Chapter 11

Asthma in the digital world

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11.1 Introduction

According to the World Health Organization (WHO) Regional Office for Europe [1], digital health is “a broad umbrella term encompassing eHealth, as well as developing areas such as the use of advanced computer sciences (for example, in the fields of “big data”, genomics and artificial intelligence) and plays an important role in strengthening health systems and public health, increasing equity in access to health services, and in working towards universal health coverage.” However, although digital health will have a major impact on population health, it may lead to unintended consequences such as perpetuating health and healthcare disparities for underserved populations. It is therefore imperative to understand the challenges faced by these populations, including racial and ethnic minorities or aging people which hinder their achievement of ideal health [2]. On the other hand, 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 [3]. 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 [4]. eHealth, as defined by the WHO, consists of the use of information and communication technology (ICT) for digital health (Table 11.1) [5,6] including electronic health

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TABLE 11.1 List of World Health Organization-endorsed definitions for digital health-related concepts (from [6]).

Concept	Definition
Digital health	"A broad umbrella term encompassing e-health, as well as developing areas such as the use of advanced computer sciences (for example, in the fields of "big data", genomics, and artificial intelligence)."[a]
eHealth	"Use of information and communication technologies (ICT) for health."[b]
mHealth	"Medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices."[c]
Telemedicine/Telehealth	"The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using ICT for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities."[d,e]
	"Some distinguish telemedicine from telehealth with the former restricted to service delivery by physicians only, and the latter signifying services provided by health professionals in general, including nurses, pharmacists, and others."[d,e]

[a] *https://www.euro.who.int/en/health-topics/Health-systems/digital-health;*
[b] *https://www.who.int/ehealth/about/en/;*
[c] *https://www.who.int/goe/publications/goe_mhealth_web.pdf;*
[d] *https://www.who.int/goe/publications/goe_telemedicine_2010.pdf;*
[e] *https://www.who.int/gho/goe/telehealth/en/.*

records, telehealth, and mHealth. The latter has been defined by the Global Observatory for eHealth as a "medical and public health practice supported by mobile devices, such as mobile phones" [7]. It can be segmented into (1) equipment/connected medical devices, (2) mHealth services, and (3) mHealth apps (apps) [8]. It includes patients and care providers using any digital technology - smartphones (apps), tablets, texting, calling, video conferencing, or monitoring devices - to deliver and monitor health care and/or perform research. According to the WHO, mHealth "has the potential to transform the face of health service delivery across the globe, and can be applied to asthma and allergies" [1].

The present paper is not intended to provide a systematic review of the current digital tools used in asthma but to provide a framework to better understand the potentials and drawbacks of some of these tools using, when available, systematic reviews. Social media will not be considered in this paper [9].

11.2 Regulatory framework for data protection

mHealth raises significant privacy and security challenges in terms of ICT privacy, data sharing and consent management, access control and authentication, confidentiality and anonymity, policies and compliance, accuracy and data provenance, and security technology [10].

The EU General Data Protection Regulation (GDPR) has brought major changes in data privacy regulations (May 2018) in the EU. The GDPR should 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. All mHealth tools used in the EU should follow the GDPR [11]. Anonymized or pseudo-anonymized data should lack identifiability. Geolocation information is also considered an identifier [12,13]. In May 2023, a new EU law will regulate mobile technology (Medical Device Regulation, MDR) [14] making its use more tightly regulated.

In the EU, apps for children collecting personal data fall under the jurisdiction of two laws: The Children's Online Privacy Protection Act (COPPA) of 1998 and the GDPR of 2018. Children in the GDPR are briefly mentioned, with Article 8 being short and not harmonized. The age for consent in mHealth apps is not harmonized in Europe, which is a serious problem. In multinational studies, the age of 16 should be used. The introduction in September 2020 of the Age Appropriate Design Code in the UK enforces organizations designing online content for UK-based children –including games publishers– to follow 15 standards supporting existing data protection laws under the GDPR (https://www.privsecglobal.com/blog/fun-and-games-protecting-childrens-data-in-the-gaming-industry).

The US regulations were reviewed [15]. The FDA and the Federal Trade Commission (FTC) guide the development and regulation of mHealth devices. In the recently enacted amendment to the Twenty-First Century Cures Act (i.e., the Food, Drug, and Cosmetic Act), some software functions are no longer considered to be medical devices [16]. Thus the FDA is now using enforcement discretion for mHealth apps that do not present risks to patients and consumers.

