

REVIEW ARTICLE

FRONTIERS IN MEDICINE

Mobile Devices and Health

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N Engl J Med 2019;381:956-68.

DOI: 10.1056/NEJMr1806949

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MOBILE HEALTH — THE APPLICATION OF SENSORS, MOBILE APPS, SOCIAL media, and location-tracking technology to obtain data pertinent to wellness and disease diagnosis, prevention, and management — makes it theoretically possible to monitor and intervene whenever and wherever acute and chronic medical conditions occur. With 81% of North American adults owning a smartphone,¹ this frontier could be reached in the foreseeable future in the United States and is particularly relevant to the management of chronic diseases. More than 40% of U.S. adults have two or more chronic conditions² and chronic conditions now account for 71% of all U.S. health care spending,³ so the promise of mobile health is especially attractive.

Mobile health is at the swirling confluence of remote sensing, consumer-facing personal technologies, and artificial intelligence (AI). Data from smartphone applications (colloquially known as “apps”) and an ever-growing range of wearable and environmental sensors can be processed with the use of machine learning and other AI techniques to support medical decision making. Here, I review the current state of sensing, digital biomarkers, and digital therapeutics (the use of online technologies in the treatment of behavioral and medical conditions); discuss the challenges of integrating mobile health into clinical care; and describe regulatory, business, and ethical issues confronting mobile health. I do not discuss sensors and apps intended solely for use by health care professionals in health care settings. Because mobile health is a nascent technology and rigorous evidence of clinical validity is generally lacking, rather than presenting a review of existing systems, I present an overview for practitioners and policy makers to understand key aspects of this rapidly evolving field (see video).

 A video overview of mobile health and an illustrated glossary are available at NEJM.org

SENSORS

PASSIVE SENSORS

Of passive sensors, the smartphone is the most ubiquitous. It has a nine-axis inertial motion sensor that tracks motion and position in three-dimensional space. A three-axis accelerometer measures acceleration in the x, y, and z axes; a three-axis gyroscope senses rotation around each axis; and a three-axis magnetometer compensates for magnetic drift to maintain position accuracy. These sensors enable physics-based capabilities, such as detecting the number of steps that a person takes during a day. Most smartphones can also sense geographic position, atmospheric pressure, ambient light, voice, and touchscreen pressure. Creative uses of these sensors and a built-in camera can turn the smartphone into a fall detector,⁴ spirometer⁵ (by sensing air pressure on the microphone), or heart-rate sensor.⁶

Wearable devices are also widespread. In the United States in 2017, 17% of adults used a wearable device such as a smartwatch or a wrist-worn fitness band.⁷ Wrist sensors have many of the same sensors as smartphones and can be used to detect motions such as those associated with smoking⁸ and seizure activity.⁹ Wrist

Glossary

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| <p>Decentralized clinical trials: Trials executed through telemedicine, mobile health, or local health care providers, with the use of procedures such as virtual recruitment, investigational products shipped directly to participants, or smartphone-based outcomes assessment.</p> <p>Digital biomarkers: Physiological and behavioral measures collected by means of digital devices such as portables, wearables, implantables, or ingestibles that characterize, influence, or predict health-related outcomes.</p> <p>Digital diagnostics: The application of wearable and ambient sensors, mobile apps, social media, and location-tracking technology singly or in combination to diagnose medical conditions.</p> <p>Digital patient experience: The sum of online interactions that a patient has with a health care organization on websites, mobile devices, or wearables across all touchpoints and phases of care.</p> <p>Digital therapeutics: Interventions that use wearable and ambient sensors, mobile apps, social media, and location-tracking technology independently or in conjunction with medications, devices, or other therapies to improve patient care and health outcomes.</p> <p>Ecologic momentary assessment: An approach that involves repeated sampling of persons' current behaviors and experiences in real time, in these persons' natural environments.</p> <p>Food and Drug Administration (FDA) approval: FDA approval is given to class III medical devices that pass a premarket approval process to "demonstrate that the device is safe and effective when used." Class III medical devices are ones that pose the highest risk. They "sustain or support life, are implanted, or present potential high risk of illness or injury."</p> <p>FDA clearance: Class I or II medical devices pose minimal or moderate risk of harm. Unlike class III devices, they are not required to undergo premarket approval. FDA clearance can be obtained through the premarket notification, or 510(k), process to "demonstrate that the device is substantially equivalent to a device already placed into one of the three device classifications before it is marketed."</p> <p>Internet of Things: The network of everyday physical objects that are embedded with sensors and software that are interconnected and can exchange data through the Internet.</p> <p>Medical device: According to the Food, Drug, and Cosmetic Act, a medical device is "an instrument ... or other similar or related article [that is] intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease ... and which does not achieve any of its primary intended purposes through chemical action within or on the body ... and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."</p> <p>Metadata: Data that describe and give information about other data — for example, the author of a document, the size of an image, or the device that generated a reading.</p> <p>Mobile health: The application of wearable and ambient sensors, mobile apps, social media, and location-tracking technology singly or in combination to obtain data pertinent to wellness and disease diagnosis, prevention, and management.</p> <p>Patient-generated health data: Health-related data that are created, recorded, or gathered by or from patients.</p> <p>Patient-reported outcome: A report of the status of a patient's health condition that comes directly from the patient.</p> <p>Software as a medical device: Software that is intended to be used for medical purposes and that performs these purposes without being part of a hardware medical device.</p> |
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sensors often also have photoplethysmographic sensors, which measure heart rate and heart-rate variability by detecting changes in reflected light caused by changes in microvascular blood flow with each heartbeat. Two commercial devices with Food and Drug Administration (FDA) clearance (see Glossary) can provide an electrocardiogram through electrodes embedded in a smartphone or smartwatch and thereby detect atrial fibrillation.^{4,10}

