Personalized Healthcare and Public Health in the Digital Age

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Abstract

This review explores the important roles that digital health plays in advancing personalized healthcare and public health, and how it may evolve in the future. For the former, we argue that digital health (1) allows self-monitoring of health and disease, (2) facilitates semi-automated disease assessment and diagnosis, and (3) connects and improves personalized healthcare and public health. For the latter, we first present the short-term focus of digital health, including its role in dealing with the COVID-19 pandemic. We then examine its mid-term challenges and provide potential mitigation strategies and resolutions. We conclude with an informed speculation on long-term outlooks of personalized healthcare and public health in the digital age.

Terms and Abbreviations

5G: The fifth-generation technology standard for cellular networks with peek download speed at 20 Gbit/s (compared to it of 4G at 1Gbit/s).

Automated and semi-automated diagnosis: An automated diagnosis is to identify a health event completely based upon decisions made by digital devices. Semi-automated diagnosis means that the digital devices only provide preliminary reports with ultimate decisions made by human specialists.

COVID-19: Coronavirus disease 2019 caused by SARS-CoV-2 viruses.

Deep learning: A group of machine-learning methods based on artificial neural networks using multiple layers of parameters to learn features from data.

ECG: Electrocardiogram.

EEG: Electroencephalogram.

Digital health ecosystem: A community of human players (*e.g.*, patients, doctors, nurses, software developers, data scientists) collaborating in concert with their connected digital environment (*e.g.*, data, devices, applications, algorithms) in activities relating to healthcare.

Feature: A characteristic of a variable of interest that can be measured and then analyzed to provide inference with regard to an (health) outcome.

FAIR: Findability, Accessibility, Interoperability, and Reusability.

IoT: Internet of Things. A system of interlinked computer and physical devices, which can exchange data and act collaboratively in the automation of individual and collective tasks.

Industry 4.0: The fourth industrial revolution, which consist of the next-generation computerization, digitalization, and automation, combining the real and virtual world via and into the IoT.

mHealth: mobile Health.

MRI: Magnetic Resonance Imaging.

Prediction, detection, intervention, and prevention: Consider an event X, such as the onset of a disease. Prediction is to forecast when X will occur and if it occurs what future courses of X will be. Detection is to identify if X has occurred and, if it has, how severe X is. Intervention is to assign treatment so as to alleviate X after it has occurred. Prevention is to assign treatments so that X will not occur or will occur at a later time.

Predictive modeling: A practice to build statistical and machine learning models to quantify either future or out-of-sample properties of a health condition, including its likelihood, severity, and longitudinal trajectory.

Prognosis and diagnosis: Prognosis means the forecasting of the likely course of a health condition before it occurs. Diagnosis means the identification of a medical condition after it has occurred and to quantify its severity.

Public health and Personalized healthcare: Public health refers to the science and practice of managing and improving the health of a population, such as those living in a city or country. Personalized healthcare is the science and practice of managing the health of a specific individual, taking into individual variabilities in genetics, medical history and existing medications.

Telemedicine: The practice where health practitioners deliver care to patients remotely via digital health and telecommunication tools.

NO WONDER they are called “patients”. When people enter the health-care systems of rich countries today, they know what they will get: prodding doctors, endless tests, baffling jargon, rising costs and, above all, long waits.

The Economist, February 2018

The alarm goes off. It’s 8 am. John takes the sleep EEG cap off his head – the EEG-connected app on his smartphone indicates that he had a good night’s sleep – and gets up. At 8:30 am he walks into the kitchen. A quick photo of his plate and the dietary app calculates the calories in his breakfast and provides suggestions for lunch and dinner. By 9 am he is on his bike to work; his smartwatch showing him the power output of the ride, while the Bluetooth headphones notify him periodically of his heart rate. He does quite well this morning, according to the workout app, ranking the 7th quickest amongst men of his age in his area…

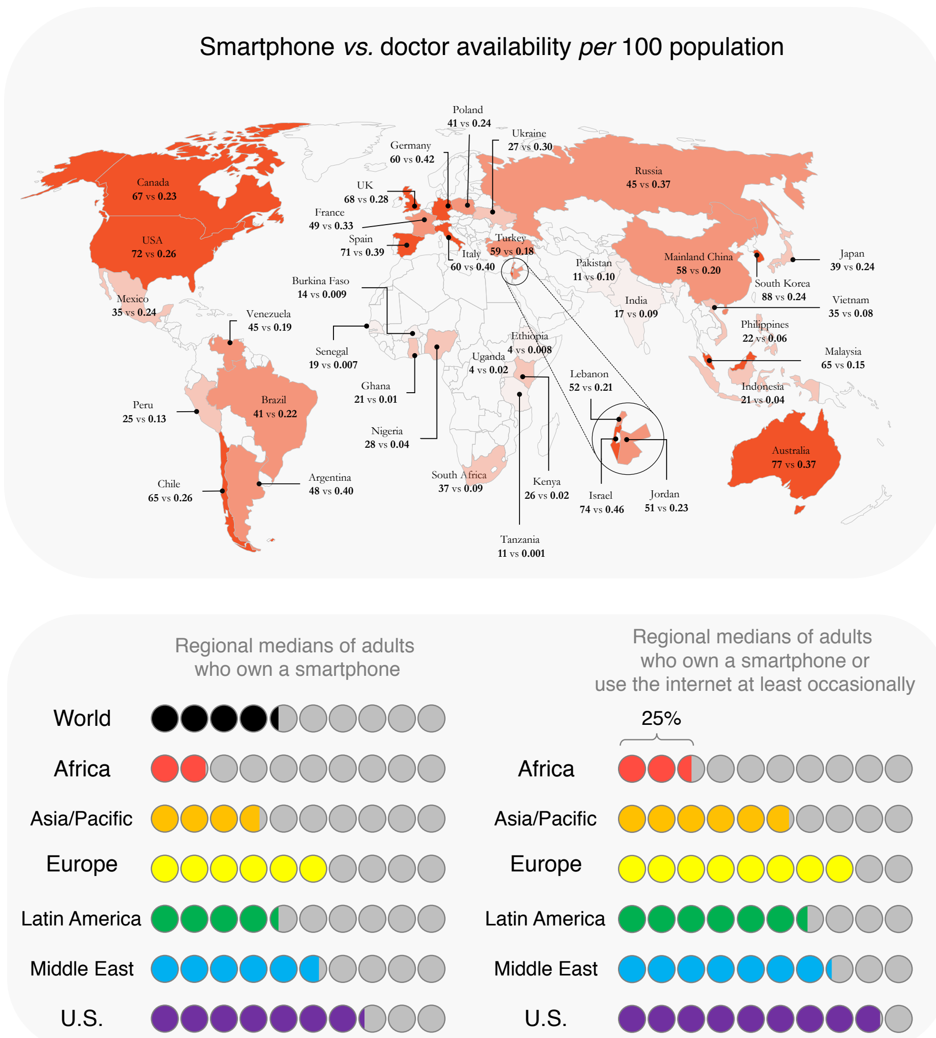

Figure 1. The contrast between smartphone and internet penetration and doctor availability across the world. Top: Smartphone *vs.* doctor availability. Under each country name are two numbers: the left is the number of smartphone owners per 100 people; the right is the number of physicians available per 100 people. **Bottom: Smartphone and internet penetration rates.** Left: Regional medians of adults who own a smartphone. Right: Regional medians of adults who own a smartphone or use the internet at least occasionally. Smartphone and internet rates are from the Pew Research Center[1]; physician rates are from the World Health Organization[2].

