogy with the diabetes approach, two types of patient-centred 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)³⁹⁻⁴¹ 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 Test⁴², Rhinitis Control Assessment Test⁴³) or asthma (e.g., Asthma Control Questionnaire - ACQ,⁴⁴) control questionnaires are based on a one-week recall period. The Asthma Control Test – ACT was based on a 4-week recall.⁴⁵

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 Symptom-Medication Score (CSMS)²¹ or the electronic daily asthma control score (e-DASTHMA, submitted).

2. Methods used to develop the Task Force

2.1. Steps for the development of the Task Force

The TF was initiated following the concept proposed in ARIA care pathways on allergen immunotherapy (Figure 2).³⁴ It was then developed, revised and submitted to the ARIA Task Force (Online supplement)

2.2. Selection of the app

In rhinitis, an automatic market research was carried out.⁴⁶ 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^{47,48} (mainly focusing on pollen and unable to develop a CSMS) and AllergyMonitor[®]^{49,50} 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.⁵¹

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 Asthma Control Test (ACT) as well as a connected inhaler system (cost around 80\$). However, it does not include daily symptoms.⁵²⁻⁵⁴ The other apps do not appear to be sufficiently validated and/or data have not been published in peer-reviewed journals.⁵¹

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.⁵⁵ The results of this TF can however be used by other apps to develop the ARIA-EAACI approach.

3. The ARIA-EAACI approach using the MASK-air[®] app in allergic rhinitis

3.1. Limitations and strengths of MASK-air[®] (online Annex 1)

3.1.1. 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 characterisation 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 studies⁵⁶⁻⁶⁰ and has brought 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.⁶¹

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

3.1.2. Strengths

Overall, MASK-air[®] has several strengths: Low cost, quickly available data, 50,000 users from 29 countries (20 languages) and inter-operable with a web-based physician's questionnaire⁶² and an e-CDSS for AR.⁶³ (Figure 3).

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.^{60,64} 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-centred care and a candidate Good Practice of OECD (Organisation 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 8,000. In asthma, all categories of patients are included and the database can be used to compare asthmatics of different severity grade.

3.1.3. 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 utilisation (EQ-5D dimensions) and potential benefits of expensive treatments such as allergen immunotherapy and biologics. Combining the results of these tools, a monetary value will be ascribed to the allergy-CSMS and to e-DASTHMA.

3.2. Development of patient-reported outcome measures (PROMs)

3.2.1. Definitions of PROMs

There is an increased focus on placing patients at the centre 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.⁶⁵ 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 behaviours such as anxiety and depression.⁶⁵ PROMs provide important indicators of treatment efficacy not captured by objective markers or clinical assessments.⁶⁶ 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.⁶⁶

3.2.2. 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).

3.2.3. 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 or⁶⁷ asthma symptoms,⁶⁸ dyspnea as well as impact of allergy on work^{58,69} and sleep.

All PROMs are highly correlated (Figure 4)^{57,59,69-72} and these correlations are unlikely to be explained by a low quality of data arising from repeated VAS measures.⁵⁸ 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.

3.2.4. Validation of the VAS scales

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

3.2.5. PROMs cut-off values (online annex 2)

In clinical and epidemiological studies, PROM cut-offs can be used to classify patients into groups of statistical and clinical relevance. The MASK-air® cut-offs for the different VASs have been arbitrarily defined according to the International Classification of Functioning, Disability and Health ICF grading.⁷³ Four cut-offs have been defined for all five VASs: 0/100 (full control), 1-19/100 (good control), 20-49/100 (partial control) and $\geq 50/100$ (poor control).

There are two statistical approaches for determining a cut-off value: percentile-oriented (i.e., “PROM distribution-oriented”) and outcome-oriented.⁷⁴ In a cross-sectional study design of 395,223 days from 23,201 MASK-air® participants, cut-offs for VAS global, nasal, ocular and asthma symptoms were assessed using outcome-oriented approaches. The proposed cut-off differentiating “controlled” and “partly-controlled” patients was similar to the arbitrary cut-off value (20/100).⁶⁷ However, a lower cut-off was obtained to differentiate between “partly-controlled” and “uncontrolled” patients (35/100 *versus* the arbitrary value of 50/100) for VAS global, nose, eye and asthma.