Innovation in electronic sensing is in many ways outpacing the imagination for how these sensors can be used clinically. Wearable sensor patch-

es can measure muscle activity and posture,¹¹ radiofrequency sensors placed over clothes can detect pulmonary edema,¹² and smart fabrics can measure variations in force, pressure, humidity, and temperature¹³ to support, for example, neurologic rehabilitation.¹⁴ A pill can be embedded with a miniature sensor that, when it enters the acidic environment of the stomach, emits a signal to a wearable sensor patch.¹⁵ This technology was approved by the FDA (see Glossary for definition of FDA approval) in 2017 for monitoring medication adherence.

Smartphones, wearable devices, and other pas-

sive sensors are increasingly being networked together with sensors embedded in everyday objects, creating the so-called Internet of Things (Fig. 1). For example, commercially available smart homes that are embedded with motion and other sensors can record vital signs and monitor the physical activity (including falls) of elderly residents.¹⁶ In Chicago, the Array of Things project involves the use of 500 sensors to collect block-level data on air pollution, noise, temperature, and pedestrian and vehicular traffic.¹⁷ These sensors can enable explorations of environmental influence on disease trajectories.

ACTIVE SENSING

Passive sensors collect observable data. Subjectively perceived states of health (e.g., pain and other symptoms) are equally important for informing patient-centered care and, at this time, can be captured only by asking the patient. Until recently, information about such outcomes has been obtained from questionnaires administered at intervals of weeks to months that ask patients to integrate their experiences during some past interval of time (e.g., “in the past 7 days, how often . . . ?”). The ubiquity of personal devices makes possible an alternative approach called ecologic momentary assessment (EMA) that is well suited to capturing some types of patient-reported outcomes. EMA involves “repeated sampling of subjects’ current behaviors and experiences in real time, in subjects’ natural environments.”¹⁸ EMAs are less subject to recall bias than infrequently administered questionnaires and can be administered multiple times a day to capture short-term variations in responses. EMAs range from simple text-message prompts to short one- or two-item app-based questions and have been used to collect information on chronic pain,¹⁹ anxiety,²⁰ substance-use disorders,²¹ and many other conditions. Widely used in the social and behavioral sciences, EMA is an emerging method for outcomes assessment in both clinical care and clinical research. Newer image-based EMAs, if designed with cultural sensitivity, offer intriguing opportunities for bridging language, literacy, and numeracy barriers.

FUNCTIONAL ASSESSMENTS

Functional assessments through sensors complement passive background sensing and active reports by patients. Functional performance can be measured by having patients perform standard-

ized tasks using mobile health technologies. Examples include performance of the 6-minute walk test with the use of smartphone motion sensing,²² assessment of parkinsonian voice tremor by means of the smartphone microphone,²³ and assessment of cognitive function, such as memory and reaction time, through apps.²⁴ Although many mobile functional assessments are in development, data on broad clinical usefulness are lacking.

DIGITAL BIOMARKERS

Raw sensor data, such as from three-axis accelerometry, are meaningless to clinicians and patients. To be useful, raw sensor data must be processed into digital biomarkers, defined as digitally collected physiological and behavioral measures that explain, influence, or predict health-related outcomes. Examples of digital biomarkers include a daily step count and average nightly sleep duration. The science of identifying and validating clinically meaningful and actionable biomarkers is in its infancy.²⁵ To develop digital biomarkers, sensor engineers, computer scientists, data scientists, clinicians, and clinical researchers need to work together to understand the nature of the clinical phenomenon being measured, match the appropriate sensors to the clinical need (while balancing technical concerns such as power consumption and usability), derive candidate biomarkers by training machine-learning models, and conduct clinical studies to validate the biomarkers. Challenges include the handling of very high data volumes, high variability both within and across patients, and the need for repeated ongoing validation as the underlying sensors and algorithms are updated.²⁵

