



How the Smartphone Is Changing Allergy Diagnostics

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Abstract

Purpose of Review Evidence-based clinical diagnosis of allergic disorders is increasingly challenging. Clinical decision support systems implemented in mobile applications (apps) are being developed to assist clinicians in diagnostic decisions at the point of care. We reviewed apps for allergic diseases general diagnosis, diagnostic refinement and diagnostic personalisation. Apps designed for specific medical devices are not addressed.

Recent Findings Apps with potential usefulness in the initial diagnosis and diagnostic refinement of respiratory, food, skin and drug allergies are described. Apps to support diagnostic personalisation are not yet available. There is an urgent need to increase the scientific evidence on the real usefulness of these apps, as well as to develop new scientifically grounded apps designed and validated to support all allergic diseases and diagnostic levels.

Summary Apps have the potential to change the diagnosis of allergic diseases becoming part of the routine diagnostics toolset, but its usefulness needs to be established.

Keywords mHealth · Allergy · Apps · Clinical decision support systems · Diagnosis · Smartphone in medicine

Introduction

Diagnosing [1] allergic disorders depends mostly on clinical history, physical examination, and on the results of complementary exams and patient-reported outcome measures. Traditionally, clinical history data is collected by face-to-face interview relying on patient's memory and personal characteristics and on physician's skills and experience. The

information from the different data sources is then interpreted mostly according to physician's judgement but should account for the available scientific knowledge.

Challenges in Allergy Diagnostics

To make an optimal diagnostic approach, we need a shared understanding of the terms used to define allergic diseases. However, disease definitions and even basic terminology, such as allergy, atopy and hypersensitivity, have been a matter of confusion with varying meanings at different time points and by different specialists [2]. In 2001, a revised nomenclature for allergic and related reactions was published by the European Academy of Allergy and Clinical Immunology (EAACI) [3], to prevent misunderstandings by patients and physicians. It was further revised in 2004 to allow a broader application [4], and it was suggested as a basis for the updates in the new International Classification of Diseases-11 (ICD-11) [5]. However, currently, even this revised nomenclature is being challenged [6].

Disease-specific guidelines that should be a consensual basis for disease diagnosis and management also evolve and, sometimes, diverge from previous or different societies

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recommendations. A striking example is asthma. Global Initiative for Asthma (GINA) 2014 guidelines [7] recognised the heterogeneity of asthma and its many phenotypes, integrating recent evolutions in the disease-related knowledge and diverging from the stricter GINA 2006 [8] asthma definition as a chronic inflammatory disorder of the airways with airway hyperresponsiveness. Also, different current recommendations suggest diverse diagnostic approaches in adults with suspected asthma. National Institute for Health and Care Excellence (NICE) guidelines [9, 10] report that asthma should not be diagnosed based on a single diagnostic test and suggest the use of both spirometry and fractional exhaled nitric oxide (FeNO); conversely, GINA guidelines [11] put the focus on symptoms and demonstration of variable expiratory airflow limitation.

The diverging definitions and diagnostic approaches add to the difficulties of initial allergic disease diagnosis. It is therefore not surprising that allergic diseases are frequently reported as under- [12–16] or overdiagnosed [13, 17–19]. One of the best examples is allergic rhinitis, with estimated proportions of underdiagnosis reaching over 70% in some settings [12, 20–23]. Besides physician's unawareness, also the patient's poor symptom recognition and beliefs [24] may contribute to rhinitis underdiagnosis and undertreatment.

Diagnosing stands for more than just establishing if a disease is present or not. It implies additional classifications regarding different disease characteristics, such as current disease status (e.g., severity, control) or underlying mechanisms (e.g., IgE vs non-IgE mediated). With increasing relevancy in food and respiratory allergies, the identification of specific molecular sensitisations has the potential to be the best current example of diagnostic refinement in allergic diseases [25]. The different classifications needed for each allergic disorder make diagnostic refinement a challenge.

