Mobile Technology in Allergic Rhinitis: Evolution in Management or Revolution in Health and Care?

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Abstract

Smart devices and internet-based applications are largely used in allergic rhinitis and may help to address some unmet needs. However, these new tools need to first of all be tested for privacy rules, acceptability, usability and cost-effectiveness. Secondly, they should be evaluated in the frame of the digital transformation of health, their impact on healthcare delivery and health outcomes. This review (i) summarizes some existing mHealth apps for allergic rhinitis and reviews those in which testing has been published, (ii) discusses apps that include risk factors of allergic rhinitis, (iii) examines the impact of mHealth apps in phenotype discovery, (iv) provides real-world evidence for care pathways, and finally (v) discusses mHealth tools enabling the digital transformation of health and care, empowering citizens and building a healthier society.

Key words

Apps, digital transformation of health, MASK, mHealth, Mobile technology, rhinitis

Abbreviations

AHA: Active and healthy ageing
AIRWAYS ICPs: Integrated care pathways for airway diseases
AR: Allergic rhinitis
ARIA: Allergic Rhinitis and Its Impact on Asthma
CARAT: Control of Allergic Rhinitis and Asthma Test
CDS: clinical decision support
CDSS: Clinical decision support system
DG CONNECT: Directorate General for Communications Networks, Content & Technology
DG Santé: Directorate General for Health and Food Safety
DG: Directorate General
EIP on AHA: European Innovation Partnership on AHA
EU: European Union
EQ-5D: Euroquol
FDA : US Food and Drug Administration
GARD: WHO Global Alliance against Chronic Respiratory Diseases
GDPR: General Data Protection Regulation
GIS: Geographic Information System
GP: Good Practice
GRADE: Grading of Recommendations Assessment, Development and Evaluation
GT: Google Trends
ICP: Integrated care pathway
ICT: Information and Communication Technology
JA-CHRODIS: Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle
MACVIA-LR: contre les MAladies Chroniques pour un VIeillissement Actif (Fighting chronic diseases for AHA)
MASK: Mobile Airways Sentinel NetworK
MeDALL: Mechanisms of the Development of ALLergy (FP7)
mHealth: mobile health
POLLAR: Impact of air POLLution on Asthma and Rhinitis
RCT: Randomized control trial
RWD: Real-world data
RWE: Real-world evidence

212 TRL: Technology Readiness level
213 VAS: Visual analogue scale
214 WHO: World Health Organization

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216 **Text:** 4839 words

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218 **Abstract:** 125 words

Introduction

Mobile technology has spread rapidly around the globe. Today, it is estimated that over 5 billion people have mobile devices, over half of which are smartphones (https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/).

mHealth (mobile health) is the use of information and communication technology (ICT) for health services and information transfer (1). mHealth, including apps running on consumer smart devices (i.e., smartphones and tablets), is becoming increasingly popular and has the potential to profoundly impact healthcare (2, 3). The rapid advances in mobile technologies have given rise to new opportunities for the digital transformation of health and the continued growth in coverage of mobile cellular networks. The potential applications and benefits of mHealth are extensive and expanding (4). Implementing mHealth innovations may also have disruptive consequences (5), so it is important to test applicability in each individual situation (6). Appropriately identifying and representing stakeholders' interests and viewpoints in evaluations of mHealth is a critical part of ensuring continued progress and innovation (7). Patient, caregiver and clinician evaluations and recommendations play an important role in the development of asthma / AR mHealth tools in supporting the provision of disease management (8).

Smart devices and internet-based applications are already used in allergic rhinitis (AR) and may help to address some of the unmet needs (2). According to recent position papers from EAACI (9) and from the American College of Allergy and Immunology (10), mHealth apps can support the provision of high-quality care to allergic patients, in particular those with AR and/or asthma. This is satisfying for patients and health care professionals, and has led to a reduction in health care utilization and costs. However, these new tools need to first of all be tested for privacy rules, acceptability, usability and cost-effectiveness. Secondly, they should be evaluated in the frame of the digital transformation of health, their impact on healthcare delivery and health outcomes.

1- Strengths and weaknesses of mHealth

Smartphones have radically changed people's lives. However, despite the global advent of mHealth over the past two decades, their use and benefits in disease management are unclear.

The benefits of mHealth include paperless information, the potential increase in medication adherence and improved monitoring (Table 1). mHealth technology has great potential to increase healthcare quality, expand access to services, reduce costs, and improve personal wellness and public health (11). However, mHealth may be harmful. Technically, the development of an app is an easy task, which incurs very low initial investments and does not require in-depth knowledge of the subject itself. The low entry barrier,

dramatically democratizing the app development environment, also results in a large number of ad-hoc apps targetting various health concerns of the public. The majority of mHealth apps have neither been tested on patients nor approved by regulatory organizations such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, many patients rely on these apps in their everyday lives.