Call it the digital health age. It is a time when health assessment, monitoring, and decisions are made using digital devices[3–6]. Their compact size makes them wearable and portable. Their diverse onboard sensors, large memory, and ever-growing computing performance make them functionally rich. Thanks to digitalization, a wealth of built-in apps are measuring a broad range of physical and physiological signals, such as heart-rate, brain activity, gait, and walking speed, either actively (during a test performed consciously) or passively (during normal daily activities as data are collected in the background). Thus, they record and monitor multi-dimensional and -functional health information semi-continuously (at small intervals) throughout the day. Their relatively low cost and high penetration rate (compared to hospital devices and physician availability, respectively) make digital health services affordable and available at an unprecedented scale (see **Figure** 1). Together, they have formed a versatile health ecosystem that is beginning to address important medical and public health needs across the world and, as such, are becoming a part of our lives (see **Figure** 2).

Indeed, mobile health, or mHealth, has been shown to increase access to health information, services and skills, and promote positive changes in health behaviors and disease management[7]. Because of their ease of use, ubiquity, and wide acceptance, the Executive Board of the World Health Organization (WHO) has regarded *mHealth: use of mobile wireless technologies for public health* as an important resource for health services delivery and public health[7]. In parallel, the World Health Assembly of the WHO has passed a resolution (Resolution WHA71.7) on digital health that urges the WHO Member States to prioritize the development and use of digital technologies in health as a means of promoting Universal Health Coverage and advancing the Sustainable Development Goals[8].

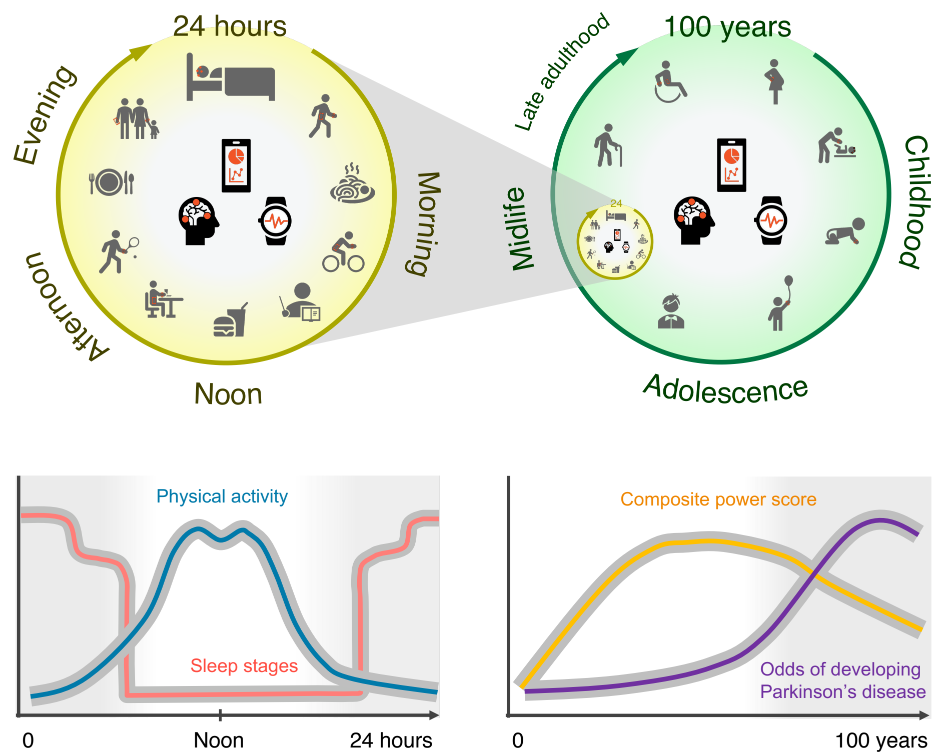

Figure 2. Two circles of digital health life: daily monitoring and lifetime monitoring. Left: Daily monitoring. Digital devices, such as smartphones, smartwatches, iECG, handheld ultrasound, and electroencephalography pads, can monitor one's mental and physical activities, diet, sleep, *etc.* and generate periodic health and/or disease reports. **Right: Lifetime monitoring.** With regular monitoring performed daily, digital devices are beginning to record health information across one's lifetime, providing information regarding power development, fitness, growth and degeneration, aging, and chronic medical conditions such as diabetes, cardiovascular disease, and neurodegeneration.

1. The roles of digital devices in personalized healthcare and public health

The chief goal of this article is to envisage in which ways digital technologies will contribute to public health and personalized healthcare in the digital age and how they may evolve. It is, however, a difficult task to foretell what future digital technologies and health concepts will be and how they will improve the way we deal with public health and personalized healthcare. Additionally, although we may reasonably assume that many of today's digital health challenges will be solved in the future, new challenges will emerge in the years to come. Bearing these caveats in mind, here we take a balanced approach, by first discussing the useful roles of digital health we see today, where relatively more is known and on which reasonable consensus of opinion is likely to be achieved. Afterward we move into less certain territories, by discussing the promises, challenges, and potential future directions of digital health.

There are, in general, three useful roles that digital health plays in personalized healthcare and public health today. It (1) allows self-monitoring of health and disease, (2) facilitates semi-automated disease assessment and diagnosis, and (3) connects and improves personalized and public healthcare.