DIGITAL THERAPEUTICS AND DIAGNOSTICS

Simply monitoring patient outcomes remotely generally does not by itself improve clinical outcomes.²⁶ Active interventions that use “digital therapeutics” are needed to directly prevent, manage, or treat medical conditions. Digital therapeutics use mobile health methods alone or in combination with medications and other therapies. For example, a growing body of evidence supports the use of digital cognitive behavioral therapy for patients with conditions such as insomnia,²⁷ substance abuse,²⁸ and attention deficit–hyperactivity disorder²⁹ and of various reminder and behavioral

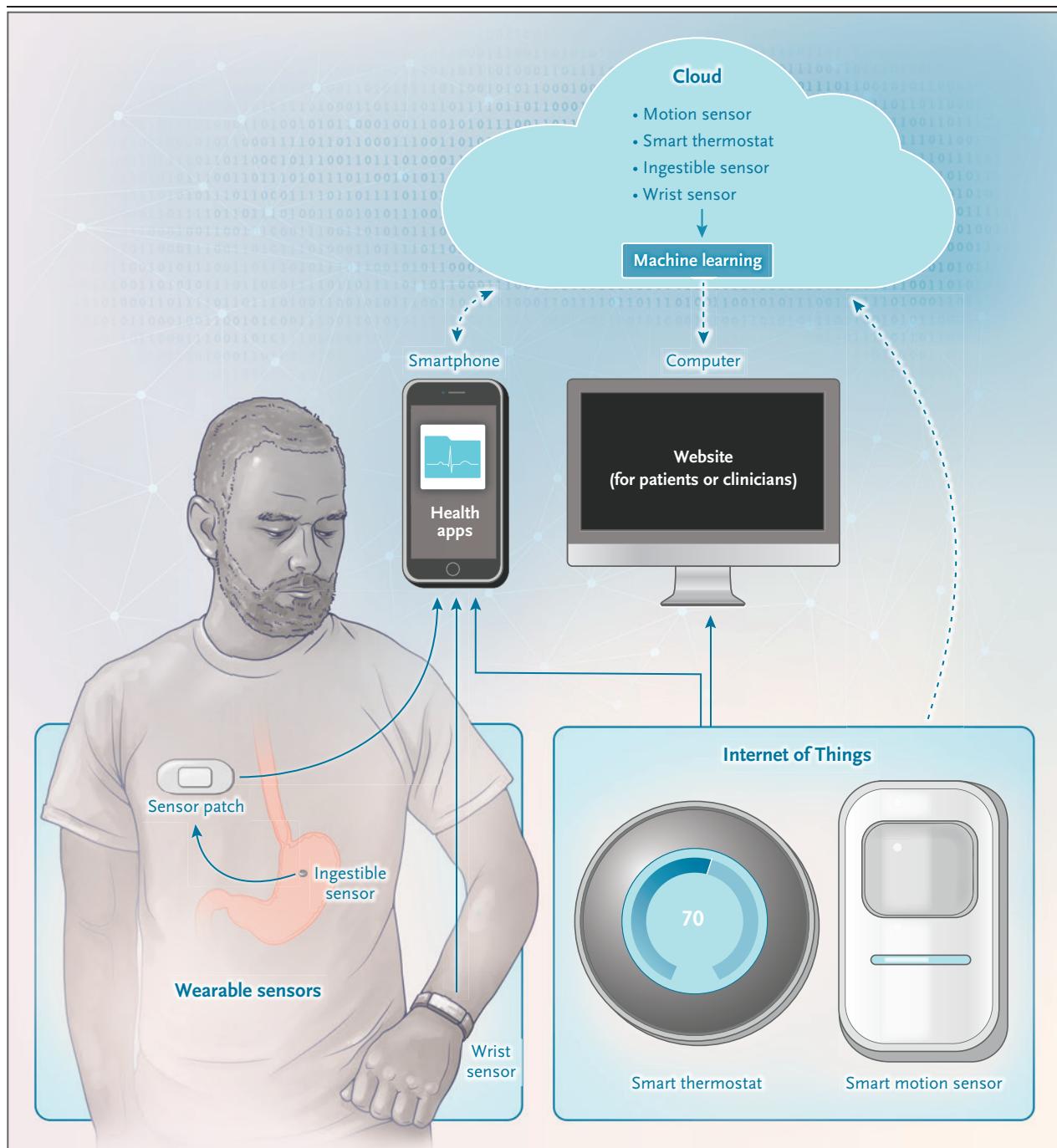


Figure 1. Data Flow of Wearable Sensors and the Internet of Things.