11.3 Electronic health records

Electronic health records (EHR) are widely used in clinical practice in asthma and in research to inform health services and health policy. Validation of asthma diagnosis in EHR is needed to use these databases for epidemiological asthma research. A systematic review in 2017 found 13 studies demonstrating a high validity of data on asthma diagnosis [17,18]. Identifying asthma cases in EHR is possible with high sensitivity and specificity by combining multiple data sources, or by focusing on specific test measures [19,20]. However, studies testing a range of case definitions show wide variation in the validity of each definition, suggesting a need for harmonization.

A scoping review (2015) attempted to define asthma and assess asthma outcomes from EHR extracting the algorithms used to assess severity, control, and exacerbations [21]. The approaches largely vary and are often underdescribed, rendering it difficult to assess the validity of studies and compare their findings. A scientific consensus should be reached on the underlying definitions and algorithms. A newer scoping review was carried out to identify and investigate severe asthma from primary care records [22]. Twelve studies were retrieved but a number of challenges need to be overcome to accurately identify and investigate severe asthma. It is possible to embed smartphone data into EHR [23].

Of note, EHR was used to better assess asthma during the COVID-19 pandemic. The OpenSAFELY Collaborative assessed the association between inhaled corticosteroids (ICS) and COVID-19-related death among people with COPD or asthma in England [24].

Although not directly related to EHR, the British surveillance practices may be interesting to mention, as they report incident cases of respiratory diseases (including asthma), with automatic methods implemented to ensure data quality [25].

11.4 Registries in severe asthma

The use of mHealth in the creation of the registers assumes a completely different role for the patient who becomes an active part in the creation of the register on a layout predefined by the physician. In addition, evaluating in real-time may be of great interest to the patient and offers the opportunity to change in real-time the direction of research and to approach the principle of data-driven thinking. Data collected from digital technologies are often available in real-time, allowing researchers to quickly grasp epidemiological insights such as disease prevalence, as well as the impact of medical interventions. (Global Forum Special Section: Social Media and Medicine. http://www.diaglobal.org/en/resources/news#article=202b2098-7868-4dfe-8a54-9c2a67e65e7d.). Advantages of mHealth-based Smart patients Registries are speed in data collection, time, cost-saving methodology, and transparency.

The Asthma Mobile Health Study [26], in which participants engaged with an iPhone built using Apple's ResearchKit framework, is an example of how mHealth can help create disease registries. All coded data sets are stored and accessible via the Synapse platform in a public project with associated metadata and documentation (https://www.synapse.org/asthmahealth) and could be considered a prototype of Smart Patients Registries. Nevertheless, this approach displayed important limitations and only a small amount of data were collected. ResearchKit provides participants the convenience of participating via an iPhone app but other devices cannot be used. People owning iPhones are not representative of the general population. They are disproportionally more educated and with higher income skewing results, and can be problematic for health research, especially on disease conditions where significant health disparities exist.

Several mHealth technologies are used to perform pharmacovigilance and surveillance, like in Cambodia and Australia, with SMS text messages to monitor adverse events following immunization [27,28]. This methodology can be used alone or to complement existing passive reporting systems and has the potential to rapidly identify emerging safety signals.

In the US, mHealth has been used to create a real-time surveillance registry for communicable diseases such as influenza ("Flu Near You", FNY), a mobile health program. Analysis of the 2013–2014 season showed potential as a viable complement to existing outpatient, hospital-based, and laboratory surveillance systems [29].

To effectively implement a digital health approach or device, it is fundamental (1) to understand the patients' perspective, perception, preferences, and knowledge of their preferred device or solution, and (2) to take the patient as codesigner of the project. Including patients' feedback implies a multidisciplinary approach, comprising professionals such as psychologists, sociologists, or digital influencers.

The Global Asthma Report stressed the need for ongoing asthma monitoring, appealing for countries to conduct asthma surveillance, with a regular investigation of trends (Global Asthma Network, The Global Asthma Report: 2018 update. http://global asthma report). The International Severe Asthma Registry (ISAR; http://isaregistries.org/), the first worldwide adult severe asthma registry (ISAR Study Group International Severe Asthma Registry) [30,31], answers the World Health Organization and Global Asthma Report calls to action. ISAR works in partnership with national and regional registries, such as the UK Severe Asthma Network and National Registry on Difficult Asthma, [32] the German Asthma Net (GAN), the Italian Severe Asthma Network (SANI), [33–35] and the Australasian Severe Asthma Network (ASAN) [36]. ISAR collects patient-level, pseudonymous, longitudinal, real-life, standardized, high-quality data, using a set of core variables, from countries across the world for ethically approved research purposes. Among others, the Spanish registry is also of interest [37,38].