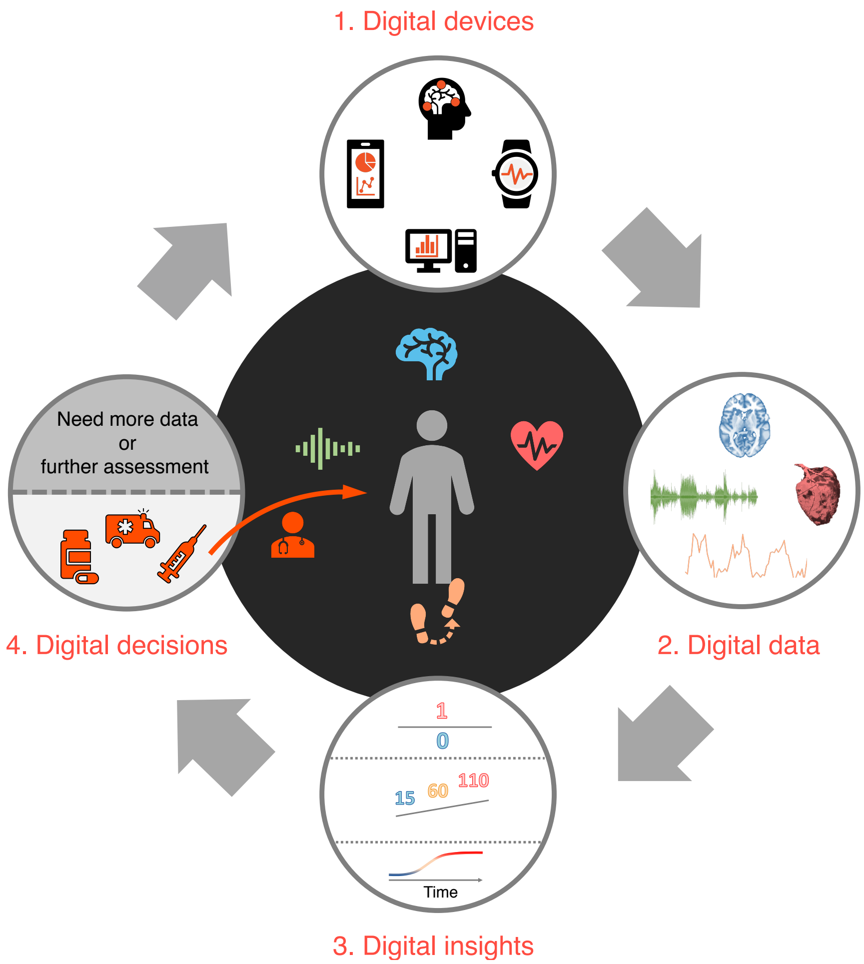

Figure 3. Digitalization cycle - bridging digital health, data, and digitally enabled decision-making. From 1 to 2: Phenotypic information is created by, and made available on, digital devices. From 2 to 4 via 3: Advanced modeling and analyses are applied on digital data to guide healthcare decisions by physicians, such as recommending potential treatments (see bottom of item 4) and suggesting conducting further diagnostic tests or analyses (from 4 to 1).

1.1 Self-monitoring of health and disease

Traditionally, acquiring bio-signals, such as neural, behavioral, and cardiovascular measurements, requires specialized medical devices, including magnetic resonance imaging (MRI) scanners and electrocardiography (ECG) monitors, and professionally trained individuals such as radiologists and cardiologists. As such, these data acquisition paradigms typically require an in-person visit to a local clinic or hospital, are relatively expensive, and, due in part to cost constraints and a lack of human and medical resources, cannot be performed frequently or in a broad population.

In the era of digitalization, digital devices become miniaturized, mobile, and wearable; data transmission becomes wireless and ultra-fast; and statistical- and machine-learning algorithms grow increasingly powerful and targeted. One can therefore begin to record, monitor, and analyze bio-signals remotely at home without incurring much cost[9] (see **Figure** 3).

The advantages of home-based self-monitoring using digital devices are threefold. Firstly, noninvasive collection of bio-signals, such as voice, dexterity, heartrate, physiology measurement, and physical activity, enable inferences to be made about health and disease conditions using digital devices[10]. Secondly, these bio-signals are acquired semi-continuously over time. Frequent data acquisition facilitates longitudinal assessment of individual health in comparison to personal and population baseline data – an important element in discovering early signs of diseases[9]. The measurements made in the real-world setting are more relevant (ecological) and can capture fluctuating symptoms with high objectivity, sensitivity, and specificity, thereby providing a powerful complement to periodic and infrequent clinical assessments. Thirdly, digital devices are inexpensive compared to professional medical devices and do not require experts to operate them. This saves tremendous medical and human resources and makes digital health available to a broad population[11].

There is no conflict between home-based and in-clinic health approaches. Although home-based monitoring and assessment at present may not be as accurate or comprehensive as medical examinations and diagnostic tests performed in the clinic, mobile digital devices possess unique merits. They: offer medical services at lower costs, expand health beneficiaries, capture data in the real-world setting, reduce travel risks and assessment burden for patients, and avoid exhaustion of finite medical resources. Their low cost and high availability are particularly useful during pressing times, such as the COVID-19 pandemic (see **Section** 2.1), where they open the door to deliver healthcare services to populations that may otherwise have little or no access to medical resources and healthcare professionals[11].

1.2 Semi-automated disease assessment and diagnosis

Physicians are in stark shortage throughout the world today (see **Figure** 1). According to the WHO, United States has 0.26 physicians *per* 100 population; some countries in sub-Saharan Africa have only 0.02 *per* 100 population; the average number across the world is 0.15 *per* 100 population[2]. In contrast, the smartphone penetration rate in the United States is 72 *per* 100 population and, although small, is increasing even in the least developed countries, with 4 to 37 *per* 100 population in sub-Saharan Africa; the global median is 43 *per* 100 population[1]. Carefully designed and delivered, digital solutions offer remarkable promise to supplement the shortage of human resources in personal healthcare and public health.

The advent of digital health paves the way for fast, remote, and large-scale data collection, and for early disease-detection and -intervention. First, convenient and low-cost technologies enable collection of meaningful data at large-scale from the healthy and diseased populations. Next, thanks to improvement in statistical modeling and deep-learning, algorithm-based frequent digital assessment enables and encourages patients to self-monitor and care for their own health[9]. In addition, as it is now possible to automatically de-identify, encrypt, and transfer health data[12], one can analyze and compare personal data with population norms to yield preliminary health reports in an automated way[13]. If potential risks are identified by the digital pipeline, machine-generated alerts can advise corresponding individuals to seek an appropriate medical consultation. In parallel, if consent is in place, the reports can be delivered remotely to healthcare professionals to prepare for consultations and even assign adequate and timely digital interventions wirelessly[14,15] (see **Figure** 4 and telemedicine below). Finally, these digital health monitoring tools empower early detection of disease and the potential to intervene earlier with suitable treatment opportunities to reduce the probability of disease conversion and development, for example in neurodegenerative and cardiovascular diseases[16,17]. Suitable treatments may include combinations of diet, exercise, and/or medicines[17–19]. Together, early detection and intervention/prevention initiatives as well as continuous monitoring performed on a broad population yield many benefits, including promoting individual health and wellbeing, lowering healthcare burden and costs, and reducing lost working time.