In the last decade, a new focus has emerged: the definition of more comprehensive disease phenotypes leading to diagnostic personalisation. Phenotypes have been described, for example, in rhinitis [26], asthma [27], anaphylaxis [28], angioedema [29] and food allergy [30]. However, these hypothesis-driven phenotypes are not static and can have a high proportion of overlap [31] which render clear-cut definitions difficult [26]. The increasing use of unsupervised clustering methods can minimise these issues [32, 33] and improve diagnostic accuracy. However, their applicability [34] and clinical relevance [35] has been questioned. Indeed, there is no validated, consensual and comprehensive classification in any allergic disorder.

The amount of diverging information and recent evolutions, together with the lack of time to fully apply that information to a specific patient, makes an evidence-based clinical diagnosis of allergic disorders increasingly challenging [36–38]. The recent evolutions in information

technology, especially with the increasing development of clinical decision-support systems (CDSS) have demonstrated potential to improve diagnostic approaches [39, 40].

Smartphone-Based Decision Support in Healthcare

CDSS are computer programs designed to assist health professionals in making diagnostic, therapeutic and prognostic decisions in health care delivery [41]. These systems allow aggregating the characteristics of each patient to a computerised knowledge base, which, through inference mechanisms, generate specific recommendations for each individual. CDSS use has been shown to be an effective strategy for the improvement and optimisation of healthcare delivery [42], although some effects still need to be further studied [43]. CDSS have become increasingly useful for physicians to enhance the quality and safety of healthcare. A survey conceived by the American Medical Association in 2016 showed that 85% out of the 1300 physicians enquired found digital health solutions advantageous to improve patient care, with diagnostic ability, safety and efficiency being considered the three most appealing factors. Indeed, 43% were already using CDSS, and 56% were intending to use [44]. Allergy diagnosis is integrated into several recent CDSS, namely regarding urticaria, food allergy, asthma and allergic rhinitis [45–49].

Being very common, personal, portable and connected, smartphones are very attractive as platforms to be used for modern ubiquitous access to health care and services. Nowadays, CDSS are progressively implemented in mobile Health (mHealth) applications (apps) to facilitate physicians' access to real-time support at the point of care [50]. The globalised use of smartphones, with improved embedded sensors, increased computational power, and lower cost, represents an opportunity for relevant advances in app development. This has created an opportunity not only for the industry to create proprietary apps linked to specific diagnostic devices but also for individual or society-driven app development. Indeed, taking advantage of smartphones to monitor health allows delivering low-cost and easy-to-disseminate tools, especially if only embed sensors are used with no need for additional devices. Around 60% of the adults in Europe have a smartphone, and in the USA, the numbers are also growing for older people [51]. A multicentre survey in the UK found that over 90% of the physicians own a smartphone, 78.3% own medical apps and 89.6% use them as part of their clinical practice [52•].

This review will approach the usefulness of apps in allergic diseases diagnosis considering three levels: in general, initial disease diagnosis, in diagnostic refinement considering standard classification systems and in diagnostic personalisation

(Fig. 1). Mobile applications that depend on the use of a specific device (e.g. MIR Smart One®, GoSpiro®) are not a focus of this review.

General Disease Diagnosis: Which Allergic Disease(s)?

