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Invited Review Article

New medical big data for P4 medicine on allergic conjunctivitis

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A B S T R A C T

Allergic conjunctivitis affects approximately 15–20% of the global population and can permanently deteriorate one's quality of life (QoL) and work productivity, leading to societal work force costs. Although not fully understood, allergic conjunctivitis is a multifactorial disease with a complex network of environmental, lifestyle, and host contributory risk factors. To effectively enhance the quality of treatment for patients with allergic conjunctivitis, as well as other allergic diseases, the field must first comprehend the pathology underlying various individualized subjective symptoms and stratify the disease according to risk factors and presentations. Such competent stratification and societal reconstruction that targets the alleviation of the damage due to allergic diseases would greatly help ramify personalized treatments and prevent the projected increase in societal costs imposed by allergic diseases.

Owing to the rapid advancements in the information and technology sector, medical big data are greatly accessible and useful to decipher the pathophysiology of many diseases. Such data collected through multi-omics and mobile health have been effective for research on chronic diseases including allergic and immune-mediated diseases. Novel big data containing vast and continuous information on individuals with allergic conjunctivitis and other allergic symptoms are being used to search for causative genes of diseases, gain insights into new biomarkers, prevent disease progression, and, ultimately, improve QoL. The individualized and holistic data accrued from new angles using technological innovations are helping the field realize the principles of P4 medicine: predictive, preventive, personalized, and participatory medicine.

Introduction

The Fourth Industrial Revolution particularly opened new frontiers in the field of P4 (predictive, preventive, personalized, participatory) medicine.[1–4] This field benefited from the vast individualized big data accrued from the Internet of Medical Things (IoMT) and biosignal sensors attached to numerous daily devices, which allow for the real-time artificial intelligence (AI)-driven

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analysis of biometric data, subjective symptoms, and lifestyle factors.[5]

Studies indicate that the prevalence of allergic diseases has increased over the past few decades.[6–9] Allergic conjunctivitis, in particular, affects approximately 15–20% of the global population.[10] Allergic conjunctivitis not only chronically affects quality of life (QoL) but also continuously leads to its deterioration through repeated allergic attacks, ultimately affecting one's work productivity and societal work force costs.[10–12] Currently, the pathogenesis of allergic conjunctivitis is yet to be fully elucidated. However, the consensus is that it is a multifactorial disease with environmental, lifestyle, and host contributory factors including pollen, particulate matter with diameters smaller than 2.5 μm ($PM_{2.5}$), diet, smoking, exercise habits, use of contact lenses, age, and family history.[13–15] The complex pathology together with the highly diverse and lifestyle-associated risk factors (of which interconnections are not fully understood) limits the effectiveness of existing epidemiological approaches in understanding the disease process.[16,17] Additionally, traditional research methods limit data collection strictly during hospital visits; hence, the continuity of data accrual is compromised, and data on lifestyle factors become inevitably subjective and less reliable. Therefore, we suggest a roadmap to better treat allergic conjunctivitis through three main objectives: 1) understanding the multiformity of allergic conjunctivitis by longitudinally observing various subjective symptoms, 2) stratification and visualization of the causative factors to better optimize a multiplex treatment regimen for patients with allergic conjunctivitis, and 3) implementation of P4 medicine to prevent exacerbation or onset of allergic conjunctivitis.

Among big data, various omics data (multi-omics) along with data gathered from mobile health (mHealth) have been invaluable in understanding chronic diseases such as asthma and dry eye disease.[18–21] The increasing prevalence of allergic conjunctivitis constitutes costs to not only individuals but also countries. Therefore, the realization of P4 medicine through visualizing the interactions among genetic, environmental, and lifestyle factors, multi-omics analysis, and the utilization of mHealth could minimize the expenditure on treating allergic conjunctivitis by reducing its prevalence and contributing to QoL improvement.

In this review, we discuss the potential impact of medical big data (including multi-omics and mHealth) on the management and treatment of allergic conjunctivitis in the context of P4 medicine.

Paradigm shift in the impact of medical big data on allergic conjunctivitis

In the field of medicine, big data held potential as a foundation for creating individualized physiological profiles, which could then be utilized to diagnose and treat patients in an individualized, timely, and effective manner.[22] Furthermore, such medical profiles could construct robust prognostic and predictive models tailored to patients' profiles and various disease states. Unsurprisingly, the breakaway from traditional hypothesis-testing research to a hypothesis-generating approach enabled by big data analysis provided much hope to researchers, regardless of their field. Until recently, however, the influx of big data far exceeded the ability to process them, and many researchers had to opt for traditional data due to budgetary and technological constraints. Owing to the rapid advances made in information and communications technology, the processing capabilities of even consumer products have increased exponentially and have enabled researchers to approach big data analysis. Currently, in the medical sector, big data are expected to assist directly in both improving the quality of healthcare and accelerating research and innovations previously limited by the access to medical big data.[23]

The collection of medical big data was likely fueled initially by the widespread move toward electronic health records, electronic medical billing, and medical image data. However, as the Fourth Industrial Revolution emerged, there has been another paradigm shift in medical data collection. Adding to the existing medical data, mostly gathered from aforementioned routes and epidemiological analyses, data from multi-omics studies and mHealth using IoMT-integrated devices have been introduced. While traditional medical big data were well suited for analyses from a population medicine perspective, they lacked applicability at an individual level due to their aggregate nature (for better or worse).