Currently, the majority of phenotypic health data are generated in the clinic from patients with relatively advanced diseases, where symptoms are clearly present and diagnostic procedures are being or have been performed. Meanwhile, there is a lack of comparable data at scale from the healthy population and those in the very early stages of disease development. Without balanced data, it is difficult to build robust predictive models. We need sufficient longitudinal data containing both signals related to early disease and features associated with disease progression. To see this vividly, consider a smartphone app that uses recorded movement patterns to predict the onset of a neurological condition. For early disease diagnosis, the smartphone algorithms need to compare how often disease-specific prodromal signals are observed in individuals during the early stages of disease development with how often similar signals are observed in matched subjects (*e.g.*, age and gender) who do not go on to develop the disease. Thus, to understand normal variability versus irregular variations associated with disease across its developmental course, we need matched longitudinal data, at scale, from healthy subjects, individuals with early disease, and patients during progressive disease stages. This is particularly important where preventative treatments and early interventions are concerned[20–22].

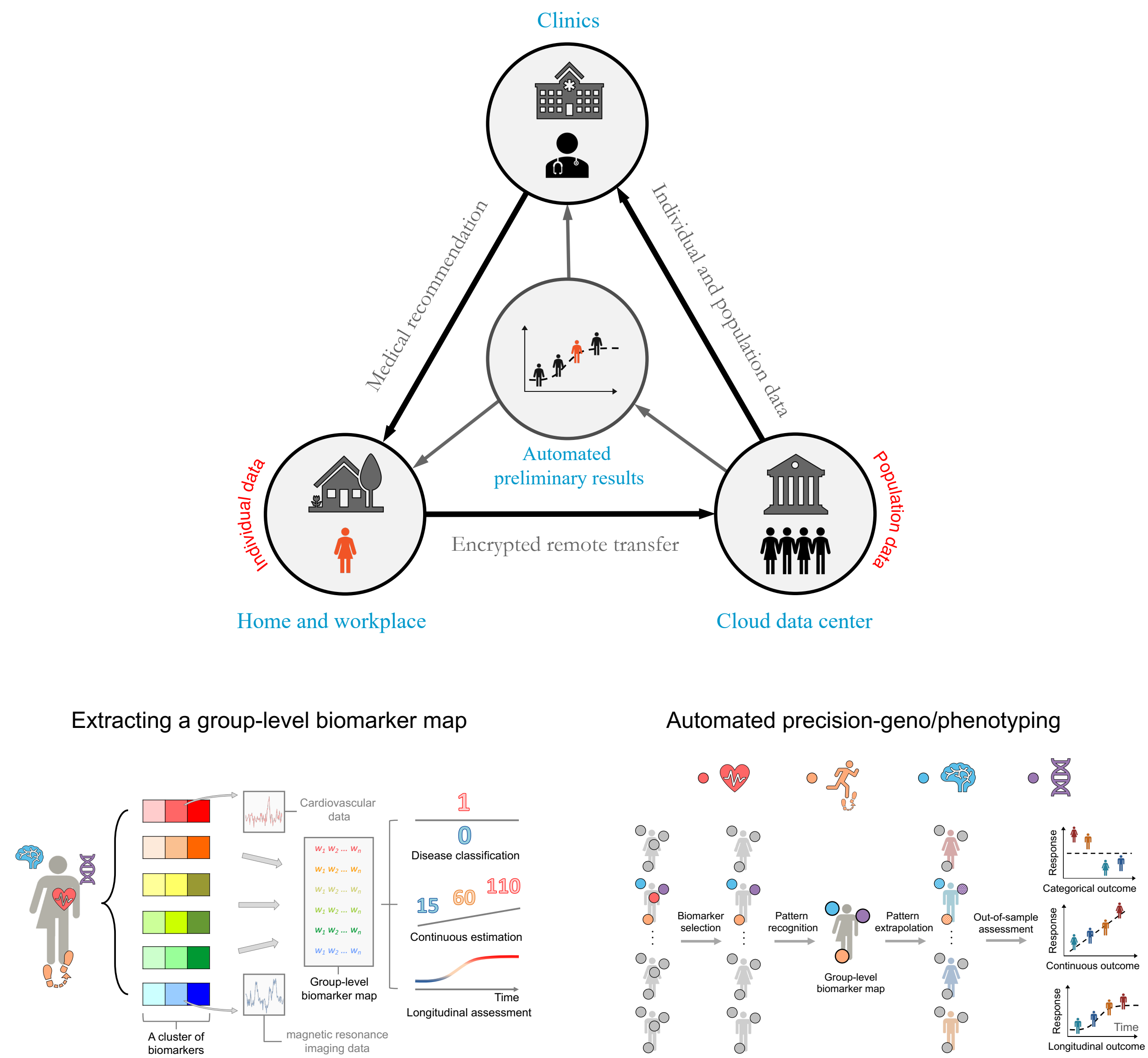

Figure 4. Semi-automated disease diagnosis and monitoring. **Top: Home-based digital health.** Individual data are de-identified, encrypted, and transferred remotely via the cloud to secured data centers – where population level disease analyses are performed. The individual data are then analyzed and compared with the population features to generate an automated preliminary diagnosis report. Should red flags be raised, the report is passed on to a medical professional. The medical professional looks at both the report and the individual-specific data to offer medical recommendations or to arrange for an on-site or remote, telemedicine, consultation, depending on which further tests are anticipated. This process continues between an individual's periodic health checks to ensure earliest possible detection of symptoms and to compensate for long consultation intervals when regular assessment is too expensive or inconvenient. **Bottom: Automated precision-geno/phenotyping.** The digital health applications facilitate ensemble-learning, where multivariate genotypic and phenotypic (*e.g.*, digital biomarker, imaging, and molecular diagnostics) data are combined to provide rich subject-specific and group-level information, which are used to position individuals within a relevant population or to predict outcomes for individuals, based on populations norms.

Naturally, one would ask, will digitalization and automation in health assessment and disease diagnosis result in job losses, for example, a reduction of healthcare personnel, nurses, clinicians, and physicians? Likely not. Firstly, such posts are in significant shortage today (see **Figure** 1). Secondly, digital health extends health services to a broader population that would otherwise be excluded from regular physical examinations[11]. Although a great deal of monitoring and assessment could be done digitally, the majority of high value medical interventions cannot be automated at present, nor in the foreseeable future. The expansion of overall coverage, therefore, results in an increasing need of labor to deal with the work that cannot be automated. Additionally, as previous industrial revolutions have done, digital transformation and revolution (see **Section** 2.3) grow the labor market by creating new jobs, such as data labeling (clinical, behavioral, and disease features need to be annotated before machine learning can establish the relationship between features and labels), intermediate medical testing and analysis (to confirm primary computer-based predictions), remote medical consulting and telemedicine. It also creates and expands domain-specific positions, such as programming (*e.g.*, designing better computer algorithms, pipelines, and systems), posts that require interdisciplinary knowledge (*e.g.*, developing predictive algorithms that incorporate biological insights), and educational jobs that train the next-generation digital-health workforce.