A few weaknesses emerge from the use of mHealth apps that are used in observational studies to assess real-world evidence for the evaluation of allergy phenotypes or treatments. As for all studies using participatory data, potential biases include (i) the likelihood of sampling bias, (ii) the difficulty to assess generalizability of the study, as app users are usually not representative of all patients with AR. In MASK, it was found that most users report bothersome symptoms (Bedard, submitted) (iii) outcome misclassification that cannot be assessed, (iv) very little information on patient characteristics, (v) lack of physicians' support in the diagnosis of AR, (vi) potential measurement biases due to the so-called "*informatics illiteracy*" of many patients (12), and (vii) poor adherence to e-Diary compilation, which makes proving poor adherence to treatment impossible.

One of the major problems with apps is the low adherence to their use. Achieving sufficient mHealth app engagement and user retention rates is a difficult task. In MASK-air (Mobile Airways Sentinel NetworK), around half of the patients use the app only once (13).

The benefits of mHealth apps are presented in Table 1.

2- Regulatory framework

mHealth raises significant privacy and security challenges in terms of IT privacy, data sharing and consent management, access control and authentification, confidentiality and anonymity, policies and compliance, accuracy and data provenance, and security technology (11).

In May 2018, the EU General Data Protection Regulation (GDPR) brought major changes in data privacy regulation in the EU. The aim of the GDPR is to protect all EU citizens from privacy and data breaches in today's data-driven world. It harmonizes data privacy laws across Europe, protects and empowers all EU citizens' data privacy and reshapes the way organizations across the region approach data privacy. Thus, all mHealth apps used in the EU should follow the GDPR. The law applies to personal data (Art. 4 para. 1 no. 1, GDPR) (14). Anonymous or anonymized data should lack identifiability. Anonymization principally enables the sharing of data in a way that preserves privacy with minimal data loss. Geolocation information is not only personal data but also has to be considered as an identifier itself (15, 16). Thus, mHealth apps should follow a geolocation de-anonymization that is rarely found in apps. The k-anonymity method is acceptable and was found to fulfill the GDPR regulations in AR (17). The GDPR fixes general rules

applying to any kind of personal data processing as well as specific rules applying to the processing of special categories of personal data such as health data (18). In May 2020, a new EU law will regulate mobile technology (Medical Device Regulation, MDR) (19) making its use tightly regulated.

The US regulations were recently reviewed in detail (20). The FDA and the Federal Trade Commission (FTC) both guide the development and regulation of mHealth devices. Since the recently enacted amendment to the Twenty-First Century Cures Act - the Food, Drug and Cosmetic Act - certain software functions are no longer considered to be medical devices (21). Thus, the FDA is now using enforcement discretion for mHealth apps that do not present risks to patients and consumers.

3- mHealth apps for allergic rhinitis

a. Apps informing on risk factors for allergic rhinitis

Risk factors for exacerbations of AR and asthma include allergen exposure (22), climatic factors (23, 24) and air pollutants (25). It is therefore of great importance to identify levels of risk factors that can induce symptoms in allergic patients. Among these, pollen exposure is the most important for pollen allergic patients. Therefore, forecasting symptoms of pollen-related AR for the individual patient should improve disease control and plan pharmacological intervention and/or prevention of exposure. Besides pollen diaries, mHealth apps allow an easy and fast documentation of pollen allergy counts (26-28). A study that analyzed 9 mobile apps delivering pollen information and pollen forecasts found that the quality of pollen forecasts needs to be improved. It recommended quality control for pollen forecasts to avoid potential harm to patients (29). AR patients could consider the need to avoid the more polluted routes when walking, biking, or exercising. In many cities, traffic air pollution concentrations decline rapidly at a few hundred metres from roadways, and web-based applications can assist individuals in finding alternative routes (30).

There are, however, drawbacks that need to be understood in order to provide better information: (i) The pollen season does not necessarily correspond to an individual patient's symptoms (31) and sub-micronic particles from pollens can induce severe symptoms such as thunderstorm-induced asthma (32); (ii) The definition of the pollen season is still unclear (33) although some clarification efforts have been made for clinical trials (34); (iii) There is a weak correlation between pollen counts and symptoms (35); (iv) Pollutants and weather conditions can interact with pollens to induce symptoms; (v) Only predictive models are to be used, not only for forecasting but also for near-real-time analysis (now-casting) since it takes a few days to count pollens (36). However, these models may need more testing in order to be fully accepted; (vi) Next-generation pollen monitoring is very promising but its cost prevents a large use (37); (vii) The onset of individual symptoms (AR, asthma, conjunctivitis) may be associated with different levels of allergen exposure in patients with different intensities of sensitization and target organ reactivity.