Recognizing these shortcomings, researchers and clinicians now reach for data beyond the footprints of traditional medical care to tailor aggregate data for individual patients. One such field of study is multi-omics. The use of omics, a method concerning global assessments and characterization of a pool of biological molecules, in day-to-day patient care settings had initially been a pipedream due to the demanding resources needed for a complete evaluation. Beginning with the Human Genome Project from 1990 to 2003, many subcategories of omics (including epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics) emerged, and the utility of omics analyses have been investigated in detail.[24,25] Although investigation continues, medicine as a field now readily has access to high-throughput multi-omics analyses, and healthcare providers are able to reach closer to an individualized, multi-dimensional understanding of one's pathology. The resulting etiological details ranging from developmental factors (genomics and epigenomics) to functional outcomes (metabolomics), as well as their connecting links (transcriptomics and proteomics), are invaluable for individualized care. Consequently, multi-omics data are imperative for constructing more robust medical big data and vital in the realization of P4 medicine.

Another key aspect of the rising paradigm shift in medical big data is the widening spectrum of the utility of mHealth in patient care and medical research. The widespread penetrance of biosensors on smartphones and wearable devices led to emergence of a phenomenon, termed IoMT.[26] IoMT contains vast, real-time data such as biosignals obtained from photoplethysmography, electromyography, electroencephalography, movement data, and body sounds at an individual level.[27] Thus, mHealth with close IoMT integration has the potential to yield highly specific health parameters for each patient. This variety and longitudinality of medical data, mixed with cloud-based computing, could lay a robust groundwork for P4 medicine.

The variety of information on individuals provided by novel medical data could be key to further implementing the principles of P4 medicine: veering away from a one-size-fits-all approach and examining holistically individualized factors to create customized targeted therapy, to maximize therapeutic value for every procedure and treatment.[28]

New medical big data on allergic conjunctivitis

Multi-omics and allergic conjunctivitis

Allergic conjunctivitis is characterized by an IgE-mediated hypersensitivity reaction,[29] resulting from mast cell degranulation secondary to direct contact with an allergen on the ocular surface. For a fundamental comprehension of a disease's pathogenesis, it is imperative to understand the various genomic impacts. Considering the importance of the genome in understanding the pathology of allergic diseases, genomic analyses of the host factors have been increasingly used in devising effective treatments.[14,30] Not only does a genomic scan reveal the molecular dynamics of the patient, but it may also reveal target proteins or metabolites that can be altered through novel drug development. Recent efforts to detect susceptibility genes associated with allergic diseases have yielded an ample amount of data. In the following section, we discuss the status and impact of novel medical big data, driven by genomics analyses of allergic conjunctivitis and other immune-mediated allergic diseases.

Genetic factors of allergic conjunctivitis were the first targets of investigation, and genetic linkage analyses of chromosomes (specifically, chromosomes 5, 6, 11, 12, 16, and 17) were performed.[31] These analyses revealed linkages between allergic conjunctivitis and chromosomes 5, 16, and 17, as well as a weak linkage with chromosome 6. In the development of most immune-mediated disease processes, including allergic conjunctivitis, cytokines and inflammatory cells are considered major players. Leonardi *et al.* used multiplex bead analysis of cell-free tears, and patients with allergic conjunctivitis were found to express higher levels of IL-1β, IL-2, IL-5, IL-6, IL-12, IL-13, and monocyte chemoattractant protein-1 in their tears than controls.[32] In a subsequent subgroup analysis, the levels of eotaxin and tumor necrosis factor-α were increased only for vernal keratoconjunctivitis (VKC) but not for other subtypes of conjunctivitis. VKC (particularly the type refractory to 0.1% tacrolimus and highly potent steroid eye drops) has shown various associations with T cell proliferation and cytokine production, illustrated by the stimulation of T cell receptor signaling pathways, T cell co-stimulation, adaptive immune response, and positive regulation of T cell proliferation.[33] These results indicate that a standard b.i.d. application of 0.1% tacrolimus was not sufficient to suppress either cytokine production or T cell proliferation and activation among patients with refractory VKC. Therefore, uncovering the schema of cytokine dynamics in allergic conjunctivitis may reveal critical biomarkers that will enable personalized visualization of disease activity and determination of therapeutic targets, ultimately contributing to the implementation of P4 medicine for allergic diseases.