Human doctors may make mistakes[23,24]. Digital health devices are also not, and will never be, one hundred percent accurate in decision-making, given the limitations in the way they are used and of the data on which algorithms are trained, by the probabilistic nature of all medical conclusions, and, not least, by the fact that they are programmed by humans. Their disadvantages, however, are outweighed by the benefits. While we continue to improve diagnostic accuracy (see below), the rate of misdiagnoses needs to be viewed in the context of the vast number of individuals that may benefit from the additional (computer-based) health-monitoring and -care. Many of the beneficiaries are individuals who would otherwise not have access to regular in-hospital visits or would suffer critical disease progression during long gaps between visits. Together, digital health and telecommunication tools enable health practitioners to deliver care remotely, at a distance, a practice collectively termed as “telemedicine”[25]. In parallel, to avoid the impact associated with potential misdiagnoses from digital devices, algorithmic caution and additional safeguards can be designed into automated processes, and appropriate checkpoints from healthcare professionals added (see top panel of **Figure** 4). More specifically, a digital device does not have to perform a complete formal diagnosis; rather, it is an integral part of an augmented patient-computer-physician triage process, involving the subject/patient, devices/algorithms, and physicians - increasing the probability of appropriate diagnosis and intervention. If the digital device failed to identify a patient (*i.e.*, false negative or Type II error), one would still have periodic medical checks. If the device misidentified a patient (*i.e.*, false positive or Type I error), a human specialist, further along the decision process, would be able to correct this error before any harm comes to the subject. Further, algorithmic parameters can be fine-tuned to minimize false positives or false negatives (depending on the potential consequences of each: *e.g.*, false positives overwhelming the healthcare system and creating undue anxiety *vs.* false negatives leading to missed cases of a serious illness needing urgent medical attention). Due to their convenience, algorithm-based assessments can be performed frequently. By so doing, trend estimations are made over time, providing more relevant and powerful health and disease information than those based on single assessments. Finally, accumulation of large-scale relevant datasets, as well as advancements in statistical modeling and deep-learning, are continuing to improve the accuracy and predictive power of digital devices, enabling semi- and, someday, fully-automated disease diagnosis and prognosis.

Deep-learning and predictive modeling are firmly established at the heart of algorithm-based assessment, diagnosis and prognosis. In medicine, machine-based predictions have already begun to outperform radiologists, pathologists, and ophthalmologists in specific diagnostic tasks, such as in mammographic screening[26], certain cancer diagnosis[6] (*e.g.*, urothelial carcinoma[27]), and retinal analyses[19,20]. Additionally, they have made progress in predicting cardiovascular disease[15], Lyme disease[13], neurodegenerative diseases[16], and patient response to treatment[29].

1.3 Connecting and improving personalized healthcare and public health

When one is infected with COVID-19 and needs to see a doctor, this is an individual healthcare problem, and the treatment one receives is a personalized one. When millions of people have COVID-19, it becomes a public health problem. The strategy a public health practitioner needs to employ is a population one – one that is suitable for millions of diagnosed people, plus the rest of the population who may be at risk.

The problems of personalized healthcare and public health, however, are not independent of one another. When a doctor makes a personalized diagnosis, he or she has to compare individual health and disease information with past and present information learned from other comparable healthy controls and patients. When a public health practitioner makes a population-level recommendation, the strategy presented is based on the outcomes of many individuals with the same disease (or at least the same syndrome), must be robust to individual variability, and is suitable for the general population and manifestations of the illness.

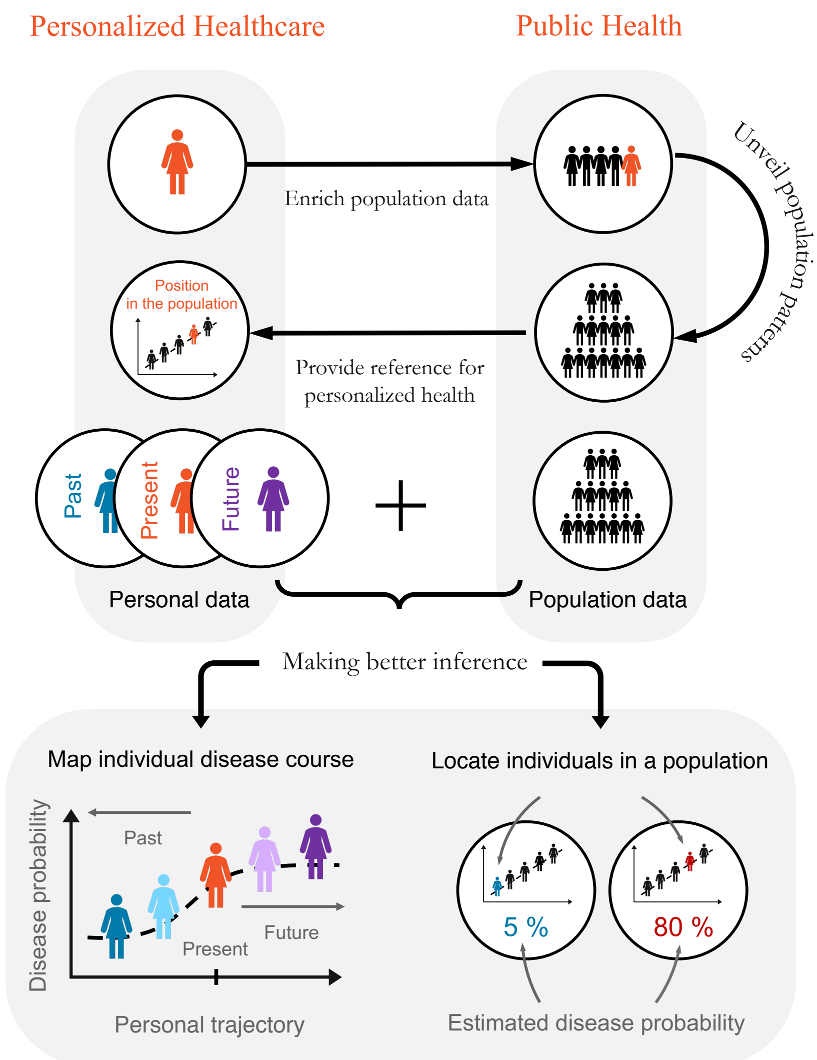

Figure 5. The marriage between personalized healthcare and public health. There is a powerful interdependent and synergistic relationship between personalized healthcare and public health in the digital age. **Top panel:** When shared, personal digital health data bring rich heterogeneous information into the population data pool. In return, features identified in large-scale public health data will provide a reference for individuals, positioning them relative to comparable cohorts in the population, based on age, sex, ethnicity, *etc*. **Bottom panel:** Integrating individual and population data. Data collected longitudinally over months and years enable risk estimation and disease forecasts, such as estimating the likelihood of disease progression or quantifying response to different treatments.