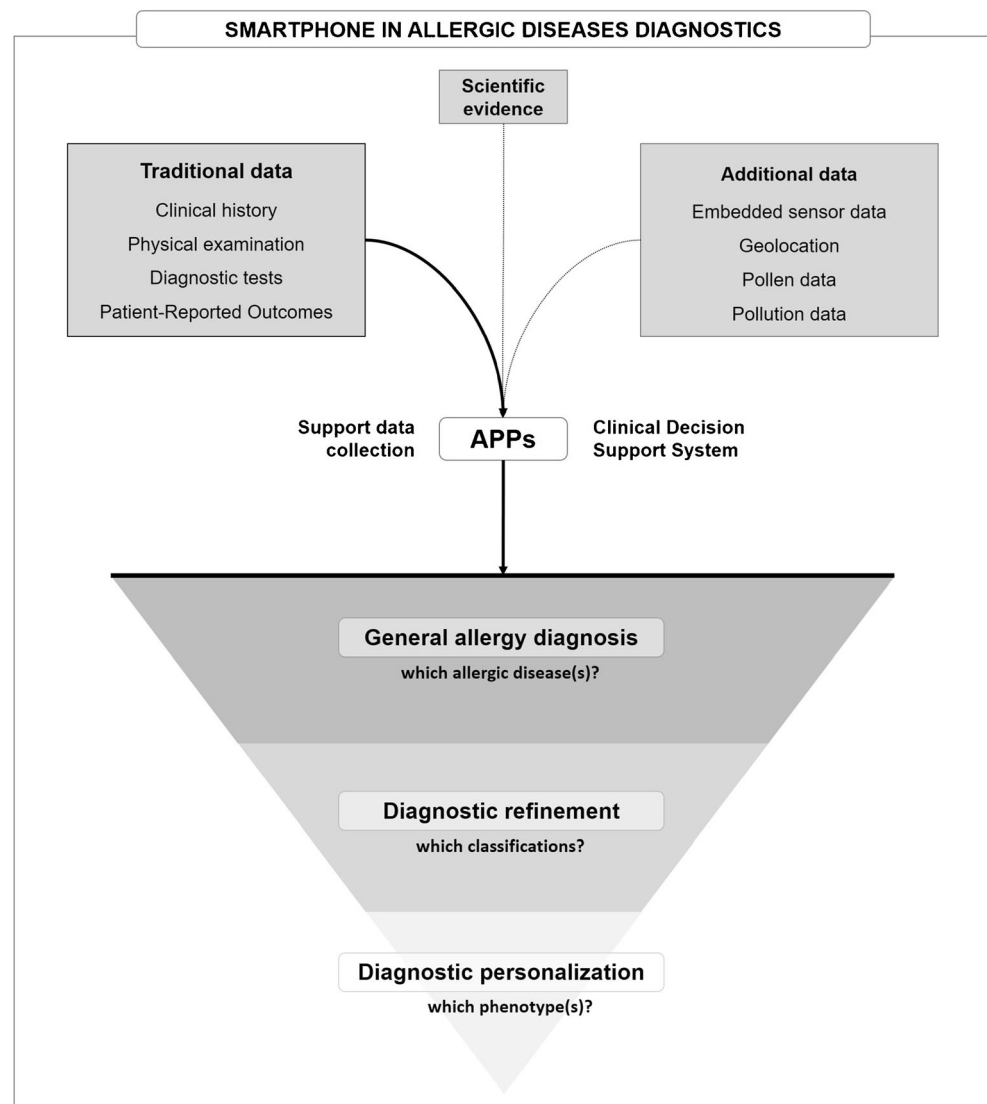
To the best of our knowledge, there are no scientifically validated apps integrating CDSS specifically designed for initial allergy diagnosis. Nevertheless, a few, not fully validated apps and some that were designed with a different primary aim can be useful in the initial screening and diagnosis of allergy.

Apps that enable the patients to record, track and report diet and symptoms have the potential to be used as triage systems for food allergy. A recent study [53] has identified and analysed 77 food allergy apps available at Apple iTunes App Store; 16% were food diaries and 14% symptom trackers.

Apps such as AlliApp: Allergy & Food Diary (<http://www.alliapp.com/#features>) or mySymptoms (<http://skygazerlabs.com/wp/>), which enable the users to keep a daily track of the ingested food and clinical signs and symptoms at the time they happen, can be useful to reveal patterns between diet and food allergy manifestations. mySymptoms additionally is developing a web-based clinician app (mySymptoms Clinic) focused on the secure share of information between patients and healthcare professionals, which can potentially be used to support more effective food allergy diagnosis.