3.2.6. Quality-of-life biomarkers

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

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 standardised HRQoL measurement in patients with asthma and comorbid allergic rhinitis in clinical practice.⁷⁵⁻⁸³ 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.

3.3. ARIA-EAACI-allergy-CSMS (Combined Symptom-Medication Score)²¹(Online Annex 3)

Validated combined symptom-medication scores (CSMSs) are needed to investigate the effects of allergic rhinitis treatments.⁸⁴

MASK-air® data assessed the concurrent validity, test-retest reliability and responsiveness of several hypothesis 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®,^{58,69} Work Productivity and Activity Impairment: Allergy Specific [WPAI:AS]),⁸⁵ (ii) quality-of-life (EQ-5D VAS)^{86,87} and (iii) control of allergic diseases (CARAT).²¹

317,176 days of MASK-air® use were assessed from 17,780 users in 25 countries.²¹ (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.^{88,89} The allergy-CSMS provided a better discrimination between treatments than VAS global or VAS nose.

3.4. Potential impact of the ARIA-EAACI allergy-CSMS in allergic diseases

3.4.1. Overall impact

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

Importantly, the allergy-CSMS is centred 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^{58,69,85}).

3.4.2. Implication in allergen immunotherapy (AIT)

In AIT, the allergy-CSMS can be used to (i) stratify patients (uncontrolled days during the allergen exposure, e.g., 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 one month of survey.

4- The ARIA-EAACI approach using the MASK-air[®] app in asthma

4.1. PROMs

4.1.1. Visual analogue scales for asthma

PROMs for asthma have also been evaluated.^{55,68} 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).

The cut-off 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).

4.1.2. 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.⁹⁰ There was a significant correlation between VAS asthma and the ACT score (Pearson -0.79132, $p < 0.0001$).

4.1.3. 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.^{39-41,55,91-95} 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 intraclass 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 (absolute Spearman correlation coefficients range: 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.

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

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

4.2.2. 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 dyspnoea 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 to 0.68). They displayed high test-retest reliability and moderate-to-high responsiveness (Figure 8).

4.2.3. 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.⁹⁶ 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 of patients with uncontrolled/partly-controlled asthma (AUC-ROC=0.74; 95%CI=0.68;0.78).

4.3. 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 cut-offs 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 2A), e-DASTHMA values will be refined (Figure 9).

4.4. Application to the treatment of mild/moderate asthma

Among other possible studies, one is of particular importance. In mild to moderate asthma, PRN PRN: (*Pro re nata*, as needed) treatment with formoterol/ICS (inhaled corticosteroids) combination is favoured to short-acting β -agonists (LABAs).⁹⁷ 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 optimising the WHO essential list of drugs⁹⁸, (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.⁹⁹

5. 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 complicated¹⁰⁰ and they often overlap.⁷⁰

MASK-air[®] can assess days with exposure to work. It can also easily compare the different symptoms during and outside exposure for all three symptoms 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 asthma ¹⁰¹ may be assessed combining e-DASTHMA and CARAT.

6. 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 phenotypes ¹⁰² 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 five 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 generalisability of these studies. ¹⁰³ 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.