Digital devices and digital data facilitate personalized healthcare and public health in a number of ways (see **Figure** 5). First, by adding individual data into the population data pool, one is contributing to the repertoire of public health data by aggregating heterogenous information. This is particularly helpful when a disease (*e.g.*, diabetes) has multiple sub-categories or -types (*e.g.*, Type 1 and Type 2 diabetes). If an existing data set is dominated by patients with Type 1 diabetes, the knowledge extracted would inevitably reflect the features of Type 1 diabetes and the Type 2 disease-specific features may be overlooked or treated as noise. With digital technology, high-quality data can be collected in an automated way to include balanced and representative samples from the public data pool that cover all disease sub-categories.

In return, features derived from public health data contribute to the improvement of personalized treatment. Since digital devices are sensitive, objective, and can collect data semi-continuously during relevant life activities, they support precision phenotyping[30,31], finer categorization of disease, and enable targeted and timely management and treatment (see bottom panel of **Figure** 4). If a particular patient displays symptoms and shares similar characteristics with a cohort in the general population, one can assign established standard-of-care treatments that have demonstrated safety and efficacy previously in similar patients. By comparing differences between subject-specific treatment response, side-effects, and symptom dynamics with population-level patterns, one can further tailor the subject-specific and -targeted treatment. This approach applies the established principles of evidence-based medicine[32,33] and personalized healthcare[34], leveraging the additional benefits of the digital health ecosystem.

Integrating public and personalized data yields better longitudinal health inference. As digital health solutions record and store data semi-continuously, one can begin to map longitudinal physiological or disease patterns and derive insights from historical trends to forecast potential future events or disease trajectories. In parallel, with periodic checkpoints, where personal health status or disease progression are compared with personal history and the population counterpart, one can receive timely health recommendations (*e.g.*, whether to see a doctor, run a comprehensive medical evaluation, or change medication) (see **Figures** 3 and 5).

2. The future of digital health

The digital age is still at its dawn. Anyone who has worked on digital data science and automated disease diagnosis and prediction will attest that, even for the most intensively studied diseases, achievements to date have been modest. On the other hand, digital technologies, imaging, and molecular diagnostics have advanced considerably over the past decade. As the momentum towards digital health accelerates, this is a good moment to reflect and consider what the road ahead may look like for digital health, which opportunities are to be embraced, and what significant challenges will need to be addressed.

We set forth the discussion of the future of digital health in time frames: short-term focus, mid-term challenges and potential solutions, and long-term outlooks. We make such a time-sensitive distinction as we recognize that there is an urgency to assess how digital health may alleviate resource limitations and reduce physician and carer burden during the current COVID-19 pandemic. Secondly, in such a fast-changing field, arguing what digital health may look like in 20 years' time may be futile. One only has to draw the parallel of trying to foresee the latest iPhone and app ecosystem from the perspective of

2007, when the state-of-the-art “smart” device was the Nokia N97. Thus, one can only hope to explore the long-term perspectives of digital health in a speculative way, although in an informed and controlled manner. The mid-term is perhaps the sweet spot, where one can actively make preparations, constructive changes, and improvements today. We, therefore, outline a few challenges we think need to be addressed with priority during the mid-term; they are foundations on which to build the coming digital health transformation.

2.1 Short-term focus: digital health during coronavirus pandemic

People in Wuhan say there are shortages of test kits and are likening the chances of getting one to ‘winning the lottery’.

- Business Insider, January 2020

As early as in January 2020, earlier than when COVID-19 began to spread across the world and been deemed a pandemic by the WHO, some had already feared that, besides the challenges the disease imposes on medical facilities, clinic personnel, and day-to-day life, the disease would trigger a testing crisis[35].

Effective and timely testing during a pandemic are central to preventing the disease from spreading further. Frequent and high coverage testing is useful to identify the infected individuals (especially those that are asymptomatic), isolating them from infecting others, providing recommendations for governments about which “social distancing” measures are working and, finally, providing early treatment for those infected. Unfortunately, by January 2020, the three companies certified to manufacture testing kits in China could only produce 100 thousand per day; by then, in contrast, three million people were already in quarantine in or near Wuhan[35]. As the virus spread, a shortage of testing was declared wherever the virus traveled. For example, from February to April 2020, a little more than 4.5 million tests were performed in the United States[36], which was significantly below the *daily* suggested target of between 5 million and 20 million[37].

Digital devices are useful during a pandemic. Smartphones not only support testing for, and track-and-trace of, the infection, but also have the capacity to engage directly with issues generated by the pandemic through digital health applications. Digital devices have shown promise in identifying high risk populations and marking high risk areas. Tencent and Alibaba have, respectively, provided their users in China with a “health code” service via their wide-reach social network platforms, WeChat and Alipay. One who has a green, yellow, and red code is, respectively, allowed to travel, asked to stay home, and is a confirmed case and should be quarantined[38]. In parallel, several European countries have introduced smartphone-based apps to identify and inform individuals at risk. These apps first record and determine if any pair of individuals are in close proximity, and if one is later registered as a case, the apps send an alert to other individuals who had close contact with the confirmed case[39]. Although such practices are useful and cost effective from a public health perspective, and have reduced the need for mass random screening and contact-tracing interviews, they have raised privacy concerns, regarding the recording of personal and location information[38,39]. We will discuss these issues in more detail in the following sections. Smartphone apps are also available to guide individual decision making, such as when to consult a healthcare provider, by integrating self-reported risk factors, symptoms, and physiological data with publicly available information and authority guidelines[40].

Digital and wearable devices bring a practical and timely opportunity to support a health system in crisis during a pandemic, improving patient outcomes and the welfare of healthcare workers. Real-time patient monitoring in a hospital setting, through integration of multiple bio-signal sensors, together with powerful algorithms (see bottom panel of **Figure** 4), can free some of the burdens on hospital staff, enabling them to manage more patients, while ensuring their attention is focused on patients with the most critical needs. Continuous real-time monitoring and assessment of abnormal bio-signals allow for earlier interventions. The combination of a new generation of wearable sensors that measure pulse rate, respiratory rate, and blood oxygen saturation is already underway. For example, a digitalized ward has been built to monitor high-risk patients with COVID-19 through wirelessly linked tablet computers and smart algorithms[41].