This figure presents a simplified view of the data flow of wearable sensors and the Internet of Things. The wrist sensor communicates with the patient's smartphone through Bluetooth. Once on the phone, the data can be displayed in the app of that sensor or can be sent to the cloud storage of the sensor. This cloud "backend" stores data and can apply machine learning or other analytic techniques to generate predictions, visualizations, or decision support. The cloud output can then be displayed on a website that is accessible to patients, clinicians, or both. The ingestible sensor is activated in the stomach. It sends a low-energy signal to a patch on the patient's chest. The patch communicates with the patient's smartphone through Bluetooth. The rest of the data flow is similar to that of the wrist sensor. The smart thermostat and motion sensor are devices on the Internet of Things. These devices can communicate directly with the cloud or through a local network or intelligent gateways. Digital biomarker computation can happen in the sensor, smartphone, or cloud. In the cloud, data can be shared and combined with data from other devices and services for use by algorithms.

management programs for patients with diabetes³⁰ and hypertension.³⁰ Digital therapeutics that combine hardware and software innovations include asthma management with the use of “smart” inhalers that track time, frequency, and location of inhaler use³¹; virtual-reality programs for pain management³²; and treatment of panic disorder with the use of carbon dioxide monitors.³³ Several such therapeutics are FDA-cleared³⁴ or -approved,³⁵ and pharmaceutical companies are beginning to take stakes in digital therapeutics companies.³⁶ Digital diagnostics represent a farther frontier, with some showing early promise but all needing much wider, more rigorous, clinical testing. Examples of promising devices include those that can aid in the diagnosis of Parkinson’s disease (with data on posture and gait³⁷ and voice²³), autism (with eye-gaze tracking³⁸), and depression (with voice analysis³⁹).

A major challenge of mobile health is the high drop-off rate in sensor and app usage.⁴⁰ In one survey, more than half of users of activity trackers stopped using their device, and a third did so in the first 6 months.⁴¹ Strategies to improve engagement include discussion between patient and provider of goals for tracking and clear plans for attaining them. Joint goal-setting followed by joint review of the data appears to motivate continued tracking and therapeutic engagement.⁴² However, it is not clear, at present, whether enhanced patient–provider communication and shared decision making improves clinical outcomes. Another driver of engagement is personal analytics that help patients understand and more effectively manage their own behaviors with respect to disease pattern, such as the relationship of diet and activity to blood sugar. Although sensors in the home and other locales may reduce the need for wearable sensors, patient engagement is still required to install and maintain these environmental sensors, and continued engagement will always be needed for active reports by patients.

INTEGRATION WITH CLINICAL CARE

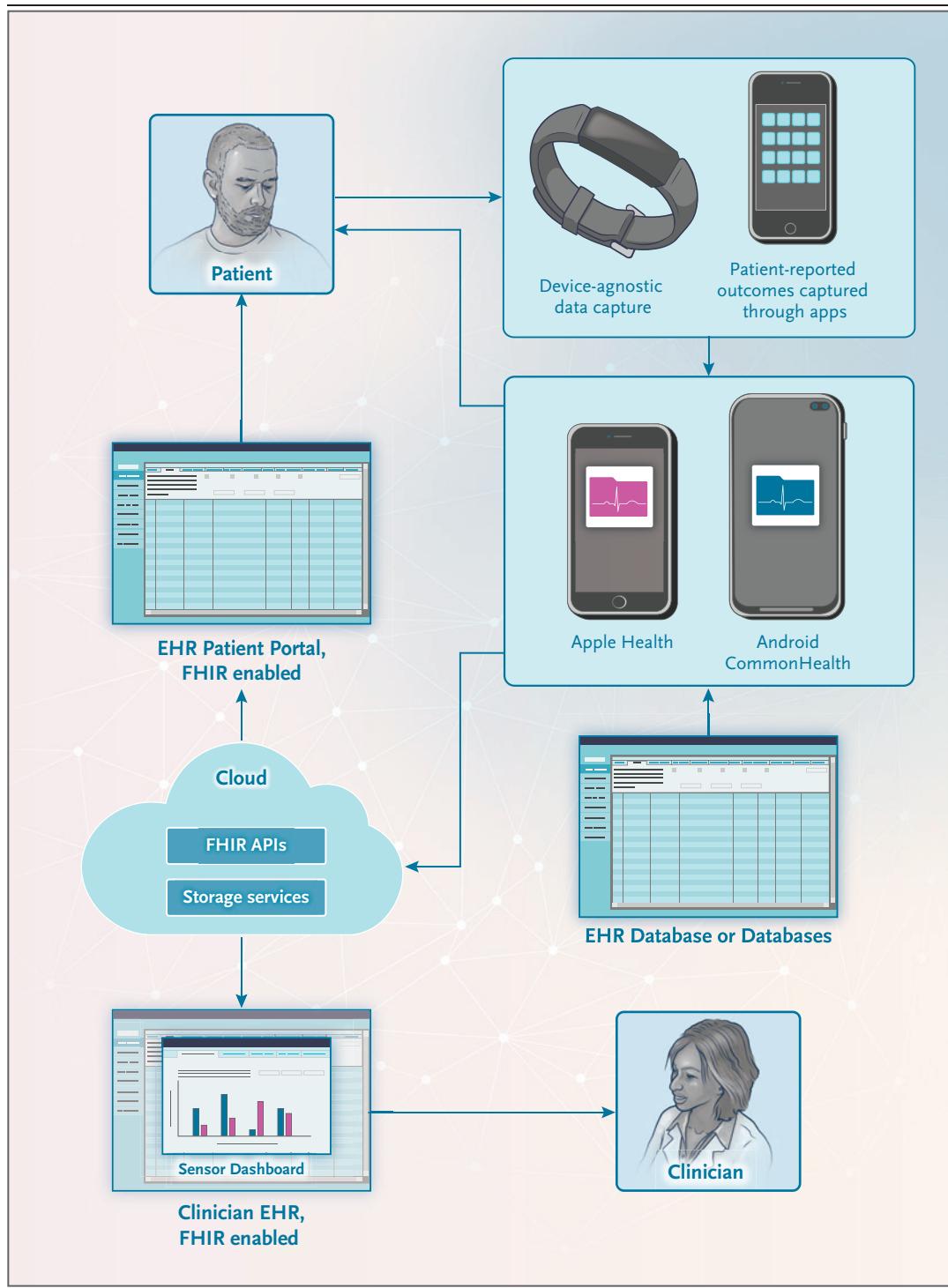
At the front lines of care, two challenges dominate the implementation of mobile health. The first is the vast quantity of data. Ancillary staff can help review and triage data, and visualization tools can mitigate the cognitive burden of inter-