11.5 Telehealth in asthma

Emerging interest in telehealth for chronic diseases prompts the need for a framework for (1) its implementation in the asthma curriculum, (2) training and appropriate supervision, (3) providing elective clinical experience, and (4) simulating telemedicine delivery [39]. The benefits of telehealth in asthma are not yet clear, [40] and more studies are needed.

Many clinics had to re-adapt their management strategies during the COVID-19 pandemic, [41,42] particularly in rural areas, [43] and telehealth played an important role in providing additional protection to both asthmatic patients and healthcare providers. [44] Virtual consultations can be more convenient and have the potential to improve access for patients. However, rules need to be implemented to avoid large differences between practices, [45] and Telehealth was a barrier to care for patients or physicians without hardware, Internet, and/or e-literacy. Many physicians embraced these technologies for the first time during the pandemic. Telehealth approaches, such as videoconferencing, have improved healthcare access, optimized disease management, improved the progress in the monitoring of health conditions, and allowed fewer exposures to patients with illnesses during the COVID-19 pandemic [46–49]. However, the duration of presential consultations is longer than pre-COVID-19 [49]. Moreover, it also isolated people, reduced social proximity, dehumanized human relatedness, and created fatigue. Despite the sudden change in the model of healthcare delivery, patients report high satisfaction with telehealth regardless of their primary diagnoses and management [50]. Patients accepted physician decision-making without customary testing (e.g., spirometry) [51]. Telehealth can also be useful for training during the COVID-19 pandemic [52].

11.6 mHealth apps

mHealth apps (apps) aim to help patients and healthcare providers, facilitating the provision of patient care. Their potential applications and benefits are extensive and are expanding in asthma by optimizing asthma self-management (medication reminders, self-monitoring of symptoms, improving access and quality of information communicated with provider), and providing educational resources to patients and parents. mHealth app questionnaires should be validated using classical methods (e.g., the asthma control test, ACT [53,54]). Criteria for the development of an app have been proposed (Table 11.2).

Asthma apps for children were studied in a systematic review (2020) [55]. The Google Play and Apple App Stores were systematically searched to identify the most adequate apps, which were then compared according to predefined criteria.

TABLE 11.2 **Criteria for the development of an app (https://digitalprinciples.org/).**

Design with the user
Understand the existing ecosystem
Design for scale
Build for sustainability
Be data-driven
Use open standards, open data, open-source, and open innovation
Ruse and improve
Address privacy and security
Be collaborative

Inclusion criteria consisted of being available free of charge, being displayed in German or English, and being suitable for children. A total of 403 apps were identified on the Google Play and Apple App Stores, but only 24 met the inclusion criteria. The English language apps were Kiss-my-asthma, [56] AsthmaXcel, [57–59] AsthmaAustralia, and Ask Me, AsthMe!, whereas the only recommended German language app was Kata.

Another systematic review evaluated asthma self-management apps by examining behavior change techniques [60]. Twenty-three apps were retrieved. Quality ratings were determined for each app using the Mobile App Rating Scale (MARS). Two apps, Kiss-my-Asthma [56] and AsthmaMD (https://www.asthmamd.org) had high-quality ratings.

Another descriptive overview of asthma apps publicly available in two stores (excluding websites, and other stores, …) assessed their usability to identify content and features up to June 2020 [61]. User ratings of the asthma app were dichotomized into two categories (low and high average). The number of ratings across all apps ranged from 188 (AsthmaMD) to 10 (My Asthma App). Three apps were available on both Android and iOS. Key features of asthma management that were common among highly-rated apps included the tracking of peak flow readings, asthma symptom monitoring, and action plans.

Other apps are also available [62]. The Asthma Mobile Health Study, in which participants engaged with an iPhone application built using Apple's ResearchKit framework, was carried out in 6,346 US participants, who agreed to share their data broadly. It has been made available for further research [63].

MASK (Mobile Airways Sentinel networK), the Phase 3 ARIA initiative [64,65], aims to reduce the global burden of AR and asthma multimorbidity, proposing digitally-enabled, patient-centered care to better prevent and manage respiratory allergic diseases. The freely available MASK app (MASK-air, formerly *the Allergy Diary*, Android and iOS) [65–68] is operational in 28 countries and 20 languages [69,70]. It is supported by several EU grants and is a GARD (Global Alliance against Chronic Respiratory Diseases, WHO [71]) research demonstration project. It is also a Direction Générale de la Santé Good Practice [72,73].

