Cross-hierarchical Integrative Research Network for Heterogenetic Eye Disease

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Society 5.0, a visionary human-centered societal model, fuels economic development and resolves long-standing social problems. The model establishes a technological foundation and social contract to integrate cyberspace into the physical (real) space fully. The medical infrastructure outlined by the model envisions a healthcare paradigm that revolves around preventative, lifelong patient- and population-centered care that functions seamlessly within one’s daily life.

In satisfying this goal, cross-hierarchical integrative data-driven biological research has received attention due to medical big data and artificial intelligence (AI) technologies, capable of highly accurate and rapid data analysis. However, the collection of big data has been a bottleneck, and the capability of AI analysis is not being utilized to its full potential. In solving this obstacle, we explore mobile health (mHealth) and multi-omics as two rich sources of medical big data. Additionally, we discuss the implications of cross-hierarchical integrative analysis that encompasses all levels of cellular function, from intracellular molecular dynamics to end-phenotypes. This is to understand ocular disease pathology and implement the pillars of P4 (predictive, personalized, preventative, participatory) medicine toward human-centered healthcare.

Here, we discuss notable studies in utilizing mHealth to stratify subjective symptoms, presentations of dry eye disease, and employing multi-omics machine learning targeted at elucidating immunologic mechanisms of corneal allograft rejection and ocular inflammation. We also discuss the role of cross-hierarchical integrative data-driven research in promoting future-oriented healthcare envisioned by the Society 5.0 plan.

Key words: Big data, mobile health, multi-omics, P4 medicine, heterogeneity
INTRODUCTION

Society 5.0 and P4 Medicine

Society 5.0 represents a visionary societal model proposed by the Cabinet Office, Government of Japan, as part of its 5th Science and Technology Basic Plan. By establishing a technological foundation and social contract in fully integrating cyberspace into the physical (real) space, it fuels economic development and resolves long-standing social problems. While Society 4.0 focuses on accessing digital information in all sectors of society, its successive model seeks to advance the interconnection between the user and the data and between the gathered data themselves. This is achieved through big data collected from the increasingly commonplace digital sensors and constant input from individuals, which is then meshed into a network known as the Internet of Things (IoT).

The accrued big data from the real space, while being collected, are analyzed by artificial intelligence (AI) in cyberspace to yield instant feedback to the real space. This constructive feedback loop ultimately generates newfound value from existing and new data. Hence, a long-term positive impact on various industries and society is expected.

Similarly, healthcare seeks to integrate big data and AI into routine care in the era of Society 5.0. Novel biosensors (such as photoplethysmogram, pulse oximeters, accelerometers, and electrocardiograms) are now emerging in commonplace smart devices. Hence, real-time medical information on individual subjective symptoms and physiological and lifestyle data is becoming increasingly accessible. Drawing a parallel to IoT, the Internet of Medical Things (IoMT) acts as a networking platform to communicate and share medical big data. The big data gathered from users, electronic medical records, and environmental/geographical reports from independent sources can be collected and analyzed by AI to implement core values of P4 medicine: predictive, preventive, personalized, and participatory medicine (Figure 1). This model will reduce the role of traditional facility-based care and introduce effective longitudinal patient- and population-oriented care based on personalized, lifetime, and preventative interventions within one’s daily life.

In the era of Society 5.0, data are commonly, and aptly, referred to as the "new oil". A robust big data accrual has the potential to establish personalized health profiles and relevant predictive models that are adjusted for individualized factors. This can then be utilized in prompt diagnosis and early intervention. As its name suggests, big data is a vast collection of data often characterized by its 3Vs: volume, velocity (update rate and influx speed), and variety. These characteristics of big data create obstacles in its management and analysis, often requiring highly specialized and costly equip-
Disease Heterogeneity and aim of this study