Google Trends are interesting for complementing pollen counts (38) but they cannot be readily used as a predictor of the pollen season. However, Google Trends, when used retrospectively, are better correlated with symptoms than pollen counts (35, 39, 40).

A large number of apps provide information to allergy sufferers regarding pollen counts and/or pollution data (41). Some examples are given below and in Table 2.

BreezoMeter uses the CAMS pollen predictions and big data analysis to provide a continuous current condition pollen index (https://breezometer.com/products/pollen-api). However, its validation is not yet available.

Air Matters broadcasts pollen and air quality data in most countries of the world (https://air-matters.com).

The Copernicus Atmosphere Monitoring Service (CAMS), implemented by the European Centre for Medium-Range Weather Forecasts (ECMWF) on behalf of the European Union, provides forecasts for birch, olive and grass pollen to allow allergy sufferers in the EU to take preventive measures days before exposure. (https://atmosphere.copernicus.eu/news-and-media/news/cams-helping-allergy-sufferers). CAMS supports a range of smartphone applications designed to limit exposure to such allergens. One of these is MetéoPollen for France (https://meteopollen.com).

AccuPollen (http://www.nynjpollen.com) and My Pollen Forecast (https://www.jrustonapps.com/apps/my-pollen-forecast) track pollen counts in the US using forecasts for pollen and climatic data.

The POLLEN app of the European Aeroallergen Network (EAN), maintained by the Medical University of Vienna (https://www.polleninfo.org), evaluates the pollen situation in European countries using the pollen counts of EAN and predictions of the SILAM pollen forecasting model (http://silam.fmi.fi).

b. Apps including health data

Many mHealth apps support patients with AR via self-monitoring through an electronic diary (e-Diary), personalized feedback and/or patient education (42). They aim to improve patient education and self-management on a daily basis but require an evidence-based evaluation given that the information provided on the app stores is limited, in particular for the apps' validity (43-45). This can be done by evaluating the effectiveness of the app with the patients' clinical outcomes (13, 28, 46). For example, children with moderate-severe seasonal allergic rhinitis, treated with daily mometasone, improved their disease knowledge thanks to daily informative messages sent by their e-Diary app (42). If patients are seeking an approach involving the minimal interaction with health care professionals in AR management (47), it is then crucial that the mHealth app is in line with evidence-based essential self-management principles. A Mobile app Rating Scale (MARS) instrument (48) - available in Australia - has been used to assess the mHealth apps for AR (Tan et al, in revision). A 'patient empowerment index through mobile technology'

was recently designed and used to evaluate AR in order to support patients choosing an mHealth app and physicians recommending it (42).

Most but not all mHealth apps which include clinical data are available in English and some are available in over 15 languages (Table 2). The majority of mHealth apps are freely available on iOS and Android. However, very few have provided clinical data supporting their validity. mHealth apps for AR include:

- Self-monitoring
- Patient's feedback
- Patient's education
- Patient's empowerment
- Pollen and/or air pollution data

At present (May 2019), some mHealth apps are in non-English languages such as ALK-Allergik (https://maviedallergik.fr/nos-services), Allergy Track, (https://www.android-logiciels.fr/allergy-track/), AllyScience (https://allyscience.ch/), e-symptoms (https://www.aha.ch/centre-allergie-suisse), i-pollen (http://www.gammehumex.fr/lapplication-i-pollen/), Plume Air Report (https://air.plumelabs.com/fr/) and Pollen App (http://www.pollenstiftung.de/ak). Others in English may be restricted to a limited geographic area such as Air Rater in Australia (https://airrater.org) or are not available from app stores.

Besides those with a commercial interest (e.g. Sensio Air https://www.wlab.io and Zyrtec AllergyCast https://www.zyrtec.com/allergy-forecast-tools-apps), there are few mHealth apps with health data on AR (e.g. AllergyMonitor®, MASK-air® ,WebMD Allergy® https://www.webmd.com/allergy-app and the Austrian Pollen Information Service www.pollenwarndienst.at) (Table 2).

c. Apps connected with sensors

In asthma, many mHealth apps are connected with sensors for inhalers (20). Such devices do not yet exist in AR but there are attempts to connect pollution sensors to mHealth apps. Unfortunately, those existing for asthma appear to be in an exploratory phase and need validation. In addition to external sensors, smartphones and tablets have embedded sensors such as camera, microphone, atmospheric pressure sensor, accelerometer and GPS. These sensors can be used to provide contextual information for the collected clinical data. Moreover, using signal processing, data from on board sensors, already available in off-the-shelf devices and used by millions of patients, are being tested as ubiquitous technologies to provide verified information on cough (49), lung function (50), adherence to inhaled treatment (51), physical activity parameters and other human behaviours of clinical interest (52).