A paradigm shift has been proposed using a mixed method study of the preferred and potential features of an asthma self-management app [74]. The pilot study showed promising results.

11.7 mHealth sensors

More than 500 asthma-related apps, whether standalone or paired with sensors on inhalers, are currently available for health education, symptom recording, tracking of inhaler use, displaying environmental alerts, and providing medication reminders [75]. Electronic monitoring devices provide objective data on date, time and number of actuations. However, only a few give no information on inhalation [76].

A systematic review has been done (May 2020) in Google Play and Apple App stores for consumer-facing apps for asthma management that pair with an inhaler-based sensor [77]. Among 2,594 apps, six were found to be evidence-based. Interventions modestly improved maintenance inhaler adherence and reduced rescue inhaler use, but did not impact control. Effects on exacerbations, quality of life, and pulmonary function were not evaluated. Positive effects on patient satisfaction were found. However, a more comprehensive evaluation of products and their impact on health outcomes and privacy is needed before clinicians and patients can weigh the benefits against the resources needed to adopt these technologies.

Portable electronic spirometers allow for at-home lung function monitoring. A systematic review of commercially-available portable electronic spirometers designed for asthma patient use was carried out in 2017 [78]. Sixteen devices allowed for the monitoring of basic lung function parameters, but only 31% provided in-app videos on how to perform breathing maneuvers. Most devices provided graphical representations of lung function results, but less than half gave immediate feedback on the quality of the breathing maneuver. Several devices (25%) were FDA-approved and their costs ranged from US$99 to $1,390. Information on data security (63%), measurement accuracy (50%), and association with patient outcomes (0%) were commonly limited. Promising data of a peak flow diary compliance with an electronic peak flow meter and linked smartphone app were published [79]. An app-based portable spirometer (VitalFlo mobile spirometer) has been validated in adolescents with asthma [80].

11.8 Platforms

More than one million health and well-being apps are available from the Apple App and Google Play stores [77]. Some apps use built-in mobile phone sensors to generate health data on asthma. A study identified the types of built-in mobile phone sensors used in apps listed on curated health app libraries, the range of health conditions these apps address, and the cross-platform availability of the apps. Eighteen apps for respiratory, dermatological, neurological, and anxiety

TABLE 11.3 Some examples of e-platforms in asthma.

Company	Website	Device
Adherium	adherium.com	Inhaler sensor
AioCare	aiocare.com	Spirometer
Aluna	aluna.io	Spirometer
AsthmaTuner [81]	karolinskainnovations.ki.se/en/companies/medituner-eng/	patient app, a cloud-based storage solution and a healthcare interface, Bluetooth spirometers
Cohero Health	coherohealth.com	Spirometer and inhaler sensor
INSPIRERS [49, 82–84]		inhaler usage detection, game, and peer support
Medtep	medtep.com	
My Air Coach [85]	myaircoach.eu	large scale platform with many exams
Nuvoair	nuvoair.com	Spirometer
Propeller Health	propellerhealth.com	Inhaler sensor

conditions were identified, representing 1.1% (8/699) to 3% (2/76) of all apps examined. Cameras, touch screens, and microphones were the most frequently used built-in sensors. Several platforms are available for asthma but few appear to be validated (Table 11.3).

An evidence-based, point-of-care tool was devised and tested to guide the completion of asthma action plans in practice [81].

11.9 Serious games

Serious games are effective and innovative digital tools for educating patients on positive health behaviors. A systematic review, published in 2020, identified in chronic diseases (1) serious games intended to educate patients on medication adherence, education, and safety, (2) types of theoretical frameworks used to develop serious games for medication use, and (3) sampling frames for evaluating serious games on medication use. Using the PRISMA guidelines, 953 publications were screened [86] but only 16 studies featuring 12 unique serious games were published from 2003 to 2019, including components medication adherence, education, and safety. Eight serious games were tested in adolescents, three in young adults, and one in adults. Limited studies exist on serious games for health that incorporate medication use.

A systematic review of serious games in asthma education was carried out up to 2016 [87]. A total of 12 articles were found to be relevant, describing 10 serious games. All serious games were directed toward children. A high average Medical Education Research Study Quality Instrument score was found. Most of the serious games were associated with high rates of satisfaction and improvement in children's knowledge. Although serious games designed for asthma education have evolved with advances in technology, results of their evaluation remained similar across studies, with clear improvements in knowledge but little or no change in behaviors and clinical outcomes.