Another technique employed to search for allergic disease-associated genes is the genome-wide association study (GWAS), a hypothesis-free methodology used to determine common gene variants among the affected cohort. At the current stages of research, candidate genes for bronchial asthma,[34,35] atopic dermatitis,[36] allergic rhinitis,[37] food allergies,[38,39] and many more allergic diseases have been recognized using GWAS. Unfortunately, GWAS specific to allergic conjunctivitis have not yet been performed; thus, there is limited knowledge on genetic factors unique to allergic conjunctivitis. Due to the high comorbidity of other allergic diseases – demonstrated by the classic atopic triad of asthma, eczema, and allergic rhinitis – and allergic conjunctivitis, an all-encompassing genomic approach to understanding the position of allergic conjunctivitis within the schema of allergic diseases is crucial to formulating an effective treatment regimen.

Although more research is warranted on allergic conjunctivitis, the rate at which genomic data have been accumulating on this topic has been unprecedented. Unfortunately, allergic diseases are highly multifactorial, with environmental, host, and lifestyle factors deeply interconnected with different stages of their pathogenesis, which complicates a clear identification of susceptibility genes.[14] This is further complicated by the coexistence of other atopic diseases such as atopic dermatitis and rhinitis, which obscure the boundaries of the phenotypic definition of allergic conjunctivitis and other similar diseases. Hence, efforts made at longitudinal monitoring through mHealth can be pivotal in incorporating detailed environmental, host, and lifestyle risk factors together with genomic data to decipher and define the specific details of allergic conjunctivitis.

Various presentations – such as age at onset, severity, and prognosis – and the complex pathophysiology of allergic disease inevitably result in variability in the process of healing without intervention or with standard treatment, not to mention side effects. Moreover, differences between Asian and Western populations have also been suggested.[40] Such demographic factors could be another facet for future researchers and practitioners to consider in treating the affected population. To resolve the increasing complexity resulting from further research on allergic diseases, a standardized method that stratifies the various diseases based on distinct phenotypes is critical as the next step in implementing P4 medicine.

Mobile health and allergic conjunctivitis

With advances in the capabilities of mobile devices, their potential as a means for improving healthcare access, quality, and value has attracted the attention of many researchers and practitioners. As mobile devices are increasingly used in medical settings, the WHO defined mHealth as a "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices."[41] A longstanding Achilles' heel of traditional hospital-oriented healthcare was the lack of continuity. However, the longitudinality of healthcare brought forth by mHealth is thought to hold the key to connecting the bridges between in-person encounters. Further, individualized data on lifestyle and environmental factors can be vital for tailoring therapies for chronic conditions such as allergic conjunctivitis, and for promoting self-management and health awareness for the healthy population.[42] Recently, owing largely to the release of ResearchKit and ResearchStack in 2015 and 2016, respectively, smartphones have gained traction in their use as a mode of collecting medical big data for clinical research.[43,44] ResearchKit and ResearchStack are open-source frameworks aimed at developing research apps for iOS and Android devices, respectively. Since their release, the modularity of the platforms has vastly helped facilitate medical research. These two frameworks are particularly advantageous in executing large-scale observational studies aiming to analyze real-time biometric and biosignal data with global opt-in sampling strategies. ResearchKit, in particular, has been widely used in generating medical big data through mHealth apps, demonstrated by the 23 publication hits on PubMed (as of March 14, 2020; Table 1). Currently, mHealth bridges the gaps of traditional research methodologies,[43] although its transformation into taking a more major role is very likely. Table 2 summarizes mHealth apps released for research on allergic diseases found in a PubMed search. Four ResearchKit-based apps have been released for specific allergic diseases: Asthma Health App,[50,53,54] Zensoku-Log,[75] Itch Tracker,[76] and Allersearch.[77] Many other apps have been released for a wide range of allergic complications such as food allergy,[78] asthma management,[43,66–68,70,79] allergic respiratory disease,[43,68,80] allergic rhinitis,[66,67,70,72–74,81] pollinosis,[65–69] skin allergy,[43] and drug allergy.[71] However, these applications are in the stages of validation, and the implementation of an mHealth app can take various forms, many of which are yet to be explored. Therefore, we advise readers to be careful when evaluating mHealth apps as final products.