Figure 2 (facing page). Integration of Sensor, Smartphone, and Electronic Health Record (EHR) Data for Patients and Clinicians.

Mobile health data are likely to be more useful if combined with EHR data for patient or clinician use. Recent technology is making this possible. In the Apple ecosystem, the Apple Health app can, for example, pull in data from a wrist sensor as well as EHR data from the patient’s health care institution or institutions. The Android CommonHealth app aims to duplicate this functionality for Android smartphones. Once sensor and EHR data are on a smartphone, they can be made available to other apps on the phone, combined with data reported by patients, or sent up to a cloud to be computed into more aggregated digital biomarkers or used with machine learning to drive decision support. The output — a visualization, digital therapeutic, or decision aid — can be delivered back to the patient through a smartphone. For clinicians using Fast Health Interoperability Resources (FHIR)–enabled EHRs, the output (e.g., a sensor dashboard) can be provided directly within the clinical workflow through a window embedded within the EHR encounter for that patient. The clinician does not need to perform any additional logins. API denotes application programming interface.

preting the data. However, the most effective response is to develop and show to clinicians only those digital biomarkers that inform clinical action or clinical understanding (e.g., temporal and severity profiles of patient symptoms). Simultaneously, these biomarkers must be of sufficient direct value to patients to justify their participation in the data-collection effort. None of this is easy. Greater investment in the science of digital biomarkers is needed to evaluate the value of mobile health data for clinical use.²⁵

The second (and related) challenge is how the inclusion and presentation of data will fit into an already complicated and overstretched workflow. Clinicians cannot be expected to log in to separate websites for every sensor or app their patients are using. That said, integration with the electronic health record (EHR) is currently extremely challenging and costly.⁴³ A recent development may offer hope: the federal government’s “meaningful use” requirements for EHR certification are calling for greater interoperability through an emerging data-exchange standard called Fast Healthcare Interoperability Resources (FHIR).⁴⁴ FHIR allows external third-party apps to integrate into the EHR workflow. For example, Apple enables data to flow from



FHIR-enabled EHRs to the Apple Health app on iPhones and from there to other apps in the Apple ecosystem (Fig. 2). With this new ability

to combine EHR and mobile health data, iOS mobile health apps may become more useful and effective. Absent an Android equivalent for

EHR access, Android apps may over time become systematically less effective than iOS apps, which raises deep ethical concerns, as discussed below. A recently started open-source project called CommonHealth (<https://commonhealth.org>) aims to mitigate this concern by bringing EHR data integration to Android smartphones.

FHIR also supports integrating the output of third-party digital health tools directly into the EHR workflow without requiring that the output be written into the database of the EHR, since such a requirement would trigger often prohibitive legal and security concerns. With this SMART-on-FHIR integration approach (SMART stands for Substitutable Medical Applications and Reusable Technologies),⁴⁵ a clinician who is signed into the patient's record can view that patient's third-party app or sensor data in an embedded window without the need for a separate log-in. This approach opens up the workflow and "screen real estate" of the EHR to essentially unlimited innovation. However, SMART-on-FHIR integration is currently very limited.

Health care organizations that wish to implement mobile health cannot overlook the logistics and legal implications of providing patients with sensors and apps. Additional staffing must be considered for assisting patients with technology setup, providing technical support, and responding to patients' questions and concerns. For example, the Ochsner Health System has assigned dedicated staff to act as "geniuses" in their O Bar, a retail-like space modeled after Apple's Genius Bar that carries Ochsner-approved apps and devices that patients can "test drive."⁴⁶ As patients independently bring mobile health data to clinicians (e.g., Apple Watch and Fitbit data) and as digital health vendors try to sell to health care organizations, health care leaders will need to grapple with how best to support mobile health and the use of patient-generated health data.⁴⁷