d- Examples of apps

- **AllergyMonitor®** (http://www.tpsproduction.com/)

AllergyMonitor® is an app that has been translated into 10 languages. Its target is to improve allergy diagnosis by matching trajectories of symptom-medication scores and pollen counts (26, 28, 46, 53, 54). Furthermore, it enhances shared decision-making by fostering the exchange of information between users and their health care professionals. The latter can access and view their patients´ recorded data in a back-office, which allows the management of patients´ clinical data and gives a structured overview on the individual disease management. The data recorded by the user then complete the set of information being integrated in the back-office in real-time. As users also register the intake of their prescribed medication, this feature allows the monitoring of compliance which has been shown to effectively increase the adherence to treatment with nasal corticosteroids and sublingual allergen-specific immunotherapy. To this end, the app includes customized lists of over-the-counter and prescribed medications for many countries, patient-doctor communication via SMS and e-mail, patient alerts for a better knowledge of the disease as well as reminders for a better adherence to treatment. The potential of data sets generated through AllergyMonitor® has also been investigated for the short-term prediction of patients´ symptoms with several symptom and medication scores for rhinitis and asthma.

- **MASK** (http://www.mask-air.com)

MASK (Mobile Airways Sentinel networK), the Phase 3 ARIA initiative, was instigated to reduce the global burden of AR and asthma multimorbidity, giving the patient and the health care professional simple tools to better prevent and manage respiratory allergic diseases. The MASK app (MASK-air®, formerly *the Allergy Diary*, freely available for Android and iOS) (55) is the most extensively published mHealth app for AR. It is an ICT system centred around the patient (13, 55-57) and is operational in 23 countries and 17 languages. It uses a treatment scroll list which includes all medications customized for each country as well as visual analogue scales (VASs) to assess rhinitis control and work productivity (58, 59). MASK-air® is being combined with data on allergen and pollution exposure (POLLAR) (25). MASK-air® results are given in Table 3.

MASK is scaled up using the EU European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) strategy (60). MASK is supported by several EU grants and is a GARD (Global Alliance against Chronic Respiratory Diseases, WHO (61)) research demonstration project. It is a Good Practice of DG Santé (62).

- **European Aeroallergen Network Pollen Information Service**

The EAN Pollen Information Service (www.polleninfo.org), developed and maintained at the Medical University of Vienna, provides a pollen assessment and a three-day forecast in co-operation with local and international institutions. It is available for European countries in over 10 languages. The app includes

symptoms and treatments. The components and functionality of the app vary between the countries depending on the requests of the national pollen observing groups.

The service also takes the user's pollen diary entries into account and calculates personal burden level. Allergic symptoms can be documented and compared with the pollen count in the pollen diary. Personal load, Pollen News, Pollen-Countdown notifications and a reminder for a doctor´s visit are all available. The pollen diary was restructured in 2018 and provides information on preventing impaired performance in everyday life, the time of the highest burden and the time(s) of being outdoors. The encyclopedia of allergenic plants is also available to answer questions on allergy.

- **e-allergy**

The under-recognition of AR is common due to a low level of public awareness as well as limitations in access to allergologists (63). AR sufferers often use OTC drugs and self-medicate. mHealth tools supporting the pre-medical early diagnosis of allergic diseases are important. They use algorithms able to classify respondents into certain risk groups of AR and asthma. An algorithm was created - with the use of advanced statistical methods (neural networks) - on ECAP (Epidemiology of the Allergic Diseases in Poland) data containing both questionnaire answers and medical diagnosis (64). This tool is constantly being updated. The latest results show a sensitivity for AR in children and adolescents of 0.852 and a specificity of 0.840 (65).

4- Clinical decision support systems (CDSSs)

A CDSS is a health information technology (IT) system designed to assist clinicians and other health care professionals in clinical decision-making. In medicine, CDSSs have become a major topic in artificial intelligence. According to the National Academy of Medicine (Washington DC) (66), "facilitative clinical decision support (CDS) is a practical necessity for every clinician in our rapidly-evolving health and healthcare landscape." A CDSS can reduce the burden that exponentially-expanding clinical knowledge and care complexity places on clinicians, other health care professionals or patients. CDSs provide clinicians and other health care professionals with knowledge and person-specific information - intelligently filtered or presented at appropriate times - to enhance health and health care (67). CDSs can enhance decision-making through the use of the following tools: (i) computerized alerts and reminders to health care providers and patients, (ii) clinical guidelines, (iii) focused patient data reports and (iv) diagnostic support (68). Many apps used in AR provide patients with some help for AR control. However, for this, they should be labelled as CE2A in the EU. Apps that do not provide help can be registered as CE1. An electronic CDSS (eCDSS) based on MASK now exists in AR and is in the process of validation (69). It is not clear whether other tools have been validated as they have not been published. CDSSs may

also be very useful in stratification strategies and in reporting outcomes in clinical trials such as in Allergen Immunotherapy (https://www.ncbi.nlm.nih.gov/pubmed/30955224).