Most diseases do not exhibit an apparent dichotomy between the healthy and the ill. Diseases are often presented as a spectrum due to their varying presentations, progression (stage) of the underlying pathology, risk factors, and multiple mechanisms to a singular disease. For instance, dry eye disease (DED) is the most common ocular surface disorder. It is highly multifactorial and heterogeneous in its presentation. DED is affected by an intricate interaction between innumerable environmental, host, and lifestyle factors, including humidity, pollen, the particulate matter under 2.5 microns (PM 2.5), diet, smoking, exercise, contact lens (CL) use, age, sex, family history, and genetics. Its presentation varies; some have less severe symptoms, such as dryness and eye fatigue and others rapidly develop severe symptoms, such as photophobia and permanently decreased visual acuity. However, despite acknowledging its various pathologic pathways, multifactoriality, and heterogeneous presentation, the current standard of care primarily revolves around a single “gold standard” treatment. The treatment has minimal consideration for drug interaction with individual factors. To effectively resolve this “one-size-fits-all” approach to DED, a previously singular disease must undergo stratification in the context of distinct pathologic pathways, contributing factors, and subjective symptom presentation. This will optimize treatment regimens for each disease stratum.

Here, ocular conditions regulated by ocular immune dynamics and inflammatory processes (such as DED and corneal transplantation) are discussed in the context of AI-driven, molecular level, cross-hierarchical integrative analysis of medical big data accrued through recent developments in mHealth and multi-omics research. Additionally, we discuss noteworthy revelations in ocular disease pathologies and future directions of the newfound value in implementing P4 medicine in the current trend toward ubiquitous, person-oriented medicine.

Cross-hierarchical integrative research network and data-driven approach

In understanding the basis of disease heterogeneity and phenotypes, data-driven biological sciences are at the forefront of medical research. In essence, such an approach starts with collecting robust biological big data, visualizing and extracting essential information, and utilizing the results in solving specific problems. The sheer amount of data and raw computational power needed for big data analysis has created an obstacle in prior generations of research, and implementation of AI technologies has enabled high-speed and high-accuracy data analysis. For better or worse, traditional hypothe-
sis-driven biological research takes quantized advancements toward a goal. Initial research on a disease starts with identifying molecular candidates, followed by separate cellular, tissue, and organism level investigations toward elucidating portions of a single pathology. Recently, due to the rapid advancements in ICT and computational hardware, multi-dimensional integrative methodologies became accessible through implementing AI in demanding tasks such as big data analysis. In the scheme of viewing AI-driven biological data analysis as “AI = algorithm + big data,” the development of the latter appears to be the bottleneck. Establishing secure and robust data accrual routes remain a challenge for utilizing AI-driven research at its full potential.

**Invisible medicine and mobile health**

Within the realm of IoMT, mHealth and wearable smart devices have received attention for their capability to provide “invisible medicine” through collecting important physiological data through biosensors and various input data without interrupting activity. mHealth is defined as “as medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices” by the Global Observatory for eHealth (GOe) of the World Health Organization (WHO). mHealth can be a valuable tool for informing patients with evidence-based medicine and motivating self-management. It can also be a platform for providers to collect real-time, objective, medical, and lifestyle data to create optimized treatment for users.

**mHealth-based cross sectional study for heterogeneity of dry eye disease**

DED is a multifactorial disorder affected by three broad individualized factors: host-related, lifestyle, and environmental factors. These factors interact with various mediators of its pathway, causing a varying degree of predisposition to DED in individuals. While the medical field widely accepts its multifactoriality and individual variability of DED presentation, an approach to provide personalized regimens remains to be explored. This is further complicated by the wide variety of symptoms associated with DED, including dryness, photophobia, eye fatigue, decreased visual acuity. These symptoms are often neglected as non-ocular or nonspecific symptoms. This leads to a wide underdiagnosis of DED, causing delayed treatment and a worse prognosis on initial diagnosis. Therefore, a prompt, comprehensive investigation is needed to visualize and stratify the heterogeneous DED presentations effectively. It must be followed by optimization of the treatment regimen for each disease stratum. An individualized, preventative, and predictive strategy may be employed to delay or stop the onset altogether with better insight into specific factors associated with each stratum.

We released an in-house iPhone application, DryEyeRhythm, in November 2016 using the ResearchKit platform to collect real-world data and perform large-scale crowdsourced clinical research on subjective symptoms and lifestyle factors associated with DED. An English version of DryEyeRhythm was also released in November 2017 to widen the userbase. Previous reports indicate that smartphone application-based crowdsourced clinical research is well-suited for early detection and long-term management of chronic diseases, such as DED and diabetes mellitus.