Newer studies have been published. A novel gamified mobile application for pediatric patients with asthma (ASTHMXcel) [57–59] improved asthma control, knowledge, and quality of life, and reduced emergency department visits and prednisone use with high satisfaction scores. A cross-sectional study validated in children an interactive tablet-based game with a portable game controller that can transduce a signal from the user's breath to generate a PEF value [88]. INSPIRERS also includes a gamified approach.

11.10 Impact of digital health on asthma

11.10.1 Phenotype discovery using digital health

An example of digital health in phenotype discovery was proposed by MASK-air [89,90]. Multimorbidity in allergic airway diseases was well known, but no data existed regarding the daily dynamics of symptoms. To better understand this, control of daily allergic multimorbidity (asthma, conjunctivitis, and rhinitis) was assessed. Eight hypothesis-driven patterns were defined based on visual analog scale (VAS) levels. A previously unrecognized extreme pattern of uncontrolled multimorbidity was identified in

2.9% of the days (Rhinitis High-Asthma High-Conjunctivitis High). This hypothesis-generating study was confirmed by classical epidemiologic studies [91,92] that showed that ocular symptoms are important to consider in severe asthma, [91] and that the severity of individual allergic diseases increases with the number of allergic multimorbidities [93]. These findings were reinforced using computational analyses suggesting common pathways in multimorbidity [94,95]. They were confirmed by a genomic approach in the MeDALL study (Mechanisms of the Development of Allergy, FP7) [96] showing a novel whole blood gene expression signature for asthma, dermatitis, and rhinitis multimorbidity in children and adolescents [97].

Persistent asthma phenotypes among adolescents were longitudinally evaluated to find asthma-related outcomes using INSPIRERS studies [83,98]. Latent class analysis was applied to demographic, environmental, and clinical variables, collected at a baseline medical visit. Three classes/phenotypes of persistent asthma were identified with different patterns in longitudinal asthma-related outcomes, supporting the importance of profiling asthma phenotypes in predicting disease outcomes that might inform targeted interventions and reduce future risk.

11.10.2 Diagnosis

Peak expiratory flow (PEF) curves are a useful but cumbersome tool in diagnosing work-related asthma. Using a digital spirometer and a smartphone app, time to a clinical decision could be shortened considerably. The physician's time spent analyzing PEF data was also shortened [99].

11.10.3 Management

A systematic review (up to 2016) identified features implemented in mobile apps that supported asthma self-management, adherence, and clinical effectiveness [100]. Twelve randomized controlled trials (RCTs) were included. The most successful interventions included multiple features, but effects on health-related outcomes were inconsistent. No studies explicitly reported adoption of and adherence to the technology system. The meta-analysis included three trials and showed improved asthma control.

Another systematic review (up to 2016) summarized the effects of apps on self-management outcomes in patients with asthma and assessed the functionalities of effective interventions [101]. Ten studies met all the inclusion criteria. App usage improved asthma control (five studies), lung function (two studies), and quality of life (three studies), while there was no significant impact on self-efficacy scores (two studies). Effects on economic outcomes were equivocal.

Newer studies have been published. Breathe is an app developed for the self-management of asthma in adults. In a quasiexperimental approach in 677 individuals with asthma [102], there were no statistically significant differences in the change of asthma hospitalizations, emergency department visits, or physician office visits by comparison with the control group. Asthma control can be accurately assessed in the home situation by combining parameters from wearable respiratory physiology sensors (WEARCOM study) [103]. The effectiveness of myAirCoach, an mHealth self-management system for asthma, was demonstrated in 42 asthmatic patients [53], improving asthma control and quality of life, with a reduction in severe asthma exacerbations.

In children, an eHealth asthma care program was implemented in daily clinical practice. It was technically and clinically feasible, enabled safe remote care, and seemed to be beneficial for health outcomes and healthcare utilization [104]. AIM2ACT is a dyadic mobile health intervention designed to increase helpful caregiver support as early adolescents engage in asthma self-management behaviors [105]. In a pilot study on 33 adolescents, participants randomized to AIM2ACT had significant improvements in asthma control scores. The continuous monitoring of pediatric asthma patients using the kHealth asthma kit generates insights into the relationship between their asthma symptoms and triggers across different seasons [106,107].