Figure 1: Benefits, limitations and risks of digital biomarkers (from ³¹)

Figure 2: Care pathway for allergen immunotherapy (from ³⁴)

Figure 3: Repartition of MASK-air® users (December 2021)

Figure 4: Correlation using the Spearman rank test between some of the MASK-air PROMs
(from ^{58,69,85,104})

Figure 5: Allergy-CSMS

Figure 6: Allergy-CSMS validation in different countries

All: all countries, BR: Brazil, FR: France, GE: Germany, IT: Italy, LT: Lithuania, ME: Mexico, POL: Poland, POR: Portugal, SP: Spain

Figure 7: Applicability of digital biomarkers in AIT for allergic rhinitis

Figure 8: Correlations between e-DASTHMA and comparators

Figure 9: Applicability of digital biomarkers in severe asthma using the diabetes approach

Table 1: e-PROMs in MASK-air

<p>1- Control digital biomarkers</p> <ul style="list-style-type: none"> ○ Daily: validated CSMS (Allergy), e-DASTHMA, VASnose, eye, asthma ○ Monthly: CARAT (A+R), ACT (A) <p>2- QOL digital biomarkers</p> <ul style="list-style-type: none"> ○ Daily: EQ-5D VAS ○ Bi-weekly: Rhinasthma (A+R) <p>3- Impact digital biomarkers</p> <ul style="list-style-type: none"> ○ VAS work ○ VAS school ○ VAS sleep
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Table 2: Methodologic validation of PROMs

Study name	Ref	Type of study	N users	N days	N countries
COSMIN guidelines	¹⁰⁵	Obs, CS-L	2,497	14,612*	15
Test-retest, intra-class coefficient	¹⁰⁶	Obs, CS-L	17,780	317,176	25
Quality of data (intra-individual response variability)	¹⁰⁷	Obs, CS	14,189	205,904	23
Independence of data	¹⁰⁶	Obs, CS	1,136	5,889	18
EQ-5D	^{85,108}	Obs, CS	1,288	NA	18
WPAI:AS	^{85,108}	Obs, CS	1,288	NA	18
CARAT	¹⁰⁹	Obs, CS	1,086	2,042	22

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

Table 3: Allergy-CSMS tested in the study²¹

- 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 EQ5D (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: $Rho = 0.42$, $N = 59,378$).

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- Randomised Controlled Trials (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

Table 5: Correlation coefficients between different PROMs in severe asthma (from ⁶⁸)

	<i>N</i> observations	Spearman correlation coefficient (95% CI)	Repeated measures correlation coefficient (95% CI) ¹¹⁰
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)

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Author contributions

- 1- Oliver Pfaar and Ludger Klimek, Jean Bousquet proposed the study. JB wrote the paper.
- 2- Mohamed H Shamji, Josep M Anto, Joao A Fonseca, Bernardo Sousa-Pinto and Wienczyslaw Czarlewski, we proposed the asthma flow chart for biomarkers.
- 3- Holger J Schünemann and Torsten Zuberbier, we are working on how to integrate the results of the TF in care pathways.
- 4- G. Walter Canonica and Fulvio Braido, we added the quality-of-life proposal.
- 5- The text was then submitted to Anna Bedbrook, Rita Amaral, Ignacio J Ansotegui, Sinthia Bosnic-Anticevich, Claudia Chaves-Loureiro, Bilun Gemiciglu, Tari Haahtela, Marek Kulus, Piotr Kuna, Maciej Kupczyk, Markus Ollert, Frederico S Regateiro, Boleslaw Samolinski, Mikhail Sofiev, Sanna Toppila-Salmi and Arunas Valiulis.