Several available smartphone apps can be used to track peak expiratory flow (PEF) measurements, which may allow the identification of individuals with excessive variability in expiratory airflow [11] and might be useful for initial asthma diagnosis and to identify subjects requiring further diagnostic evaluation including full pulmonary function testing. The most recent systematic content assessment of asthma apps found 24 apps that record PEF measurements [54•]. For

Fig. 1 Smartphone apps can integrate traditional clinical data, scientific evidence and additional data sources, including data collected through the sensors embedded in the smartphone, to support data collection and provide clinical decision support to the proposed three-level allergy diagnostics



example, AsthmaMD (<https://www.asthmamd.org/>) is an app that allows patients to track their PEF and symptoms and provides an action plan for asthma attacks. It also gathers anonymous data for the researchers to understand associations between environmental factors and asthma. Asthma Coach (<http://myhealthapps.net/app/details/317/asthma-coach>), developed by the Asthma Society of Ireland, also allows patients to record and track their PEF together with their symptoms and medication usage. Both apps enable the sharing of PEF values/graph with clinicians. Although they were both primarily designed to track and support self-management of exacerbations in individuals that already have asthma diagnosis, the recorded trends of PEF values can be used to assess previously undiagnosed subjects.

Another app with potential usefulness in the diagnosis of allergic respiratory diseases is ResAppDx (<https://www.resapphealth.com.au/resapp-provides-update-on-australian-study/>). It is being developed for the diagnosis of a broad spectrum of respiratory diseases based on cough-sound analysis, using the smartphone microphone to record and machine-learning algorithms to analyse them [55]. ResAppDx is currently being tested, in the USA, in a prospective study with infants and children with signs or symptoms of respiratory disease [56]. The purpose of this study is to evaluate the efficacy of the app in the diagnosis of childhood acute respiratory diseases, including pneumonia, bronchiolitis, asthma/reactive airways disease, croup, lower respiratory tract disease, viral lower respiratory tract infection and upper respiratory tract disease. However, ResAppDx is not publicly available yet and lacks published evidence. In the next months, it is expected that new data become available on the ability of this app to accurately determine the presence of respiratory diseases, and of asthma in particular.

There are few apps approaching drug allergy diagnosis, and most were developed to assess the causal connection between drugs and their adverse effects. One example is the adverse drug allergy (ADR) causality app [57] that uses the Liverpool ADR causality assessment tool [58] to classify the suspected ADRs as definite, probable, possible or unlikely (https://play.google.com/store/apps/details?id=appinventor.ai_miemaalenovo.AdverseDrugReaction_CausalityAssessment). It was designed for healthcare professional use and, although it intends to classify adverse reactions as a whole (not exclusively allergic or hypersensitivity), it allows to assess the causal probability in suspected allergic reactions to drugs. There are reports of an ongoing prospective paediatric study using this app [59], but we did not find any published validation data yet. Specifically for penicillin allergy, Blumenthal et al. [60•] reported the use of a computerised CDSS implementing a previously tested clinical guideline [61] that aided healthcare providers to stratify patients according to the risk of allergic reaction and then recommended if and how specific beta-lactam antibiotics

should be used. This computerised CDSS improved risk stratification for true penicillin allergy and increased the use of penicillin or cephalosporin overall by nearly twofold when comparing to the standard of care [60•]. In this study, it was tested in a mobile-friendly Web site. Reports on its use as a fully smartphone-based app are still lacking.

We described apps with potential usefulness in the diagnosis of food allergy, respiratory diseases and drug allergy. Most were not specifically designed for diagnosis, and not all are currently publicly available. There is a striking need for new apps specifically developed and validated to support the diagnosis of these and other allergic diseases.

Diagnostic Refinement: Which Classifications?

As diagnosing stands for more than just establishing if a disease is present or not, app contributions for additional classifications regarding different disease characteristics are also appealing for daily practice. No app was specifically designed to support diagnostic refinement. However, some apps primarily developed to support patients' self-monitoring and management can help to refine the initial diagnosis.