2.2 Mid-term challenges and potential solutions

The rise of digital health has made frequent, remote, and semi-automated assessment and monitoring of health status and disease progression available to an unprecedented number of individuals. Its advantages, as we have discussed above, however, are not without challenges.

Perhaps the immediate concerns are data privacy[42] and data quality[43]. In terms of data privacy, how can one ensure that personal data are captured, transferred, stored, and analyzed securely? Besides being stored safely, can they be stored economically? In terms of data quality, do collected data contain useful signal (versus noise); are they biologically and clinically meaningful; do the analyses and conclusions overfit the data and overstate the effect? For the former line of questions, mitigation is already underway through improving government policies[44], company regulations[45], and (computational and storage) technology[3]. For the latter, integrating protective measures, introducing rigorous quality controls, developing efficient, targeted algorithms, and performing comprehensive out-of-sample or out-of-population cross-validation and testing, are critical.

The next set of considerations concern accuracy, flexibility, and robustness[6]. A human doctor has the advantage of interacting directly with a patient, including observing complex body language and emotion, to make personalized medical judgements. Smart devices, sensors, and wearables have the advantage of objectivity and sensitivity, but they generally lack the ability to directly detect and integrate emotional information and personal feedback. Improved, more holistic, devices and algorithms that can incorporate dynamic, interactive user feedback, such as emotions and verbal input, are important yet scarce in literature or are under development in relative isolation[46–51].

Related to digital accuracy are ethics and the ability to handle subject-level, group-level, and stochastic variability (or noise) appropriately. Regarding data ethics[52,53], how can we ensure results derived from digital data are not biased and do not disadvantage a particular group? The solution, we think, needs to start at the foundation, including designing rigorous experiments, collecting representative samples, and building comprehensive modeling pipelines. By representative samples, we mean that one has to consider subjects that reflect the target population in as many dimensions as is practicable, including distribution of sexes, ethnicities, ages, technologies, instruments, *etc*. If the goal is to study a specific disease, one needs to carefully coordinate the ratio between healthy and diseased subjects. By building comprehensive modeling pipelines, we mean to develop powerful statistical and deep-learning frameworks that comprise rigorous cross-validation and testing mechanisms to ensure that the boundaries of the models are well understood, and that the models are reproducible for the intended use (see **Figure** 4). Additionally, we need to introduce adequate measures for quality control. A recent development, *Z-inspection*, facilitates the testing and certification of the quality and ethical standards of different artificial intelligence (AI) algorithms[54]. Regarding variability or noise, a human doctor is very good at filtering noise and extracting essential information generated by traditional medical devices in a controlled environment. Digital devices and sensors that we carry around will, inevitably, be affected by environmental noise. This needs to be carefully accounted for to maintain sensitivity, specificity, and accuracy. Unfortunately, it is at present difficult for a digital device to make accurate detections in a live environment, for example, to distinguish hand tremor from hand movement during a walk or to identify subtle changes in voice in live settings[55,56]. Thus, it is important to develop the next-generation digital devices targeted at performing robust health monitoring, assessment, and diagnosis in a live, potentially noisy environment.

Most digital health devices at present are still domain specific[4,6,13,15,16]. In other words, each device is specialized to perform one or a small number of tasks. This is acceptable, if one's goal is to gain insight into a particular illness – similar to the situation where one goes to see a specialized human doctor. Yet, for the majority who wish to perform comprehensive self-checks and -monitoring at home, with a goal to detect early signs of disease without *a priori* knowledge about which disease(s) may develop, a domain-specific device becomes less convenient and effective. For this purpose, a comprehensive battery of bio-signals would need to be analyzed and, ideally, on a single ubiquitous device such as a smart phone/watch (see **Figure** 4). For example, to give a relatively comprehensive picture of one's daily metabolism, the device needs to not only integrate multivariate cardiovascular digital biomarker data, hormonal, and metabolic data, but also consider a modeling architecture that enables interoperability and interpretability in combination[57,58]. Although the concept of combining datasets and algorithms may seem straightforward, given the fragmentation of healthcare and the lack of comprehensive global data standards, it will likely face major challenges, such as complex semantic integration, meta-analysis, and model integration[33,57,59,60], which need to be addressed before moving forward. Beginnings, however, are already being made, evident in the virtual ward with the integration of multiple wearable sensors[41], and attention drawn to the FAIR Data Principles[49] in relation to health data. The FAIR Data Principles, coupled with ensemble learning[57], pave the way for interoperability between different devices, algorithms, datasets, and manufacturers.

While lasting rapport and trust can be established between a family doctor and a patient, it is difficult at present to form any personal relationship between digital devices and patients. Future devices may consider incorporating more sophisticated and generalized AI algorithms that can ask and answer, with a degree of empathy, more targeted and relevant questions with more natural and human-like qualities. Inspired by human intelligence, AI has begun to benefit health in component tasks, as described in the examples above. However, it may one day develop into a 'superintelligence' that may not comply with medical values and societal expectations. Naturally, this raises questions around optimizing, managing, and controlling AI. Some of these questions are already being actively discussed, debated, and pursued[62,63]: is it right to design an AI that treats medical events probabilistically (for example, choosing to save four patients who are moderately ill over two patients that it considers severely ill, based on outcome probabilities); how could penalties and stopping rules be imposed to safeguard a goal-based AI program once it has been initiated (which, given a goal, would make plans and exhaust as much resources as it can until the goal is realized); how could we prevent AI from applying adversarial strategies; and, more broadly, how could we avoid losing control of AI-based medical systems (see above and the section below)?

Another issue is the contrast between the usefulness and the (low) acceptance of digital devices among the aging population. On the one hand, the aging population will benefit tremendously from digital health, receiving continuous, home-based, and automated digital care and monitoring[9,64]. On the other hand, there is a stark gap between the younger and the older generations in terms of digital device and internet usage[1,65]. The low penetration in the aging population is, in part, due to the fact that many smart devices were only introduced recently, especially in emerging and developing countries: many did not grow up with such devices and are unlikely to adopt them as they age. The relative complexity of such devices and applications also makes it challenging for older generations to adapt and incorporate them into their lives, as easily as "digital natives" do. In the long run, the low acceptance of digital devices will be mitigated, as the current "digital generation" grows older. Yet, in the present and near future, ease-of-use remains as important as powerful functionality, to enable the elderly and others with cognitive impairment to benefit from digital health solutions.

Last, but not least, is the talent challenge - the rarity of professionals and organizations with integrated interdisciplinary knowledge. At present, a doctor may need to consult with data scientists to interpret the output of automated algorithms. Equally, a state-of-the-art deep learning engineer must rely on domain experts to explain the biology concepts and medical situation. Disciplinary experts together with multi-disciplinary teams are essential in scientific research and technical development today and will continue to be an integral, indispensable part in the digital age. However, a new generation of professionals with interdisciplinary training in life science, medicine, public health, and the computational domains will be in high demand in the coming years. Positioned at the nexus of disciplines, they will be the integrators in complex teams, bridging multiplex interactions, multi-domain operations, and disciplinary experts.