The onset and progression of allergic conjunctivitis are strongly influenced by many environmental, lifestyle, and host factors.[13–15] Due to the complex nature of their interactions, the phenotypes and presentations of allergic diseases vary case-by-case, and this heterogeneity manifests as differences in the severity, onset, and prognosis of the disease for every patient.[82] However, despite knowledge of the diverse mechanisms underlying the pathogenesis of allergic diseases, the current standard of care does not provide individualized treatments. This is partly due to its multiorgan-

Table 1
Published clinical research using ResearchKit apps.

App	Release date	Disease	Developer	Publication date	Authors	Journal
mPower	2015/3	Parkinson's disease	University of Rochester Medical Center, USA	2016/3	Bot *et al.*[45]	*Sci Data*
MyHeart Counts	2015/3	Cardiovascular health	Stanford University, USA	2017/1	McConnell *et al.*[46]	*JAMA Cardiol*
mPower	2015/3	Parkinson's disease	University of Rochester Medical Center, USA	2017/2	Doerr *et al.*[47]	*JMIR Mhealth Uhealth*
Back on Track	2015/7	Acute anterior cruciate ligament tears	University of Freiburg, Germany	2017/2	Zens *et al.*[48]	*JMIR Mhealth Uhealth*
Mole Mapper	2015/10	Melanoma	National Cancer Institute, USA	2017/2	Webster *et al.*[49]	*Sci Data*
Asthma Health	2015/3	Asthma	Icahn School of Medicine at Mount Sinai, USA	2017/4	Chan *et al.*[50]	*Nat Biotechnol*
mPower	2015/3	Parkinson's disease	University of Rochester Medical Center, USA	2018/4	Nguyen *et al.*[51]	*Stud Health Technol Inform*
Autism & Beyond	2015/10	Autism spectrum disorder	Duke University, USA	2018/1	Egger *et al.*[52]	*NPJ Digit Med*
Asthma Health	2015/3	Asthma	Icahn School of Medicine at Mount Sinai, USA	2018/3	Chan *et al.*[53]	*Sci Data*
Asthma Health & My Chart	2015/3	Asthma	Icahn School of Medicine at Mount Sinai, USA	2018/6	Genes *et al.*[54]	*NPJ Digit Med*
Flu-Report	2016/11	Influenza	Juntendo University Faculty of Medicine, Japan	2018/6	Fujibayashi *et al.*[55]	*JMIR Mhealth Uhealth*
Feverprints	2016/3	Fever	Boston Children's Hospital, USA	2018/8	Hausmann *et al.*[56]	*J Gen Intern Med*
PARADE	2016/7	Rheumatoid arthritis	GlaxoSmithKline, USA	2018/9	Crouthamel *et al.*[57]	*JMIR Mhealth Uhealth*
Healthy Pregnancy Research Program	2017/3	Pregnancy	Scripps Research Translational Institute and WebMD, USA	2018/9	Radin *et al.*[58]	*NPJ Digit Med*
GlucoNote	2016/3	Type 2 diabetes	The University of Tokyo, Japan	2019/4	Yamaguchi *et al.*[59]	*JMIR Mhealth Uhealth*
MyHeart Counts	2015/3	Cardiovascular health	Stanford University, USA	2019/4	Hershman *et al.*[60]	*Sci Data*
DryEyeRhythm	2016/11	Dry eye disease	Juntendo University Faculty of Medicine, Japan	2019/5	Inomata *et al.*[19]	*Ophthalmology*
N/A	2017/6	Perioperative functional capacity assessment	University of Chicago, USA	2019/9	Rubin *et al.*[61]	*Anesth Analg*
LocoMonitor	2016/2	Locomotive syndrome	Juntendo University Faculty of Medicine, Japan	2019/11	Yoshimura *et al.*[62]	*J Orthop Sci*
N/A	2017/5	Sexually transmitted infections	Washington University School of Medicine, USA	2019/11	Ahmad *et al.*[63]	*J Am Med Inform Assoc*
DryEyeRhythm	2016/11	Dry eye disease	Juntendo University Faculty of Medicine, Japan	2019/11	Inomata *et al.*[20]	*JAMA Ophthalmol*
Luna	2018/2	Menstrual pain	The Institute of Complementary and Integrative Medicine of the University of Zurich, Switzerland; the Institute for Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Germany; and Smart Mobile Factory, Berlin, Germany	2020/2	Wang *et al.*[64]	*JMIR Mhealth Uhealth*
DryEyeRhythm	2016/11	Dry eye disease	Juntendo University Faculty of Medicine, Japan	2020/2	Inomata *et al.*[21]	*Ocul Surf*

targeting characteristics – including the eyes, ears, skin, nasal cavity, respiratory system, digestive system, and central nervous system – which necessitates concurrent considerations by many specialists, and the need to establish an organic cross-disciplinary communication became a barrier to tailoring treatments for each patient. Further, which specialists are needed to care for patients throughout the "atopic march"[83] constantly changes from childhood to adulthood, an obstacle to in-depth cohort studies of the population with allergic dysfunctions, and the insufficient global standardization of medical big data in this field further limits progress in big data analysis.