11.10.4 Adherence to treatment

Nonadherence to asthma daily controller medications is a common problem, reported being responsible for over 50% of asthma hospitalizations. In chronic diseases, many mHealth apps are available to improve medication adherence [108,109]. Adherence in RCTs is high but does not reflect the real-life situation. Alternative measurements of adherence in real-life settings are needed, with mHealth possibly helping patients and healthcare providers to improve adherence.

A systematic review (2019) studied apps improving adherence to inhaled corticosteroids (ICS) among patients with persistent asthma, as well as patient satisfaction [110]. Twelve trials found a small but significant overall effect of eHealth interventions on adherence to ICS. However, there was considerable heterogeneity among studies. Participants found the interventions to be helpful and satisfactory.

Newer studies have been performed. A large study on 37,359 commercially insured patients with asthma identified from administrative claims in the HealthCore Integrated Research Database (HIRD) between April 1, 2018, and March 31, 2019 explored Structural Determinants of Adherence Rates using the Patient Activation and Encouragement Tool TRUSTR [111]. The mean adherence rate was 59%. Statistical modeling results revealing structural determinants, such as the opportunity to nudge, were higher among younger patients, as they have a higher probability of being nonadherent. Methodologically, the lateralization approach demonstrated the potential to capture real-world evidence beyond clinical data and merge it with clinical data. Adults with uncontrolled asthma and prescribed ICS (inhaled corticosteroids) and SABA (short acting ß-agonists) were enrolled in a 14-week study. In another study, inhalers were fitted with electronic medication monitoring to track real-time usage [112]. Patients received reminders and feedback on ICS and SABA use via a smartphone application and clinician phone calls. Patients maintained high baseline ICS adherence and decreased SABA use. Adherence and usage patterns of ICS-LABAs by using inhaler-monitoring technology was studied in a real-world study [113]. The study supported the use of inhaler sensors as tools to directly and accurately measure ICS-LABA adherence and rescue medication use.

In 234 adolescents, in a randomized controlled trial, the ADAPT (ADolescent Adherence Patient Tool) intervention increases medication adherence in adolescents having poor adherence rates at baseline [114].

11.11 Conclusion

Although digital health in asthma is raising a lot of promises, many earlier studies were unsuccessful. Newer studies in large samples are more informative but there are still several unmet needs in our knowledge. Several principles can be raised:

(i) The mHealth tool should be validated but validation is exceptional and there may be serious drawbacks.
(ii) Digital health devices should follow some recommendations such as those of the digital principles' organization (https://digitalprinciples.org/, see Table 11.3 in Section 11.5).
(iii) The methodology should be excellent and the sample size sufficient. Unfortunately, this is not the case in most studies, but several protocols have been published and new studies are in process.
(iv) Barriers to digital health design and research should be understood [115,116]. These include physician financial reimbursement and licensing for tele-healthcare services. Other limitations are related to liability, professionalism, and ethical issues such as breach of patient confidentiality and privacy [9].
(v) Acceptability of digital tools is of paramount importance and may need automated systems requiring minimal input from the user and providing timely advice with shared-decision making [117,118]. Users should take part in cocreating their tools, not only autonomously developing skills about their health (beyond disease management), but also about technologies (understanding the stakes related to technologies, learning how these are developed).
(vi) A range of available digital health interventions has been explored in pediatric asthma with promising but variable results, limiting their widespread adoption in clinical practice. In this age group, specific ethical issues should be considered [119,120].

However, digital health is a new paradigm that is assessed using current state-of-the-art methods. It may need innovative approaches for assessment and use of the strength of big data analysis. As an example, in MASK-air, we rarely use longitudinal approaches, given that, in the real-life setting, very few patients are adherent to both the app and the treatment, making longitudinal studies difficult to interpret. On the other hand, we have used cross-sectional data and identified novel phenotypes of multimorbidity as well as novel patterns of treatment combining monotherapy and comedication [89]. When analyzed with classical methods, these novel findings could not have been discovered. Moreover, in classical trials, patients are perfectly characterized, whereas in many mHealth studies, due to privacy, only age, sex, and a few clinical features can be studied. However, the data obtained are compelling.

Using machine learning with mHealth biomarkers that will be derived from the tools presented herein and discovering novel approaches for the follow-up of patients will probably be considered as change management for asthma in order to reduce severity in a cost-effective manner [73]. However, novel thinking may be needed to appreciate the revolution brought by these approaches. These include novel approaches exploring other realities of asthma as a psychosomatic disease resulting from the social and economic context including (1) the availability/affordability of medications, (2) disparities within a country, and (3) the proposition of a global approach tailored to the healthcare services of the country or region and its affluence [121].

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