2.3 Long-term outlooks: the advent of a digital health ecosystem?

Digital health is destined to play a critical role in the future of personalized and public health worldwide, thanks to miniaturization (*i.e.*, the trend to manufacture smaller devices), the development of newer biosensors, the collection of ultra-large-scale medical and life science data, enhanced communication and data security technologies, the maturation of AI, modifications in local and global politics, and the adoption of new economic and social norms. Yet, with ongoing and rapid changes, it would be foolish to believe that we can fully predict how these factors will synergize to mold the future digital health ecosystem. Thus, with regard to the long-term outlooks of digital health, we can only hope to speculate, in an informed way, through the lens of what we see today.

The primary focus of the future of digital health will likely be on building economic, powerful digital health ecosystems. With the arrival of 5G, new generations of smart devices, and increasingly powerful high-performance computing services in the cloud, establishing digital health ecosystems is no longer a privilege of science fiction (think of the *Tricorder* from *Star Trek*). The benefit that a digital health ecosystem can bring are multifaceted. At its heart, we think, are to lower significantly the entry barriers for digital health services and to bring the low- and middle-income countries into the community, not only to benefit from, but also to participate in, the development of this exciting global effort. Eventually, there may be an international public health cloud (see top panel of **Figure** 4), providing FAIR data storage, ultra-fast computing services and data analysis pipelines, enabling terminal digital devices to execute complex tasks that are orchestrated and executed in the cloud. With digital device availability increasing (see **Figure** 1) and the threshold of entering the ecosystem falling, the stark shortage of medical professionals we face today will be offset to some degree. Having the digital health ecosystem take on much of the routine work, the existing, although potentially still being in shortage, medical personnel can focus on addressing the most pressing clinical and public health issues.

Next, we may see an expedited digital health revolution, thanks to the fourth industrial revolution, or Industry 4.0[66]. The concept of Industry 4.0 is an evolving one, but it generally involves the next-generation computerization, digitalization, and automation, combining the real and virtual worlds via, and into, the Internet of Things (IoT)[66], which consists of real-time analytics, machine learning, commodity sensors, and embedded systems[67]. Built on the IoT, Industry 4.0 promises platforms that are useful to achieve more accurate, automated digital health[68]. Industry 4.0 connects patients, machines (including devices and sensors) and medical personnel and supports their communication via the IoT. Such connectivity makes it possible for medical systems to accumulate meaningful *big data* from heterogeneous modalities, large populations, over time, and in both healthy and diseased subjects. The analysis of longitudinal big data, in turn, improves patient identification, disease estimation, and disease trajectory monitoring (see **Figure** 4). As big data continue to amass, the system learns and continuously refines itself, forming an ever-smarter intelligent healthcare assistant (see **Figures** 3 and 5). The smart system will, over time, be able to take on and automate some traditionally labor-intensive tasks, which will gradually re-shape the roles that human actors (patients, professionals, and healthy subjects) play in the healthcare system. As a layer of safeguard, the ecosystem will require advanced forms of regulation and interventions when parameters are beyond the limits of their models or predictions lack the required confidence, conflicting results arise, or particularly sensitive decisions are to be made.

Much of this article has focused on digital assessment and monitoring; but future digital health ecosystems will also include digital therapy. The growth of augmented and virtual reality (VR) interfaces, traditionally used in gaming, architecture, surgery, *etc*.[69] offer new avenues for digital therapeutic applications. For example, assessment of visual, behavioral, and emotional states may be a more enjoyable and relevant experience when incorporated into an immersive, reality-like game. Certainly, for broad adoption and reimbursement, where appropriate, these digital interventions will need robust evidence to demonstrate their safety and health-economic benefits, in the same way that new medicines have had to do for many years[70]. Yet, beginnings have already been made. Newer digital therapeutic approaches, such as exergaming (combining VR and gaming) and Brain-Machine Interface[71], are starting to assist individuals with aging, injuries, disability, and neurological illnesses[71–75]. The reality has begun with the first prescription digital therapeutic for the treatment of substance use disorder (SUD) approved by the Food and Drug Administration (FDA) in 2017[76], and very recently the first-ever video game was approved by the FDA as a mental health treatment in children with attention deficit hyperactivity disorder (ADHD)[77].

Central to the realization of well-accepted digital ecosystems is timing. Digital health ecosystems that are nascent today will become increasingly complex in every dimension – scientific, technical, social, political, economic, *etc*. Thus, if development in one dimension is lagging, the ecosystem as a whole will not function properly, nor will it deliver a friendly user experience or produce self-sustainable revenues. It will eventually be abandoned by the users (patients, doctors, and the manufacturers). Another critical component of digital health is the development of “killer applications” that are *both* functionally powerful and easy to use. Reflecting on past techno-social disruptive transformations: there was no market for the personal computer (PC) before the advent of the spreadsheet application; without online media and mature wireless communication technologies, Apple’s Newton was not as compelling a proposition as its successor, the iPad, is today. There are many more examples and, unfortunately, ideal timing and “killer applications” are oftentimes only obvious with the benefits of hindsight. Knowing this, one should not be discouraged by failed attempts or deterred from testing new ideas and introducing novel applications. It was only after repeated ‘failures’ that we finally witnessed the success of the PC and the Tablet. It will also take trial and error before the next generations of digital health devices, possibly a ‘digital doctor’ someday, achieve wide recognition and adoption. Repeated failures and experimentation, attended by curiosity, imagination, and enthusiasm, will bring us progressively closer to success.

With little doubt, digital devices in personalized healthcare and public health will continue to improve and evolve. Eventually, they will form a comprehensive healthcare ecosystem that integrates a web of patients, data, analytics, and healthcare professionals. The key nodes of this web are all of us, people, who are or someday will become patients and hope to receive early or timely digital health services including digital-diagnoses, -monitoring, and -therapy. But along the journey towards achieving these goals lay some sizeable challenges, which span data and algorithm quality, FAIRness, privacy, safety, ethics, and more. Challenges which we must acknowledge, confront, and overcome. It is high time to combine efforts from academia, industry, non-profit, public, and government organizations, to seize the opportunities and, united in collaboration, deliver more effective and affordable personalized healthcare and public health to all in the digital age.

“So, are we ready to enter the digital health age?” John asked. But the alarm goes off again. It is bedtime. John dims the lights, clicks the music app to enter a sleep song album, and puts the EEG cap back on.

The dream begins.

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