5- Potential of mHealth apps for allergy phenotype discovery

Conventionally, phenotypic studies have relied on traditional observational designs. Apps provide a new source of information on daily symptoms and the opportunity to discover new phenotypes. Few studies have been published concerning allergy phenotypes assessed with an app.

A prospective analysis has compared six disease severity scores for AR against pollen counts (53). Many different and incomparable symptom (medication) scores are used to assess AR control. Disease severity scores for seasonal AR evaluated by an internet-based platform provide similar results at population level but are heterogeneous in individual patients.

Multimorbidity in allergic airway diseases is well known (70), but no data has ever existed regarding how multimorbidity impacts the daily dynamics of specific symptoms, including severity and work. MASK-air® has enabled this investigation in a novel approach of the intra-individual variability of allergic multimorbidity from day to day (71). AR and rhinoconjunctivitis did not appear to be the same disease. Moreover, MASK-air® identified a previously unrecognized extreme pattern of uncontrolled multimorbidity (uncontrolled rhinitis, conjunctivitis and asthma on the same day) (71). However, mHealth apps are only tools generating hypotheses and need to be confirmed in classical epidemiologic studies. Differences between AR alone or associated with conjunctivitis were already known (72) but new studies carried out following MASK-air® data showed that (i) ocular symptoms are more common in polysensitized patients whether or not they have asthma (73), (ii) ocular symptoms are associated with the severity of nasal symptoms (74), (iii) ocular symptoms are important to consider in severe asthma (74) and (iv) the severity of allergic diseases increases with the number of allergic multimorbidities (75). This is the first time that novel allergic phenotypes have been discovered using an mHealth app and then confirmed by classical epidemiologic studies.

5- Real world evidence using mHealth in next-generation care pathways

mHeath apps for a better AR management are growing in number. However, their usefulness for doctors and patients is still being debated. Most studies have also highlighted certain shortcomings and limitations, mainly concerning security and cost-effectiveness (76).

a. Adherence to treatment

mHealth may help to better understand adherence to treatment and its determinants as well as how to improve it. In medicine, many mHealth apps are available to support people in taking their medications and thus to improve medication adherence (77, 78). However, a meta-analysis found that the majority did not have many of the desirable features and/or were of low quality (77). A systematic review including 16 RCTs found that mobile phone text messaging approximately doubles the odds of medication adherence, resulting in a net increase in adherence of 17.8% (78). A Cochrane systemic review of 7 trials in cardiovascular disease found that, while the results are promising, there is insufficient evidence to draw conclusions on the effectiveness of text message-based interventions for adherence to medications. The authors suggested that sufficiently powered, high-quality randomised trials are needed, particularly in low- and middle-income countries (79).

Adherence in randomized control trials (RCTs) is high but does not reflect the real-life situation (29,30) and alternative measurements of adherence in a real-life setting are needed. The best studies would be using electronic devices that count and record the drugs taken. However, these devices are still exploratory and expensive and, as such, they are not currently a viable solution for large studies in AR patients (80) or individual patients. A potential palliative solution can be to use the smartphone's camera to register the drug uptake. The photo of the drug is then processed by image recognition algorithms to provide verified data on adherence to AR treatment during the patient's daily life. However, there are technical challenges and limitations to some types of vials and packaging. The automatic detection of progression of use of the liquid in the vial using computer vision may be of special relevance for sublingual allergen immunotherapy for which adherence can be a major issue (81). Other approaches already being tested for asthma but not for AR are mobile direct observation of therapy (82) and multicomponent interventions based on mobile technologies (83). Although there are already some mHealth apps for AR, there are few studies evaluating their benefits and impact (76). One study suggested that a short message service (SMS) helps to improve AR treatment (84). Internet-based telemonitoring using the AllergyMonitor® improved adherence to intra-nasal corticosteroid treatment and disease knowledge among children and adolescents with seasonal AR as well as adherence to sub-lingual immunotherapy (46). In MASK-air®, a major lack of adherence to treatment was observed for all medications (85). Auto-medication was very common (12) suggesting that patients, like allergists when they are allergic (86), do not follow physicians' prescriptions or guidelines.

b. mHealth in observational studies allowing novel assessment of patients' behaviour

The treatment of AR is complex as many drugs are available in oral and/or topical formulations, and allergen immunotherapy and avoidance increase the complexity of the management. Many AR guidelines are evidence-based and have led to a better understanding and management of AR (87-89). However, guidelines are mostly based on RCTs, typically undertaken on highly-selected populations and often with limited/unclear generalizability to routine care contexts. Large observational implementation studies are needed to triangulate RCTs as they reflect "real world" every-day use and practice more closely than RCTs in terms of the heterogeneous patient populations included and the variety of medical interventions assessed. In RCTs, each subject is randomly assigned to a treatment or control group, whereas observational studies examine the possible effect of a treatment on subjects where the investigator has no control over the experiment and cannot randomize subject allocation (94). However, observational studies provide clinically relevant information in addition to RCTs. Real-world evidence (RWE) using RCTs and real-world data (RWD) is becoming increasingly important in supporting regulatory decisions using mobile technology (95).