mHealth is currently thought to hold the key to creating personalized medicine for allergic diseases.[43] mHealth app-based research, over traditional research methodologies, enables easier access to environmental factors using Global Positioning System (GPS) and climate data. Lifestyle factors using real-time and longitudinal biosignal sensor data and host factors using individual host data to form a potent database. The convenience and continuity of patient-reported outcomes – generally as questionnaire-style surveys that contain information on disease activity and QoL – that mHealth was able to provide has been remarkable.[84] mHealth apps can be used to perform large-scale cross-sectional research and to reach out to younger populations who less frequents medical facilities.[19–21] A global implementation of mHealth apps also has the potential to organically standardize the collected big data and enable global-scale cohort studies.[19,73] Such utility of mHealth fits perfectly in P4 medicine through the observation of various subjective symptoms of allergic diseases, which can ultimately be analyzed to visualize and stratify the patient population. Once a deeper understanding of the disease pathogenesis and its variability is attained, allergic diseases could be managed effectively using personalized treatments to prevent the onset or progression of the disease altogether before any chronic damage.[43,85]

Cloud-based research is effective in the early detection and management of chronic diseases such as dry eye disease and diabetes mellitus.[19,20,86,87] Our team developed AllerSearch – an iOS app based on ResearchKit aimed at gathering real-world data on individual subjective symptoms and lifestyle factors on allergic

Table 2
Smartphone applications released for monitoring of allergic conditions.

Release date	App	OS	Condition	Developer
2013/2	WebMD Allergy app[65]	Android & iOS	Pollinosis	WebMD, LLC, USA
2013/2	AllergyMonitor[66–69]	Android & iOS	Pollinosis and asthma	Technology Projects & Software Production, Italy
2013/6	POPET app[70]	Not available	Allergic rhinitis and asthma	POPET LLC, France
2015/1/22	Adverse Drug Reaction Causality/ Severity/Preventability[71]	Android	Drug allergy	Universiti Sains Islam Malaysia, Malaysia
2015/3	Asthma Health App[50,53,54]	iOS (ResearchKit)	Asthma	Icahn School of Medicine at Mount Sinai, USA
2015/8/1	Allergy Diary[72–74]	Android & iOS	Allergic rhinitis	MACVIA-ARIA Sentinel Network
2016/2/16	Zensokulog[†,75]	iOS (ResearchKit)	Asthma	Juntendo University Faculty of Medicine, Japan
2017/4/12	Itch Tracker[76]	iOS (ResearchKit)	Pruritus	Nestlé Skin Health (Maruho Co., Ltd.)
2018/2/1	Allersearch[77]	iOS (ResearchKit)	Pollinosis	Juntendo University Faculty of Medicine, Japan

OS, operating system; MACVIA, Contre les MAladies Chroniques pour un VIeillissement Actif; ARIA, Allergic Rhinitis and its Impact on Asthma.
† Applications released in Japanese are romanized as pronounced.

pollinosis – and has conducted a large-scale cloud-based clinical study since February 2018 (Fig. 1A).[77] Pollinosis has a wide range of effects on various physiological systems, and to effectively implement mHealth in our research, we have facilitated active communication among specialists in the fields of ophthalmology, otorhinolaryngology, internal medicine, allergy medicine, patient and public involvement (PPI), and epidemiology and statistics in the development of our app. After obtaining consent on data collection through an on-app consent form (Fig. 1B), AllerSearch gathers information on subjective symptoms, environmental factors, and lifestyle factors – including pollen distribution, $PM_{2.5}$, preventive measures, QoL questionnaires, conjunctival images, location, movement speed, and acceleration – with the help of smartphone-embedded sensors and patient participation. An outline of one's basic profile includes height; weight; age; biological sex; family composition; presence of allergic pollinosis; medical history of conditions such as hypertension, diabetes, heart disease, respiratory disease, brain disease, liver disease, renal disease, hematologic disease, malignancy, and mental illness; and lifestyle and environmental information such as smoking status, exercise pattern, contact lens use, sleep pattern, home environment, and preventative behavior regarding pollinosis such as use of a mask, eye drops, nasal drops, air purifier, glasses, and washing the eyes (Fig. 1C). In addition, the app requests information on QoL and work productivity (Fig. 1D). To maximize the ease of using the app for facilitating frequent data input by the participants, we have simplified the user interface to shorten the input process, as shown in Figure 1E, and allowed for a longitudinal collection of real-world big data on pollinosis.