OTHER CHALLENGES

VALIDATION AND REGULATION

Higher-risk mobile health technologies are considered medical devices under the Food, Drug, and Cosmetic Act. The FDA regulates medical devices under processes that were designed for medical-grade hardware devices, such as hip implants, with known physical properties that

change little after market release.⁴⁸ Mobile health technologies, in contrast, often combine hardware (e.g., a glucometer) with software (e.g., algorithms for the management of type 1 diabetes) and can be extremely dynamic, with frequent hardware and software updates. A different regulatory approach is needed. The FDA proposes to regulate these technologies (now termed "software as a medical device") through a new Digital Health Software Precertification Program.⁴⁹ This "Pre-Cert" program, currently under pilot, proposes to precertify companies that demonstrate a "culture of quality and organizational excellence" for streamlined review of their applications. Products of precertified companies do not have to be associated with improved clinical outcomes before market release but will instead be subject to postmarketing performance monitoring to support the claims of safety and effectiveness by the company.

Many details of the program remain to be determined, including how companies can gain or lose precertification status, how different levels of risk of harm will be determined and handled, and how real-world performance will be assessed through postmarketing monitoring and with what consequences. Trust in mobile health technologies and the extent of their adoption will depend on how these and other details are resolved. Thus, the stakes for success of the Pre-Cert program are very high. The desire to support innovation must be balanced against grave concerns about insufficient or delayed oversight.

In addition to these technologies, the accuracy of digital biomarkers also requires validation. For example, commercial sensors are relatively consistent with each other on step count but not on sleep duration or sleep cycles or duration of physical activity.⁵⁰ Because most commercial devices restrict access to their raw data and algorithms, independent verification and validation of the majority of current digital biomarkers is not possible. Greater transparency and accountability, the setting of metadata standards (standards on how to describe data, such as their provenance), and external validation will facilitate evaluation of digital biomarkers proposed for use in clinical care.^{51,52} This can be achieved by making available reference data sets and through publication of tests of validation. An illustrative example is Sage

BioNetwork's Parkinson's Disease Digital Biomarker DREAM Challenge that made available data from studies of digital biomarkers of tremor and dyskinesia.⁵³

Clinicians, patients, and payers would benefit from digital health formularies that list sensors and apps that are vetted for clinical use, much like medication formularies for drugs. The latest of several attempts to launch such a digital health formulary is by Express Scripts.⁵⁴ Other efforts include the establishment of principles and guidelines for app development⁵⁵ and rigorous evaluation,⁵⁶ but best practices for screening, integrating, and appraising apps remain to be established.

MARKET GROWTH AND CLINICAL VALUE

Despite the regulatory flux, the digital health sector saw a record \$8.1 billion in investments in 2018.⁵⁷ A recent change in the Medicare Physician Fee Schedule that allows physician billing for time spent managing and interpreting data from remote monitoring (e.g., electrocardiographic, blood-pressure, and glucose monitoring) for management of chronic conditions⁵⁸ provides an incentive for the use of mobile health data in the clinic. However, no standard models exist for who should pay for mobile health technology that is recommended or prescribed to patients.⁵⁹ In clinical research, decentralized clinical trials (see Glossary) are using digital biomarkers as end points and replacing in-person study procedures with virtual and mobile procedures.^{52,60} ResearchKit by Apple⁶¹ and ResearchStack by Android⁶² — mobile research platforms that facilitate large-scale virtual recruitment and outcomes assessment — are expanding the reach of clinical studies, analogous to the effect of mobile health on clinical care.

Underlying these market developments is a persistent question: to what end is mobile health? Tracking and reporting data are means to an end, not the end itself. Achieving clinical value, the ultimate goal, may occur through the use of mobile health data as cognitive aids to patients and clinicians (helping people understand or think through an issue), decision aids to patients and clinicians (helping people decide on an action), or motivational aids for patient engagement and activation (Table 1). More collaboration is needed among clinicians, patients, and technologists to drive the development of clinically use-

ful mobile health technology and to imagine clinically useful applications of novel sensors, while remaining cognizant of potential harms. Clinical researchers need to develop new evaluation approaches because years-long studies are poorly suited to the pace of change of mobile health technology. Finally, clearer demonstrations of the clinical and business value of mobile health will come when factors far beyond technology itself, such as integration into clinical workflow, payment model, and validation methods, are addressed in tandem with sensor and software development.

ETHICS

The tremendous promise of mobile health for transforming clinical care and research is tempered by deep concerns about the effect of these technologies on equity, privacy, and patient autonomy. Although there is essentially no digital divide according to race in the United States,⁶⁷ Internet and smartphone adoption is lower in lower-income, disabled, elderly, and rural populations. Moreover, Android users, who account for more than half of U.S. smartphone users,⁶⁸ have lower average income than iOS users.⁶⁹ If iOS mobile health apps are systematically more effective than Android apps at improving health outcomes (e.g., owing to differential access to EHR data, as discussed above), health disparities will worsen. As health institutions increasingly develop a mobile presence with branded apps and other initiatives regarding digital patient experience (see Glossary), they must be careful not to increase health disparities — for example, by offering unequal services to iOS users and Android users.