A pilot study in over 2,900 users allowed differentiation between treatments (12) showing that the assessment of series of consecutive days was useful in understanding treatment patterns. The study showed that patients did not necessarily use treatment on a daily basis and in a regular way; rather, they appeared to increase treatment use when their symptom control worsened. Differences in efficacy between medications were observed. This pilot study was confirmed in almost 9,000 users (96). The studies confirm the usefulness of mHealth in accessing and assessing everyday use and practice in AR (12). It is hoped that mHealth apps will increase patient empowerment and improve adherence.

c. Next generation guidelines

The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on many factors. GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines have considerably improved AR management. However, there is an increasing trend to use RWD to inform clinical practice, especially as RCTs are often limited with regards to the applicability of results. The MACVIA algorithm proposed an AR treatment by a consensus group (97). This simple algorithm can be used to step-up or step-down AR treatment. Next-generation guidelines for the pharmacologic treatment of allergic rhinitis (98) were developed using existing GRADE-based guidelines (87-89), RWD provided by mHealth apps (12, 85, 96) and additive studies (allergen chamber studies (99)) to refine the MACVIA algorithm (97).

6- mHealth tools enabling the digital transformation of health and care, empowering citizens and building a healthier society

The recent report on the State of Health in the EU (State of Health in the EU "Companion Report 2017", https://ec.europa.eu/health/state) concluded that rethinking our health and care systems can ensure its sustainability aiming to continue health promotion, disease prevention and to provide patient-centred care that meets citizens' needs (https://ec.europa.eu/transparency/regdoc/rep/1/2018/FR/COM-2018-233-F1-FR-MAIN-PART-1.PDF).

Digital solutions for health and care can increase the well-being of millions of citizens and radically change health and care services. In its mid-term review on the implementation of the digital single market strategy (https://ec.europa.eu/transparency/regdoc/rep/1/2017/EN/COM-2017-228-F1-EN-MAIN-PART-1.PDF), the EU Commission took further action in three areas:

- Citizens' secure access to and sharing of health data across borders.
- Better data to advance research, disease prevention and personalized health and care.
- Digital tools for citizen empowerment and person-centred care to allow citizens to assume responsibility for their health, improve their well-being and quality of care and contribute to sustainable health systems. By using digital solutions, such as wearables and mHealth apps, citizens can actively engage in the health promotion and self-management of chronic diseases. Digital tools can potentially disseminate scientific knowledge in an easily accessible form, so as to help people stay in good health – thus preventing them from turning into patients. Building on scientific information on risk factors, digital solutions can be used across all sectors, including education, transport, and urban policies to promote information and awareness campaigns on healthy lifestyles. Digital tools also enable citizens to provide feedback and data about their health to their doctors. This can improve the quality of health services and ultimately people's health and well-being.

Digital tools can also empower patients in the context of the UN sustainable development goals and in particular regarding those related to sustainability and natural resources (100). Future apps in AR could consider providing information to promote behavioural changes that could reduce the planetary impacts of human activity.

In the context of implementing communication on the digital transformation of health and care, DG SANTE, in collaboration with the newly-established EU Commission Expert Group "Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases" (https://ec.europa.eu/health/non_communicable_diseases/steeringgroup_promotionprevention_en), supported the scaling-up and wider implementation of good practices in the field of digitally-enabled, integrated, person-centred care. MASK was one of the nine Good Practices selected along with chronic disease and Parkinson's disease (62).

8. Global implementation

When mobile technology was initiated, it was thought that it would be used mainly in developed countries. However, smartphone ownership is growing rapidly around the world. According to ITU (International Telecommunication Union, Geneva), in 2015, there were more than 7 billion mobile telephone subscriptions across the world, over 70% of which were in low- or middle-income countries (101). However, in these countries, smartphone use is still much more among the young and educated (https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/).