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Fig 1

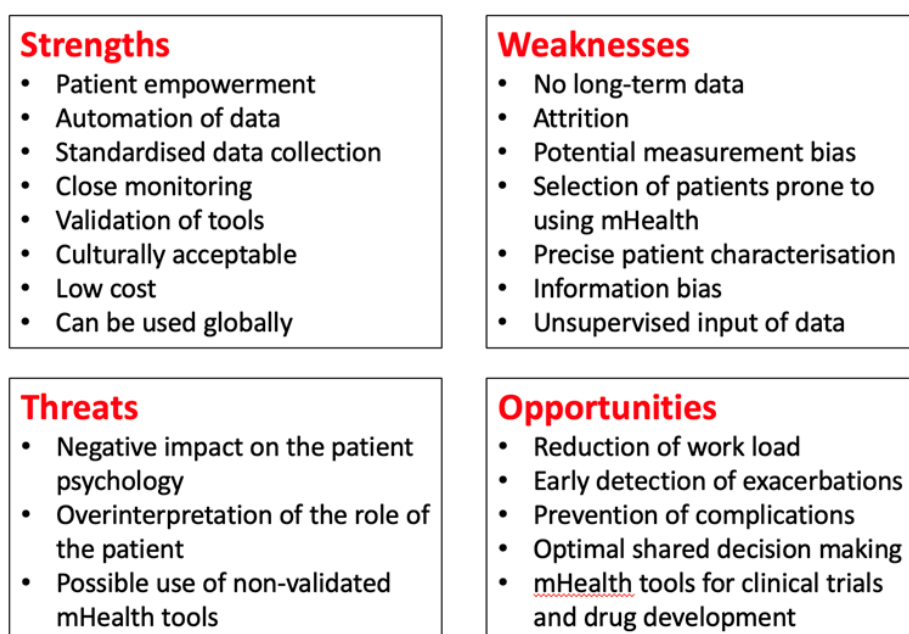


Fig 2

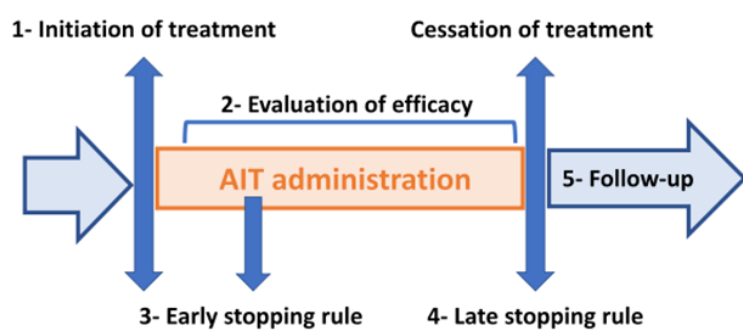