There is an even more profound digital divide. Use of mobile health and Internet of Things technologies requires digital literacy skills. Patients are essentially being asked to install and maintain their own medical devices and to be adept at managing their own data deluge, a tall order when the majority of U.S. adults are in the lowest three of six proficiency levels for literacy and numeracy⁷⁰ and more than 60% are in the lowest two of four proficiency levels for problem solving in technology-rich environments (defined as “using digital technology, communication tools, and networks to acquire and evaluate information, communicate with others, and perform practical

Table 1. Mechanisms of Mobile Health and Potential Benefits and Harms.*

| Mechanism and Examples | Potential Benefits | Potential Harms |
|--|--|--|
| Cognitive aid to patients† | | |
| Visualization of blood glucose level, diet, physical activity, and insulin use in one place in patients with type 1 diabetes ⁶³ | Understanding of individualized responses of blood glucose level to diet and exercise | Confusion, misinterpretation |
| Cognitive aid to practitioners‡ | | |
| Visualization and summarization of home blood-pressure readings | Quick assessment of ambulatory blood-pressure control without need to mentally estimate average home blood pressure from manual logs | |
| Symptom profiles (e.g., from ecologic momentary assessments) that characterize patient experience | Window into patients' lived experience to inform patient-centered care | Exacerbation of health disparities as practitioners have less insight into health states of patients who are not willing or able to track themselves |
| Decision aid to patients‡ | | |
| Reminders about medication adherence | Improved medication adherence | Reduction of medication nonadherence to a problem of forgetting, ⁶⁴ improving adherence for business rather than clinical reasons |
| Decision aid to practitioners‡ | | |
| Alerts triggered when a patient is using a smart inhaler above a specific threshold frequency | Treatment intensification earlier in course of disease progression | Inaccurate alerts, high volume of alerts, medical liability for ensuring real-time response |
| Motivational aid for patient engagement and activation | | |
| Patient tracking of chronic pain | Data and graphing of subjective state validate patient experience, help improve engagement with care providers ⁴² | Data-driven perfectionism (e.g., orthosomnia from sleep tracking) ⁶⁵ |
| Adaptive goals and rewards for number of steps taken per day ⁶⁶ | Individualized strategies for initiating and maintaining health behavior change | |

* Mobile health can affect clinical outcomes through multiple mechanisms. Some mobile health solutions will use more than one of these mechanisms. Each mechanism also requires addressing multiple nontechnological factors (e.g., definition of when the intervention should be delivered and integration into clinical workflow). The rapid evolution of mobile health technology complicates the demonstration of benefits and harms.

† Cognitive aids help people understand or think through an issue.

‡ Decision aids help people decide on (and take) action.

tasks⁷¹). This gap is further compounded by the paucity of mobile health technologies in languages other than English.

With respect to privacy and autonomy, the potential threats are particularly worrisome. Mobile health technologies will increasingly connect to the Internet of Things, in which, like a "one-way mirror,"⁷² our virtual bodies and behavior will be visible on a grand scale for purposes to which we have not directly consented. When personal health and nonhealth data congregate in the cloud, companies and governments may access physiological biomarkers to monitor

employee stress in the workplace, or marketers may offer us only certain products at differential prices based on our health history. Coupled with algorithms that are not in the public domain, these approaches could deliberately or inadvertently reinforce and entrench existing biases against disadvantaged groups, and incautious deployment of mobile health technology could potentially result in loss of privacy and autonomy amounting to net harm to patients. Table 2 lists actions that patients, practitioners, researchers, and policymakers can take to guide the evolution of mobile health.

Table 2. Actions for Stakeholders in Mobile Health.*

| Stakeholder and Action | Illustrative References |
|--|---|
| Patients and caregivers | |
| Understand trade-offs in remote monitoring | Consumer Reports guide to digital security and privacy ⁷³ |
| Discuss with clinicians what data to track and why, to facilitate joint goal setting | Patient and doctor jointly define interventions and outcomes of interest for personalized N-of-1 studies ⁴² |
| Practitioners | |
| Discuss with patients what data to track and why, to facilitate joint goal setting | Patient and doctor jointly define interventions and outcomes of interest for personalized N-of-1 studies ⁴² |
| Use patient-generated health data to facilitate doctor–patient communication, gain a more holistic sense of a patient’s health experience, and increase patient engagement and activation† | Use of observations of daily living ⁷⁴ |
| Researchers and funders | |
| Avoid exacerbating health disparities | Minimization of selection bias in the development and testing of technologies ⁷⁵ |
| Pursue, fund, train for, and support interdisciplinary science of digital biomarkers | Agenda for the development and evaluation of digital biomarkers ²⁵ |
| Develop and use broader range of evaluation approaches | Evaluation of mobile health technology ⁷⁶ |
| Health care administrators | |
| Address digital patient experience, with emphasis on trust, equity, privacy, security, and appropriate patient expectations | Recommendations on role of health information technology in addressing health disparities ⁷⁷ |
| Support patient use of digital health technologies | Ochsner Health System O Bar ⁴⁶ |
| Choose best path toward piloting, deployment, validation, or adoption of digital health technologies | Digital health testing algorithm ⁷⁸ |
| Policymakers and payers | |
| Avoid increasing health disparities | Recommendations on role of health information technology in addressing health disparities ⁷⁷ |
| Ensure scientific rigor, transparency, accountability, equity, and adaptability in mobile health regulation and policy | Agenda for the development and evaluation of digital biomarkers, ²⁵ FDA Digital Health Software Precertification Program ⁴⁹ |
| Collaborate across institutions and vendors to achieve transparency, accountability, and validation | Health information technology innovation pipeline ⁷⁹ |