Participatory medicine is a relatively new concept revolving around active cooperation of the patient and general population in improving healthcare.[2] mHealth, through its ability to enable communication between participants and researchers, has shown great utility in the field of participatory medicine as well. AllerSearch is currently sponsored by the Japan Agency for Medical Research and Development (AMED) and implements PPI as a core aspect of its design. AllerSearch provides participants with live updates on the collected data and their analysis in the form of distribution maps with subjective symptoms reported by users (Fig. 1F), as well as relevant climate information such as pollen distribution status, $PM_{2.5}$, and the Asian dust phenomenon (Fig. 1G). Additional information, namely, the number of participants, geographic distribution of subjective symptoms, and common measures to prevent pollinosis symptoms, is available for access online (http://allergy-search.com/analytics/index.php),[88] allowing for a bidirectional flow of information between researchers and participants.

mHealth shows great utility in the field of allergic disease by facilitating a real-time large-scale collection of data on a wide range of subjective symptoms as well as lifestyle factors to establish a solid foundation for medical big data and P4 medicine.

Pros and cons of crowdsourced study using mHealth

In the context of large-scale crowdsourced clinical research, implementation of mHealth can greatly streamline the informed consent request[89] and collection of medical big data,[19–21,64,90] biometric data,[49,52,56] and geographic data,[20,21,50,55] while

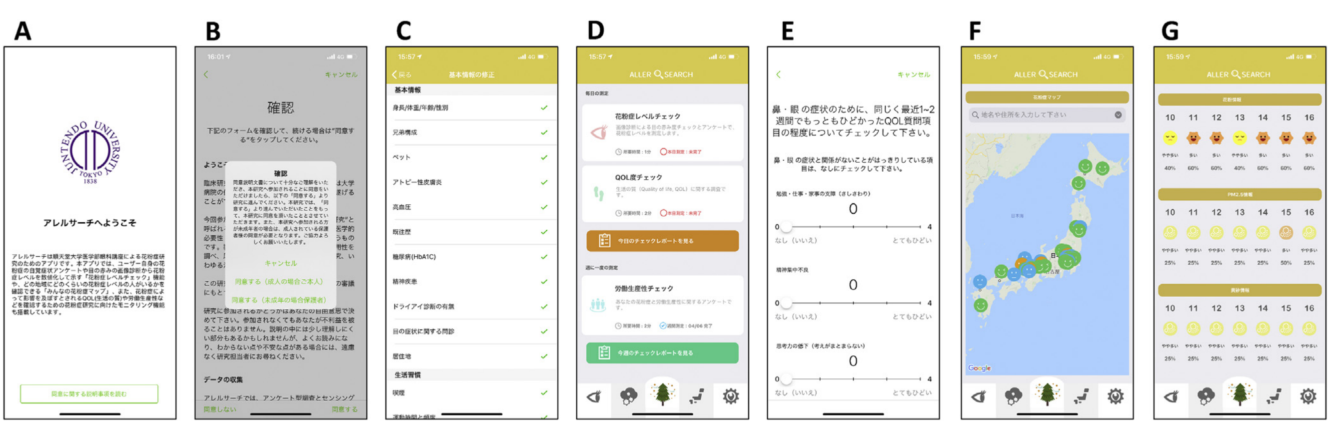

Fig. 1. Screenshot of AllerSearch (Language: Japanese). Welcome screen (**A**). Consent screen for participants (**B**). Screen for entering participant characteristics (**C**). Task screen (**D**). Questionnaires on quality of life (**E**). User's subjective symptom map (**F**). Forecast for pollen, $PM_{2.5}$, and yellow sand (**G**).

reducing research costs compared to traditional research methodologies (Table 3).[5,43] mHealth-driven research not only allows for real-time data collection but also reduces barriers to access through remote data collection and mobile device-attached sensors that expand the types of collectible data, including various biosignal, GPS, and accelerometer data. The vast increase in frequency of data collection and analysis enabled by mHealth helped create a robust biological dataset.

To develop a smartphone app, one should expect to pay between approximately $1400 and $40,000, according to a previous report.[90] Owing to the numerous premade design templates in ResearchKit, we reduced the expenditure on app development to a relatively low amount without needing to create an app from the ground up. However, one should expect additional costs from software updates that might be necessary to keep the apps up-to-date, which are generally done by third-party companies. Thus, the development and maintenance costs of a released smartphone app become an obstacle to limited-budget research.