There are several apps for self-management of asthma and allergic rhinitis that can support diagnostic refinement by integrating validated questionnaires with cut-offs for established disease classifications. We describe four examples.

InspirerMundi (<https://play.google.com/store/apps/details?id=com.bloomidea.inspirers>) is an asthma self-monitoring app, which assesses patient's treatment adherence rate and disease control using the Control of Allergic Rhinitis and Asthma Test (CARAT) scores [62]. It relies on gamification and on an inhaler usage detection tool to address treatment non-adherence [63]. The monitoring component of this app includes self-reported symptoms and exacerbations, along with CARAT scores and daily/weekly symptom questionnaires. The data on inhaler adherence and disease control over time can be remotely shared with the clinician allowing for improved asthma control and risk classifications. A feasibility prospective observational study is ongoing [64].

The POPET (physician on call patient engagement trial) app allows patients with allergic rhinitis and asthma to access their disease control through the Rhinitis Quality of Life Questionnaire (RQLQ) [65] or Asthma Control Test (ACT) [66]. This app was developed for patients and respective clinicians specifically for POPET studies [67•], as a tool to track patient health status and medication usage and to share motivational and educational content. Patients using the app are also able to submit their overall health status on a 7-point scale, track their medicine use with a diary, share a status update with clinicians, send and receive messages, and ask for immediate assistance with an urgent message option.

Clinicians can review patient health status and medication adherence, answer to patients' messages and send predefined disease/treatment information and motivational nudges. Cingi et al. [67], in a randomised trial, found that patients in the intervention groups, which received the complete app, had better health outcomes and quality of life compared to the control groups, which received an application that did not include the communication, health status or medication usage tracking features [67]. This trial was an important step to demonstrate the value of the POPET app. However, results could have been more fruitful if the value of the app had also been assessed in the perspective of clinicians, namely by evaluating its potential for diagnostic and therapeutic refinement.

Allergy Diary (<http://www.allergydiary.com/allergy-diary-app/>) is a freely available app centred in the patient, designed for monitoring allergic rhinitis and its impact on asthma (ARIA), as part of the MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK) system [68]. It reports allergic rhinitis symptoms impact, medications, ARIA guidelines classification and ARIA score. Its usefulness in assessing allergic rhinitis control and symptoms has been confirmed [69]. Visual analogue scales (VAS) are used to assess the daily impact of nasal, ocular, asthma and overall symptoms, producing a classification concerning the current disease control. The results are displayed in easy-to-read graphs, showing symptom control changes over time. Allergy Diary includes a specific feature for secure data sharing with clinician use at the point of care. In the future, using the included geolocation function, the user will be alerted when his/her specific allergic triggers are being signalled as a problem in that area, by merging the data with other sources of information such as pollen and pollution exposure [70]. Also, the user will be able to compare the level of symptom control with other allergy sufferers in an area. Allergy Diary is being used in the Pollar project which aims to understand the effects of air pollution in allergic rhinitis (<https://www.eithealth.eu/pollar>) [71].

AllergyMonitor (from TPS Production) is an app that allows daily monitoring of respiratory allergic disease severity and symptom scores [72, 73] (<https://play.google.com/store/apps/details?id=com.tpsproduction.allergymonitor&hl=pt>). It has a patient-dedicated front-end and a physician-dedicated back-office where the healthcare provider can register medication and have access to real-time monitoring of patients' symptoms. The front-end app can also be used without back-office input. In AllergyMonitor, the level of symptoms severity is recorded for nasal, ocular and bronchial symptoms, with the use of four different emoticons, each one representing a severity grade (no symptoms, mild, moderate or severe) [73]. Besides symptom severity, it collects data on the global well-being (measured with a VAS) and the impact of allergic diseases on sleep, work/school performance and daily activities. Daily and rescue medication are also recorded. Based on the patient's answers, AllergyMonitor algorithms