Fig 3

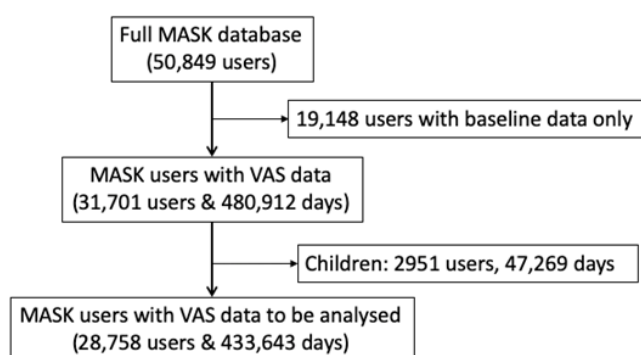


Fig 4

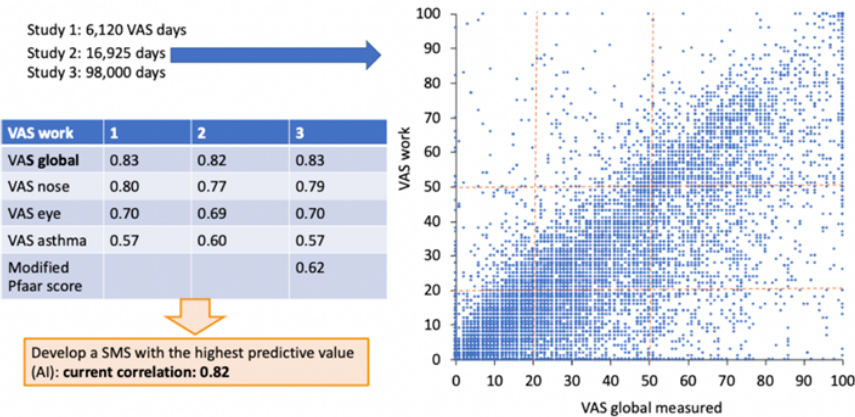


Fig 5

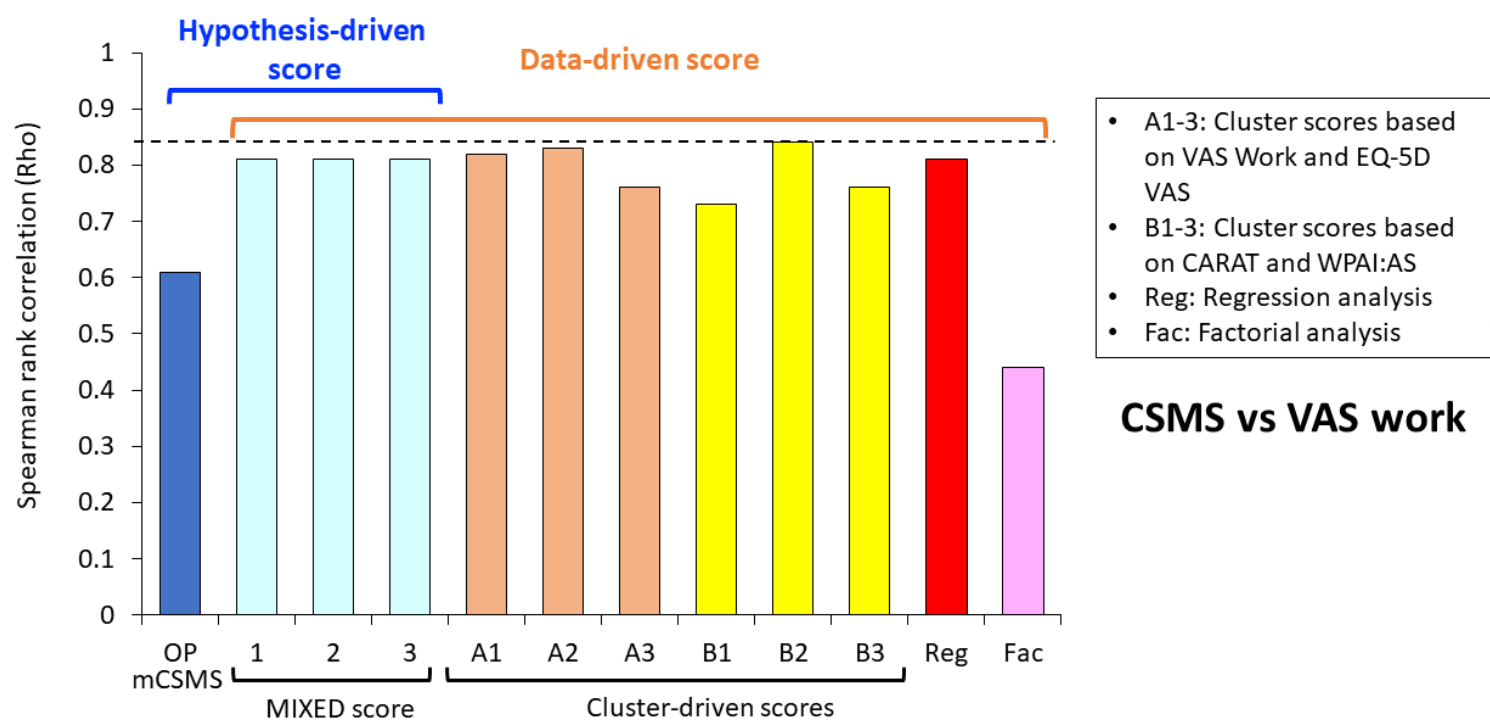


Fig 6