Some other limitations of large-scale crowdsourced clinical research that remain to be resolved include the inconsistency in acquisition of consent forms, and the need for various interdisciplinary skillsets and technologies for big data analysis. However, certain limitations – namely, the possibility of selection and recall biases, the validity and reliability of the collected data, lack of clinical examinations for diagnosis, and the retention rate of the app (Table 3)[19–21] – are being addressed by various researchers, and we share some noteworthy considerations before implementing mHealth as part of a research design.

mHealth-based research is inevitably prone to biases, including selection and recall biases, due to its reliance on questionnaires (as part of its data collection) and mobile devices. Hence, the accuracy of episodic memory recall (henceforth recall) is critical for the reliability of the collected data. However, recall is regularly affected by the conscious and subconscious psychology of the study participants, which may result in recall bias. The need for a mobile device capable of executing the app also results in a selection bias toward a select population that has access to such devices. This, in the case of ResearchKit-based apps, limits the selection pool to iPhone users. The same limitation applies to ResearchStack-based apps; only Android users will be able to access the apps; hence, additional resources must be invested to develop apps that can run on multiple operating systems and devices. While ease of access for the younger population that accesses medical facilities less frequently definitely merits the use of mHealth, the limited usability of mobile devices among older people creates a hurdle for certain populations.[19–21] The economic status of participants could be another bottleneck for sample selection, as the penetrance of mobile devices could depend on the population's financial status, and mHealth-based research cannot prevent the unavoidable selection bias that stems from the active participation by people who are interested in the topic.[91] Thus, one must be mindful of such biases and make attempts to alleviate them through adjustments in the app and research design.

Another limitation of large-scale crowdsourced research yet to be addressed is the validity and reliability of the data collected through mHealth devices. Few developers, including those of DryEyeRhythm, Depression Monitor, and Back on Track, have completed the validation of questionnaires implemented in their mobile apps,[19–21,48,92] and such direct adaptation of a previously validated questionnaire can be a simple method to ensure validity of the data accrued through an app. For apps that remotely collect unprecedented types of data, developers are establishing methods to validate such data as seen in the cases of Mole Mapper[49] and mPower,[45] which incorporated image interpretation of skin burns and motion sensors, respectively. However, there is still a lack of global standardization in validating the various novel mHealth data. Thus, the timely establishment of quality assurance for mHealth apps is vital for maximizing the utility of mHealth.

Despite the biases of mHealth, they are steadily being addressed by researchers. Fortunately, with increasing usage of smartphones worldwide and simpler user interfaces,[93] the concern of usability among older generations will likely resolve over time, aided by their replacement by a mobile device-apt population. This inadvertently reduces the selection bias that stems from device and app usability, further strengthening the credibility of the collected big data. The novel medical big data, however, necessitate the participation of professionals who are skilled in extracting and analyzing relevant information from a large data pool, which will require knowledge in both statistics and medicine. Specialists in the field of bioinformatics already fit this description in the medical field. However, the hardware and software engineering and AI management that are projected to be key components of mHealth call for interdisciplinary fields that can foster specialists knowledgeable in mobile devices, their software development, and medicine.

Future directions of allergic conjunctivitis treatment toward P4 medicine

Fortunately, the Fourth Industrial Revolution helped build an immense library of medical big data through the collection of health and multi-omics study data, elucidating the complex network of pathologic factors through the rapid advancements in the field of AI analysis. The new light brought to various gene loci, biomarkers, and lifestyle risk factors is now being applied with P4 principles for the prevention, treatment, and attenuation of allergic conjunctivitis and other immunologic diseases. This will allow for visualization of various disease stages, QoL, and the specific pathophysiology on a case-by-case basis, enabling both effective and efficient treatment that benefits patients and healthcare providers.[15]

Particularly with allergic diseases, the phenotypic heterogeneity is unusually high.[82] Using this characteristic, the heterogeneity in the phenotypes and pathophysiology of one's disease could help track back and illuminate specific pathologic pathways to create personalized treatments. For such a purpose, novel functional and biopathological analyses are on the rise, including deep phenotyping[94,95] and endotyping,[30,96,97] which respectively concern the observable end-characteristics and various disease mechanistic pathways, to stratify the patient and public population through

Table 3
Pros and cons of crowdsourced studies using mobile health.

	Pros	Cons
Consent	Simple and comprehensive	Reliability
Data	Medical big data	Analysis environment, analysis technology
	Real-time data	Recall bias
	Remote (geological) data	Selection bias
	Biological data	Data reliability and validity
	Frequent and continuous data	Lack of clinical tests necessary for diagnosis
	Real-world data	Retention rate
Function	Geolocation	Complex for elderly people
	Biological sensor	Limited use depending on OS
	Real-time support/feedback	
Cost	Low	Development costs (consignment costs)
		Update cost

OS, operating system.

multi-dimensional analyses and provide timely, effective interventions.