WHO recognizes the significant role that digital technologies can play in strengthening the health systems in countries to achieve universal health coverage, the health-related Sustainable Development Goals and other health objectives. In 2018, 121 countries had national eHealth strategies, representing the beginning of a shift from an unsustainable project-based approach towards a systematic, integrated approach designed for cost-effective investment and alignment of partners (102). The joint WHO-ITU initiative "Be He@lthy, Be Mobile" for the prevention and management of noncommunicable diseases, their comorbidities and their risk factors, including improving disease diagnosis and tracking, is of great importance. MASK is one of the examples of the "Be He@lthy, Be Mobile" handbook on how to implement mBreatheFreely for asthma and COPD (103).

Conclusion

mHealth has the potential to profoundly impact healthcare (3). mHealth apps now represent an important evolution of health and care for AR since RWE has identified patients' behaviours and practices and this will have a profound impact on current guidelines and care pathways. Rhinitis is not a severe disease but it does have a major impact on social life, school and work productivity (104). Asthma-rhinitis multimorbidity plays a key role in understanding asthma and can be used as a model of multimorbidity. Moreover, asthma and rhinitis have a life course approach whereas most chronic diseases start early in life but are only clinically evident in adulthood. The revolution is underway for AR and asthma, and the lessons learnt are transposable to other chronic diseases and will design innovative health strategies and services as well as change management (105).

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Table 1: Global applicability of mHealth Apps in allergic rhinitis (adapted from (13))

Applicability	mHealth Apps
Clinical practice	Physicians will be able to read the files of the patients in order to: • Optimize treatment for the patient and, in particular, for the current or the next pollen season. • Assess and increase adherence to treatment. • Help in shared decision making. • Prescribe allergen immunotherapy (AIT) more rapidly when the patient is not controlled despite optimal pharmacologic treatment. • Determine the efficacy of any treatment including AIT . • Apps are an essential tool for providing personalized medicine in AR and asthma.
Change management	• Many patients are uncontrolled and non-adherent to treatment. Apps can indirectly assess and help (e.g., reminders) adherence. • Patients appear to use their medications as needed and not on a regular basis as prescribed • Change management is needed and may be facilitated by apps
Patient empowerment	• Better understanding of the symptoms • Sentinel network linking aerobiology data and control • Improved adherence • Self-management • Alert systems • Messages sent by the app.

Clinical trials	• To assess environmental control measures
	• To assess pharmacotherapy
	• For RCTs, it is essential to have clarity on definitions, and relevant tools. Apps allow
	  • To better stratify the patients, in particular for AIT
	  • To assess the efficacy of treatments during the trial
	  • To assess the efficacy when the treatment is stopped
	• Feasibility of real-life studies
	  • To confirm RCTs
	  • And bring new hypotheses for the treatment of AR and asthma

Registration and reimbursement of medicines	• Controlled trials designed with a uniform approach will be more easily evaluated by the Health Technology Assessment agencies (such as NICE) for reimbursement. • Better understanding of direct and indirect costs • Controlled trials designed with a uniform approach will help to synchronize the data from real-life world regarding clinical effects and safety/tolerability of new drugs (post-marketing pharmacovigilance for some apps)
Research on mechanisms and genetics	• A uniform definition and a collaborative approach to epidemiological, genetic and mechanistic research are important and will be enhanced by the stratification of patients using apps. • Different levels of phenotype characterization (granularity) can be applied to assess phenotypic characterization in old age subjects.
Epidemiology	• In epidemiologic population studies, standardized definitions and tools are fundamental. • Apps may allow novel approaches combining classical cross-sectional and longitudinal studies with real life studies in large populations.

Employers	• AR and asthma represent a major burden for the employers, and the estimated annual costs in the EU range from 30 to 60 B€. Better control of the disease was shown to reduce costs. • Apps have the potential to improve the control of allergic diseases and to significantly improve work productivity at the EU level.

Table 2: Examples of mHealth apps for allergic rhinitis

		Pollen	Other risk factors	Health data	
Multicountry					
	Air Matters	X	X		https://air-matters.com
	AllergyMonitor	X		X	
	Austria Pollen Information Service	X		X	www.pollenwarndienst.at
	Breezometer	X	X		https://breezometer.com/products/pollen-api
	The Weather Channel	X			https://play.google.com/store/apps/details?id=com.weather.Weather
	POLLEN & PHD	X		X	https://www.polleninfo.org, two separate but interlinked apps
	MASK-air			X	https://www.mask-air.com
	Pollen alert Europe	X			https://play.google.com/store/apps/details?id=com.bluesula.allergyalarmeurope&hl=en
Argentina	Alerta Polen Argentina	X			https://play.google.com/store/apps/details?id=com.mobillers.alertapolen&hl=es
Australia	Air Rater				https://airrater.org
Denmark	Dagens Pollental	X			https://www.astma-allergi.dk/dagenspollental
France	ALK-Allergik				https://maviedallergik.fr/nos-services
	Allergy Track				https://www.android-logiciels.fr/allergy-track/
	i-pollen				http://www.gammehumex.fr/lapplication-i-pollen/
	Plume Air Report				https://air.plumelabs.com/fr/
Germany	Pollen App	X		X	http://www.pollenstiftung.de/ak
Italy	Pollen App	X	X		https://itunes.apple.com/it/app/polliniitalia/id621302844?mt=8
		X	X		https://www.ilpolline.it/i-calendari-pollinici
	Allergy Control	X	X	X	https://itunes.apple.com/it/app/allergy-control/id973452501?mt=8
	Allergy Monitor	X		X	https://play.google.com/store/apps/details?id=com.tpsproduction.allergymonitor&hl=it
	MeteoAllergie	X			https://play.google.com/store/apps/details?id=com.dlsolutions.meteoallergie&hl=it