automatically produce several symptom scores [73] available as single daily scores or as a slope for a longer observation period. These prospectively recorded symptom scores can be compared with the slopes of locally relevant pollen counts [72, 73] allowing a better assessment of the clinical relevance of different pollens sensitisations. The use of a previous web-based version of AllergyMonitor has shown to improve adherence to nasal steroids [74] and good potential in the forecast of allergic rhinitis symptoms (up to 4 days before the event) using predictive models [75]. AllergyMonitor use as a tool to improve pollen allergy diagnosis and consequent allergen immunotherapy prescription has been described [72] and is now being evaluated in a multicenter observational longitudinal study ongoing in seven southern Europe countries (Portugal, Spain, France, Italy, Albania, Greece and Turkey) [76]. This study will assess the impact in the prescription of allergen immunotherapy of integrating AllergyMonitor data and an innovative component-resolved diagnosis (ESEP, Euroline Southern European Profile test) with traditionally acquired clinical history and skin prick tests results.

Regarding potential app use in the refinement of skin allergy diagnosis, three examples are described below. These apps do not have, yet, published validation data, but they all include validated questionnaires to assess disease severity and/or control.

Patient-Oriented SCORing Atopic Dermatitis (http://www.poscorad.com/page_uk.html), PO-SCORAD app enables patients to fill out the PO-SCORAD index and send it to their clinician. PO-SCORAD is a self-assessment severity score [77] that allows patients/caregivers to comprehensively evaluate the actual course of atopic dermatitis using a tool similar to the one used by their physicians [78]. This index was developed by the European Task Force on Atopic Dermatitis and derived from SCORAD [79], a validated atopic dermatitis severity clinical assessment tool. The graphical visualisation of PO-SCORAD between visits promotes patient empowerment and discussing this data with the clinician might improve diagnostic classification and help shared-decision making.

Eczema Area and Severity Index (EASI) app (<http://www.easicalc.uk/>) is a real-time support tool allowing clinicians to assess the severity of atopic dermatitis. EASI is one of the best-validated outcome instruments for atopic dermatitis [80, 81] and was chosen by the International Harmonising Outcomes Measures in Eczema group to be included in the core outcomes set for clinical trials [82].

The Urticaria app, developed by the Global Allergy and Asthma Patient Platform (<http://www.ga2p2.org/news-research/161-urticaria-app-for-iphone-and-android>), was designed to be used by patients to monitor urticaria severity and control over time. Patient has access to an initial screening test and also to three validated questionnaires that assess the severity and impact of urticaria and angioedema: urticaria

control test [83], 7-day urticaria activity score [84] and the angioedema activity score [85]. Moreover, general information on urticaria and a diary to document the course of the disease (symptoms, severity, medication, triggers, photos) are also available.

The examples of apps for asthma, allergic rhinitis, atopic dermatitis and urticaria presented in this section are data collecting tools of validated classifications over time and can inform clinicians of the patients' status from initial diagnosis onwards. There is an urgent need to increase the scientific evidence on the real usefulness of these apps, as well as to develop scientifically grounded apps for diagnostic refinement concerning other allergic diseases.

Diagnostic Personalization: Which Phenotype(s)?

The path for personalised integrative care management of allergy involves the identification of disease phenotypes through extensive knowledge and a combination of diverse components [26–31]. Diagnostic personalisation is the new challenge in allergy diagnosis, and apps will be on the frontline. In fact, the enhanced embedded sensors and increased computational power of smartphones allow collecting diverse patient information and combining self-reported data with other sources, such as georeferenced environmental factors. This ability to efficiently collect an enormous amount of information gives apps substantial potential both for the identification of new phenotypes at a population level and for the phenotypic classification of individual patients.