Along with detailed demographic and lifestyle information, DryEyeRhythm allows data collection on DED-related subjective symptoms and depression screening results. This is done with the Japanese version of the Ocular Surface Disease Index (J-OSDI) and Self-rating Depression Scale (SDS), respectively. Additionally, as our previous investigations showed a positive correlation between tear film break-up time (TFBUT) and maximum blink intervals (MBI), a blink interval measurement function is provided as a simple DED screening tool in DryEyeRhythm.

In our large-scale crowdsourced clinical research using DryEyeRhythm, we identified numerous contributory factors of DED aggravation through big data analysis. This study included 5,265 users between November 2016 and November 2017 and odds ratios (95% confidence interval) on individual aggravative factors and DED subjective symptoms. The identified factors include younger age (every 1 year): 0.99 (0.98-0.99), female sex: 1.60-2.14, collagen disease: 2.81 (1.34-5.90), depression: 1.68 (1.23-2.29), current use of CL: 1.24 (1.09-1.41), hay fever: 1.18 (1.04-1.33), extended screen time.
(every 1 hour): 1.02 (1.01-1.03), and smoking: 1.53 (1.31-1.79). CL use, smoking, and screen time are modifiable risk factors that may prevent disease progression and improve long-term prognosis for DED patients.

Another of our follow-up studies revealed that many individuals experiencing DED symptoms remained undiagnosed12. This study targeted undiagnosed Japanese users who had downloaded DryEyeRhythm between November 2016 and January 2018. It investigated distinct risk factors and characteristics of potentially undiagnosed DED patients12. The application was downloaded 18,891 times, yielding 21,394 individual profiles and DED data, and 4,454 users were ultimately included in the study. Amongst this, 53.8% (2,395 users) met the diagnostic criteria of DED without an official diagnosis from a healthcare provider. Notable odds ratio of DED-related factors pertaining to undiagnosed individuals include younger age (every 1 year): 0.99 (0.987-0.999), male sex: 1.99 (1.61-2.46), absence of collagen disease: 0.23 (0.09-0.60), absence of mental illnesses (other than depression and schizophrenia): 0.50 (0.36-0.69), absence of ophthalmic surgery (other than cataract surgery and laser-assisted in situ keratomileusis): 0.41 (0.27-0.64), absence of current use of CL: 0.64 (0.54-0.77), absence of previous use of CL: 0.45 (0.34-0.58). These unique characteristics of undiagnosed individuals are crucial in the initial triaging of the suspected DED patients, especially for those with atypical or “non-specific” symptoms of DED. Effective screening and early diagnosis of the undiagnosed population will lead to a better treatment efficiency and prognosis. It may also positively impact population health and minimize societal costs on DED treatment.

The societal climate advocating the importance of mental health and quality of life has received attention in recent years28. Notably, DED and depression share common risk factors concerning hormonal imbalance, metabolic defect, and neuro-psychiatric dysfunction, leading to increased comorbidity suspicions between the two diseases13, 29, 30. Our results indicate that the severity of DED is positively correlated with the likelihood of ongoing depressive symptoms18. The odds ratio of depressive symptoms (SDS score ≥40) for users with severe DED symptoms was 3.29 (2.70-4.00). A subsequent AI-based hierarchical cluster heatmap of the individual items of OSDI (12 items) and SDS (20 items) enabled a comprehensive visualization of correlated DED and depressive symptoms (Figure 2A).

Interestingly, subjective symptoms of DED related to environmental factors (OSDI items 10-12) were associated with depressive symptoms. With DED symptom monitoring through smartphone applications, it is possible to flag patients with increased risk of depression and recommend proper screening and intervention from healthcare providers. Moreover, it can assist in the prevention, early detection, and treatment of depression. Implementing of mHealth-driven big data collection,
longitudinally collect subjective symptoms, and monitor DED-contributory lifestyle factors on an individual level may play an important role in realizing the principles of P4 medicine in DED management.