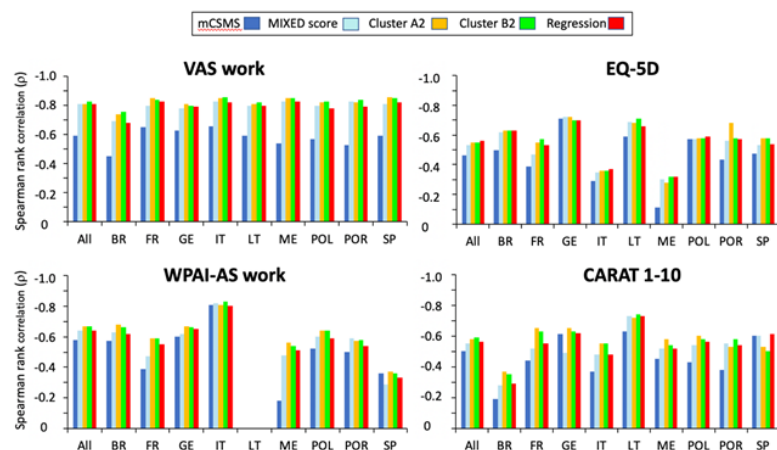


Fig 7

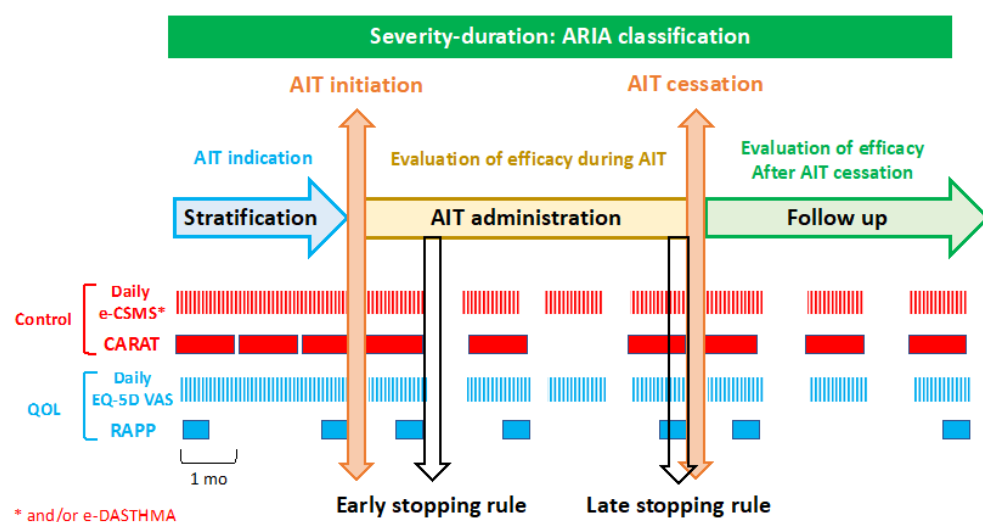


Fig 8

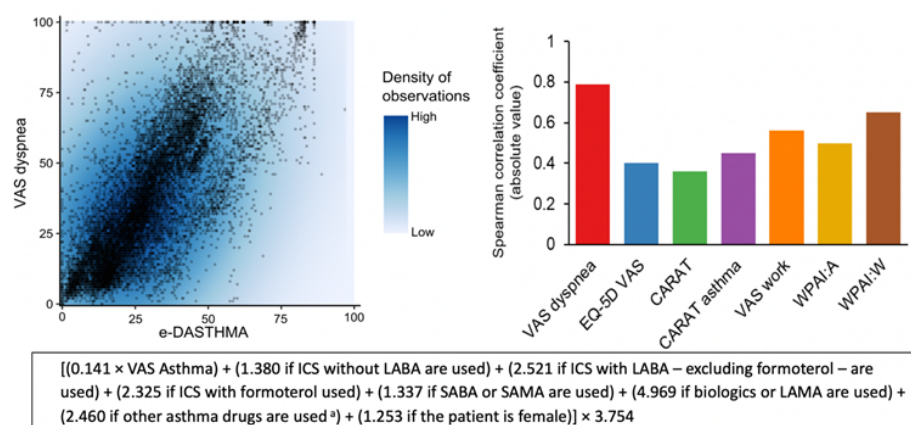


Fig 9