App-based data collection allows gathering information from many individuals, which can be used to improve knowledge of disease phenotypes. A recent example is the identification of a previously unrecognised extreme pattern of

uncontrolled disease associated with eye, nose and asthma multimorbidity, using data from Allergy Diary [71•]. However, using unsupervised methods to identify patient clusters within the app-collected data poses additional challenges such as clustering with time-series or missing values imputation that still need to be addressed [86•].

The use of apps to facilitate the classification of the individual patient into a specific phenotype has not explicitly been targeted yet. With the increasing use of unsupervised methods to identify phenotypes, which perform a less physician-friendly patient clustering [34], the development of CDSS that support phenotypic classification readily available in a smartphone-based app has great potential. However, the current lack of consensual phenotypes in the various allergic diseases is a challenge.

Recently, the concept of “treatable traits” has arisen as a new approach to the classification and management of respiratory diseases [87], moving away from the classic diagnostic approach, based on disease identification and strict diagnostic labels [88]. Treatable traits are being discussed as the way to personalised medicine, at least in chronic respiratory diseases [88]. This concept stresses the identification of the pathophysiological mechanisms and factors that contribute to a disease, based on both known phenotypes and endotypes [34, 87]; these identified “traits” should be targeted for treatment. Although a treatable traits approach in respiratory diseases has already been summarised [87], it still needs further appreciation. Moreover, the applicability of this concept to other allergic diseases has not been described. However, with further clarifications of the concept, apps may help its dissemination into routine care.

Apps for diagnostic personalisation, either through phenotype or treatable traits identification, are not yet available to the best of our knowledge. It is believed that they will be the next generation of diagnostic apps and will probably be available soon.

SWOT ANALYSIS: SMARTPHONE-SUPPORTED ALLERGY DIAGNOSIS			
STRENGTHS: - Common, personal, portable, low-cost and connected devices - Improved embedded sensors for data collection - Real-time support at the point of care (CDSS) - Readily available scientific knowledge - Some apps already available		WEAKNESSES: - Few validated apps and studies to assess effect on outcomes - Reliable, standardized information on app features is lacking - Systematic assessment of app data quality is not available - Several apps with published data are not publicly available - No apps available for diagnostic personalization	
OPPORTUNITIES: - Increasing need of CDSS due to the amount of scientific information, physician time pressure and increasing complexity of diagnostic personalization - Diagnostic personalization improvement by the inclusion of data from other sources (e.g. pollen, pollution, sensors) - Apps for the many allergic diseases still not addressed		THREATS: - Evolving nomenclature in allergic diseases - Evolving and diverging allergic disease guidelines - Distinct “traditional” disease classifications - No uniform phenotype classification - Evolving concepts (e.g., treatable traits)	

Fig. 2 A SWOT analysis on the use of smartphones for the diagnosis of allergic diseases. CDSS Clinical Decision Support Systems

Figure 2 presents a SWOT analysis summarising the current scenario on the use of smartphones for the diagnosis of allergic diseases.

Conclusions

Allergy diagnosis is a challenging area, and smartphone apps can facilitate physicians' access to real-time support at the point of care. The apps described can be used to define and refine the diagnosis of respiratory allergic diseases, food, skin and drug allergies, although none has been fully validated to assist in diagnostic decisions. Apps to support diagnostic personalisation are not yet available, but we believe this should be the way forward for the next generation of apps.

The need for more apps is striking, and even though already existent smartphone apps can potentially improve allergy diagnosis, its real usefulness has not been established in real-world studies. New scientifically grounded apps need to be developed and validated, namely to assist diagnosis personalisation. Smartphones and their heirs will become part of our toolset for routine allergy diagnosis, but its quality and usefulness hinges on the multidisciplinary research that is only being started.

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Compliance with Ethical Standards

Conflict of Interest Ana Margarida Pereira and João Fonseca are investigators in studies with InspirerMundi, Allergy Diary and AllergyMonitor. Cristina Jácome is an investigator in studies with InspirerMundi. Rute Almeida is an investigator in studies with InspirerMundi and Allergy Diary.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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