MASK-air				X	https://www.mask-air.co

	Bollettino meteo Pollini e allergie in Italia	X			https://www.3bmeteo.com/meteo/italia/pollini
	RAPP (Rhinitis and Asthma Patient Perspective)			X	https://play.google.com/store/apps/details?id=com.wellnessandwireless.rapp
NL		X			https://pollennieuws.nl/
		X			https://hooikoortsradar.nl/
Poland	e-allergy			X	
Portugal	INSPIRERSMUNDI			X	https://www.facebook.com/Projeto-Inspirers-218849795347948
Spain	INSPIRERSMUNDI			X	https://www.facebook.com/Projeto-Inspirers-218849795347948
	R-Alergo	X			http://alergialafe.org/noticias/172-r-alergo
	Polen Control	X			https://www.seaic.org/inicio/polen-control
	Niveles de Polen	X			https://play.google.com/store/apps/details?id=es.diox.android.alergia&hl=es
	Intolerapp	X			https://socialmediatica.com/intolerapp-la-aplicacion-ideal-para-alergicos-e-intolerantes-alimentarios/
	ALK Polen	X			http://www.ticsalut.cat/observatori/es_apps/265/al-k-polen
	Planttes	X			http://www.planttes.com/
Switzerland	AllyScience				https://allyscience.ch/
UK	My Pollen forecast UK	X			https://itunes.apple.com/gb/app/my-pollen-forecast-uk/id1244428929?mt=8
	Piri	X			http://www.piriallergy.com/pollen-count.html
USA	AcuPollen				http://www.nynjpollen.com
	My Pollen Forecast	X		X	https://www.jrustonapps.com/apps/my-pollen-forecast
	Plume Air Report	X		X	https://plumelabs.com/en/air/
	Poncho: wake up wheather	X			https://www.crunchbase.com/apptopia_app/39a4271c-7286-4523-bed3-7cecdf55e0bf
	WeathterBug				https://www.weatherbug.com

Table 3: The global MASK Good Practice and IT solution (modified from (62))

App (MASK-air) deployed in 23 countries: TRL9 (Technology Readiness level), Electronic clinical decision support system (ARIA e-CDSS): TRL 7, e-physician questionnaire deployed in 16 countries: TRL9.

- App: 29,000 users, 23 countries, 17 languages
- Tested with patients
- GDPR including geolocation (17)
- Good Practice of the EIP on AHA, follows CHRODIS (106)
- Good Practice on digitally-enabled, integrated, patient-centred care endorsed by DG Santé (62)
- Based on 11 EU grants (MeDALL (107), GA^{2}LEN (108)) including - in 2018 - POLLAR (25), VIGOUR, DigitalHealthEurope, Euriphi (Digital transformation of health) and -in 2019- Gatekeeper
- From a validated "research" tool (2004-2018) to large scale deployment (2019-)
    - Validation with COSMIN guidelines (109).
    - Baseline characteristics (110)
    - Work productivity (111, 112)
    - EQ-5D and WPAI-AS (113)
    - Novel phenotypes of allergic diseases (71)
    - Adherence to treatment (12, 85)
    - Novel approaches to inform the efficacy of treatment (12, 96)
- Patient's organizations and scientific societies involved
- GARD (WHO alliance)
- Presented during WHO and EU ministerial meetings (114, 115)
- Next-generation care pathways meeting (Dec 3, 2018) with the EIP on AHA, POLLAR (EIT Health) and GARD
- 51 MASK papers in 12 languages (116-119)
- Dissemination according to the EIP on AHA (60)

Transfer of innovation (TWINNING (120))

- Interoperable platform with MASK
- 25 Reference Sites of the European Innovation Partnership on Active and Healthy Ageing plus Argentina, Australia, Brazil, Canada, Mexico (116-119)
- 900 patients enrolled
- GDPR solutions solved

ARIA e-CDSS

- Interoperable platform with MASK
- Based on an expert meeting (97), and validation by Delphi questionnaire (69) and real-world evidence using MASK-air (12, 96)
- Electronic version available (69)