CL is a well-established, effective tool in improving one’s visual acuity and quality, with the global user population nearing 140 million people\(^{31}\). However, the discomfort derived from its use, ranging from ocular to non-ocular symptoms, causes discontinuation of CL in 12–58% of its users\(^{14}\). A significant portion of the discomfort experienced amongst CL users is currently correlated with the development of DED, which is broadly termed “CL-associated DED (CLADE)\(^{32}\). As with classical DED, CLADE is highly heterogeneous in presentation, and multifactorial with influence from the environmental, lifestyle, and host-related factors, which created obstacles in comprehensively investigating its pathogenesis\(^{31,33-35}\). To overcome these obstacles, we stratified the collected subjective symptoms of CLADE through dimension reduction and clustering techniques\(^{44}\). This strategy revealed 14 distinct clusters of CLADE (Figure 2B), with subsequent hierarchical clustering elucidating individual characteristics of each cluster (Figure 2C). Such stratification methods to group various symptoms of a seemingly singular disease may hold a crucial position in establishing digital phenotyping protocols in the field of mHealth, as well as genomics-integrated comprehensive analysis of lesser understood diseases.

**Multi-omics approach for the ocular immunology**

The immune system comprises numerous cell types and subtypes, with three major cell types being T cell, B cell, and macrophage\(^{30}\). Both DED and corneal transplantation are deeply connected to the inflammatory and immune dynamics of the anterior ocular surface\(^{37-42}\). Foreign objects and eye inflammation promote antigen-presenting cells. It is followed by the initiation of Th1 dominant immune reaction in nearby cervical lymph nodes, disrupting various ocular tissue function\(^{43-46}\). Regulatory T cells (Tregs) have received attention as a potential therapeutic target for this mechanism\(^{47-49}\). They were found in 1995 for their role in suppressing effector T cells and maintaining tolerance to self-antigens. Therefore, artificially proliferating and homing Treg activity in the cornea appeared promising in maintaining immune tolerance in corneal allograft recipients and suppressing inflammation in DED patients\(^{50,51}\). Our recent findings revealed that Tregs possess a significant degree of plasticity and readily respond to their environments and inflammatory signals\(^{47,52,53}\). This led to decreased immunosuppressive activity of Tregs, evidenced by the loss of Foxp3 transcription factor expression and redifferentiation into helper T cells\(^{50}\). Additionally, the population of Tregs in an average individual constituted both Tregs with stable Foxp3 expression and plasticity of Tregs (exTreg). The latter lost the expression of Foxp3, reflecting their nonuniform cell differentiation, and immunosuppressive molecules\(^{50}\). Separation of immune cells by the cluster of differentiation (CD) antigens through flow cytometry may be an option\(^{54-56}\), but the practical ceiling on the number of antigens that a single operation can simultaneously measure limits the use of flow cytometry to reliably isolate stable Tregs. Through such methods, the isolated cell population will inevitably contain cells undergoing different stages of differentiation with different functions. This will limit its application for research and therapeutic purposes. Therefore, in elucidating the mechanism behind Tregs plasticity, an approach to accurately determine the characteristics and differentiation pathway of individual Tregs in an unevenly distributed cell population is required. One promising solution to this puzzle is multi-omics data collection with subsequent AI analysis of the resultant big data, unveiling fundamental molecular mechanisms behind Treg plasticity and heterogeneity\(^{2}\).

The multi-omics analysis yields a comprehensive, cross-sectional snapshot on various levels of cellular function and their interactions. These interactions reflect one’s physiologic status, including genome, epigenome, transcriptome, proteome, and metabolome. This status may act as a cornerstone in elucidating complex physiologic phenomenon and disease mechanisms\(^{57,58}\). Single-cell RNA sequencing (RNaseq) may help investigate the heterogeneity in the immune cell population\(^{59}\). This technique provides insight into minute details on intracellular dynamics, including transcription factor networks. These networks can help identify molecular explanations for the variability and plasticity of immune
cells. Subsequently, holistic data analysis on Treg genomic expression in response to inflammatory and immune system activation through multi-omics and AI machine learning techniques could specify the molecular dynamics underlying corneal allograft rejection and DED pathogenesis. Homing and stabilizing Treg function on the ocular surface may help better understand the immune cell differentiation pathways and therapeutic targets. In addition, deeper insight into the previously unknown mechanisms of immune cell responses to external factors and cells’ end characteristics could reveal molecular details that accurately detect pathologic gene subtypes, contributing to DED or corneal allograft rejection. These mechanisms ultimately uncover novel inflammatory and immune system targets.