Owing to the convenience and "pocketability" of modern mobile devices, mHealth is ideally positioned for monitoring subjective symptoms and lifestyle factors. The new digital biomarkers identified through analyzing novel medical big data could enable "digital phenotyping,[98]" which can play a huge role in the prevention and management of diseases as well as implementing P4 medicine in various medical fields. While conventional healthcare revolves around equipped facilities, mHealth expands the frontier of healthcare to daily lives, focusing on preventative efforts to maximize the efficiency of medical resources.[19,20] With a rapidly aging society as in Japan, there is a dire need for evidence-based health and medical guidance programs, not to mention the urgency to advance P4 medicine for preventative and preemptive means to extend societal contributions on a nationwide scale. As a catalyst for such a paradigm shift, mHealth has permeated throughout medical research and healthcare. Having demonstrated their aptness in handling chronic diseases,[19,20,86,87] the medical big data collected for the visualization of allergic and immunologic diseases, including allergic conjunctivitis, show great potential in promoting self-management by providing the population with tailored advice for treatment and prevention. Eventually, governmental and industry cooperation will be needed to incorporate medical knowledge in the management of outdoor and indoor environments, as allergens are highly associated with the landscape and household goods, and an AI and IoMT analysis of such allergen sources could aid in the research to minimize the progression and aggravation of allergic symptoms.

Patient and public involvement and patient privacy

To truly manage the current and impending damage caused by immune-mediated allergic diseases, the promotion of mHealth, continued research, and joint societal efforts are imperative. The virtuous cycle between individual efforts, society-wide co-production – including the triad of industrial, governmental, and educational entities – and the return as accomplishments in the research sector is needed to tackle conditions with increasing exigence such as allergic diseases.[15]

In relatively recent periods, researchers have explored the incorporation of public participation as a core part of their research methodologies. Such direct public involvement, termed PPI, attempts to better reflect the purposes of research and ultimately benefit the people involved and the society.[99] By recognizing the importance of public and patient perspectives from its design stages, this effectively makes research "'with' or 'by' members of the public."[100] However, the implementation of participatory medicine for allergic diseases has trailed behind that for rarer diseases and cancer, and efforts at investigating the efficacy of PPI in the context of allergic disease research have been insufficient.[2,101–103]

For this reason, the recent feats of PPI in the development of mHealth smartphone apps and the establishment of their long- and short-term objectives have been invaluable. The extrapolated effects on the promotion of various other genres of research beyond mHealth should lay groundwork for future clinical research as well as robust connections between medicine and society. The added experience-based societal and public insights on unmet medical needs help healthcare providers alleviate them by tailoring research and mHealth app development accordingly. To investigate the increasing prevalence of allergic diseases, our team developed AllerSearch, a PPI-implemented mHealth app starting in October 2019.[104] A significant portion of AllerSearch design concerns the refinement of PPI implementation for effective interaction between the involved parties. For this purpose, we aim for rapid utilization of patient/public inputs as well as medical data on lifestyle and environmental factors, namely, the three basic needs (food, clothing, and shelter) and climate data on airborne allergens. Such multidirectional communication will create an active network of information between participants and researchers, and the collected insights on PPI implementation could be shared with the research community to promote the usage of PPI. As the culture of medical big data is trending toward sharing among researchers, we also expect to contribute to the reliability and validity of medical big data on allergic diseases.

However, the caveat to this culture of sharing is the increasing concern for medical information privacy, and thus, the establishment of a secure data sharing network is of utmost importance. Indispensable for medical data privacy are a global international contract and individual nations' legal frameworks on medical data communication. Without adequate intervention, patients' privacy is at risk due to the ambiguity of outdated legal documents pertaining to electronic medical data, as well as the easy access to one's own health data. Notably, the General Data Protection Regulation from the European Union and Health Insurance Portability and Accountability Act from the Unites States – both legal foundations of medical data privacy – are in the process of revision, illustrating societal efforts to safely adopt the computational revolution into the healthcare sector.[23]

In this review, we discussed the advances in adapting the pillars of P4 medicine – predictive, preventive, personalized, participatory medicine – and its driving forces, namely, mHealth and medical big data analysis. The mHealth and multi-omics driven accrual of a novel class of medical big data is thought to be pivotal in unveiling the complex pathophysiology of allergic conjunctivitis, as well as other immune-mediated allergic diseases, to better realize P4 medicine in the affected population. This will ultimately allow for timelier diagnoses, effective treatment regimens, efficient allocation of medical resources, and prevention of disease onset. In the near future, we hope that mHealth will provide a platform for integrating holistic biometric and biosignal data with commonplace in- and out-patient healthcare settings, bringing i2b2 (Informatics for Integrative Biology and the Bedside) one step closer to reality.[105]

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Conflict of interest

The authors have no conflict of interest to declare.

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