**Discussion**

The medical infrastructure outlined by the Society 5.0 plan enables patient- and population-oriented medicine, focusing on preventative and lifetime healthcare within one’s daily life. Cross-hierarchical data-driven analysis strategies integrating mHealth and multi-omics data appear promising in elucidating disease heterogeneity and its underlying pathology. This is imperative in implementing the principles of P4 medicine. The current healthcare paradigm revolves around facility-based care. A patient- and population-oriented healthcare infrastructure that melds seamlessly into daily life remains to be fully established. Advancements are made in a nonintrusive, longitudinal collection of medical big data due to the increasing penetrance of wearable smart devices and IoT devices. There is a lack of analysis and evidence that allows practical application of the collected data into disease-preventative behavior modification and intervention. Therefore, societal efforts should promote research utilizing the collected medical big data, including our investigations on large-scale mHealth-based crowdsourced clinical research. The findings must integrate to lay the groundwork for implementation.

Recent clinical evidence suggests that subjective findings reported by patients, in addition to clinicians, are valuable in understanding health outcomes. Patients’ own report of health status, also known as patient-reported outcomes (PROs), have presented challenges for providers. There is an ongoing discussion on effective ways to merge PROs within the traditional healthcare operation toward patient care and communication. Conven-iently, mHealth takes a unique position. It is a tool for nonintrusive lifestyle data collection and a platform for users reporting ePROs (such as subjective symptoms). Prompt distribution of collected evidence and its implications to the population of interest was a longtime challenge for public health care agencies. We developed a framework that promotes participatory medicine by allowing real-time access to the aggregate data collected from our in-house smartphone application in a public webpage. The ease of establishing a feedback structure through mHealth and AI analysis, which can continuously collect individual data on subjective symptoms and lifestyle factors followed by prompt analysis report to the population, can have significant implications in providing evidence-based and ubiquitous healthcare under the principles of P4 medicine.

Digital phenotyping is another subject that has received attention in mHealth. As the sensors and inputs attached to smartphones and wearable smart devices continue to diversify, research on converting the gathered user inputs into useful biomarkers can provide a new aspect into one’s health status. This perspective can differentiate in the stratification, visualization, and individualization of complex disease presentations. The resultant findings can then be utilized in preventative, predictive, and personalized medicine. Especially concerning the demand on nonintrusive healthcare that functions within one’s daily life during the ongoing- and post-SARS-CoV-2 pandemic era, digital phenotyping with mHealth devices may help push the boundaries of the prospective global healthcare paradigm.

As medical big data on individual multi-omics and mHealth continues to accumulate in ocular disease research, new findings on ocular pathologies suggest improvements in diagnosis and treatment. In advancing ocular diseases, such data may play a critical role in innovative clinical research. Results show promise in stratifying heterogeneous presentations of previously singular ocular diseases through mHealth and in elucidating a comprehensive understanding of disease pathogenesis through integrating single-cell analysis with omics data.
These integrative approaches merge digital biomarkers and continuous user reports (mHealth) with clinical and basic science data (multi-omics). Hence, we can gain a holistic perspective on ocular physiology and pathology, a crucial first step toward P4 medicine (Figure 3). These principles have implications for other systemic diseases, such as cancer medicine, cardiovascular disease, respiratory medicine, and type-2 diabetes, beyond the field of ocular diseases. They can be applied to any field and pathology that needs further investigation on its mechanisms and treatment. In clinical practice, these integrative approaches will lead to new digital care models for human-centered ophthalmology including telemedicine, at-home monitoring, and AI-driven preventive and personalized care.

Conclusion

Diseases are often heterogenous and multifactorial due to the complex underlying pathology and the multiple pathways to a single disease. The medical infrastructure outlined by the Society 5.0 plan enables cross-hierarchical data-driven analysis integrating mHealth, multi-omics data, and AI technology. Such infrastructure may accelerate the discovery of pathological mechanisms, underlying genetic components, valuable biomarkers, novel treatments, and individualized regimens to prevent disease onset or progression. These are crucial first steps toward implementing P4 medicine. To effectively promote and establish an infrastructure that can effectively introduce the principles of P4 medicine, a social agreement must be made on reinforcing individual participation. This must advocate support from government agencies toward relevant research and development and demand reciprocation by enhancing the society through innovations and newfound insights.

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Figure 3 Cross-hierarchical integrative research network for heterogeneity of the eye disease A1: artificial intelligence. The figure is used from Inomata T. et al with permission.
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Competing interests

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