* This table lists examples of actions that various stakeholders can take to guide the evolution of mobile health. No endorsement of the illustrative references is implied.

† Patient-generated health data encompass both sensor data and data from patient reports.

CONCLUSIONS

Mobile health technologies are evolving from descriptive monitoring tools to digital diagnostics and therapeutics that synergize tracking with behavioral and other interventions to directly affect health outcomes. Major challenges include the discovery and validation of meaningful digital biomarkers, regulation of and payment for mobile health technologies, and their integration into frontline care. Clearer articulations are needed of how mobile health technology can concretely affect clinical outcomes, along

with more rigorous evaluations of clinical effectiveness.

Networked mobile health technologies have the potential to harm. Concerns about digital surveillance are not unique to mobile health,⁸⁰ but health-related risks can be reduced through improved digital literacy among patients, ethical codes of conduct for developers and regulators of mobile health, and transparency and accountability in how health care organizations adopt mobile health technology. The transformative potential of mobile health compels clinicians to take an active role in ensuring that this new



An audio interview with Dr. Sim is available at NEJM.org

frontier will be safe, fair, and just for all patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Pew Research Center Global Attitudes Project. Smartphone ownership is growing rapidly around the world, but not always equally. February 5, 2019 (<https://www.pewresearch.org/global/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/>).
2. Buttorff C, Ruder T, Bauman M. Multiple chronic conditions in the United States. Santa Monica, CA: RAND, 2017 (<http://www.rand.org/pubs/tools/TL221.html>).
3. Agency for Healthcare Research and Quality. Multiple chronic conditions chartbook. April 2014 (<https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf>).
4. Apple. Apple Watch Series 4 (<https://www.apple.com/apple-watch-series-4/>).
5. Goel M, Saba E, Stiber M, et al. SpiroCall: measuring lung function over a phone call. In: Proceedings of the 2016 CHI Conference on Human Factors in Computing Systems — CHI '16. Santa Clara, CA: ACM Press, 2016 (<http://dl.acm.org/citation.cfm?doid=2858036.2858401>).
6. Coppetti T, Brauchlin A, Müggler S, et al. Accuracy of smartphone apps for heart rate measurement. *Eur J Prev Cardiol* 2017; 24:1287-93.
7. Statista. Wearable user penetration rate in the United States, in 2017, by age (<https://www.statista.com/statistics/739398/us-wearable-penetration-by-age/>).
8. Saleheen N, Ali AA, Hossain SM, et al. puffMarker: a multi-sensor approach for pinpointing the timing of first lapse in smoking cessation. *Proc ACM Int Conf Ubiquitous Comput* 2015;2015:999-1010.
9. Empatica. Embrace2 seizure detection (<https://www.empatica.com/>).
10. AliveCor. KardiaMobile (<https://www.alivecor.com/>).
11. MC10. BioStamp nPoint: wearable healthcare technology & devices (<https://www.mc10inc.com>).
12. Gao J, Ertin E, Kumar S, al'Absi M. Contactless sensing of physiological signals using wideband RF probes. In: Forty-Seventh Asilomar Conference on Signals, Systems & Computers, Pacific Grove, CA, November 3–6, 2013. Piscataway, NJ: Institute of Electrical and Electronics Engineers, 2013:86-90.
13. Gonçalves C, Ferreira da Silva A, Gomes J, Simoes R. Wearable e-textile technologies: a review on sensors, actuators and control elements. *Inventions* 2018;3:14 (<https://www.mdpi.com/2411-5134/3/1/14>).
14. McLaren R, Joseph F, Baguley C, Taylor D. A review of e-textiles in neurological rehabilitation: how close are we? *J Neuroeng Rehabil* 2016;13:59.
15. Hafezi H, Robertson TL, Moon GD, Au-Yeung KY, Zdeblick MJ, Savage GM. An ingestible sensor for measuring medication adherence. *IEEE Trans Biomed Eng* 2015;62:99-109.
16. Majumder S, Aghayi E, Noforesti M, et al. Smart homes for elderly healthcare — recent advances and research challenges. *Sensors (Basel)* 2017;17(11):E2496.
17. Array of Things. Introductory video (<https://arrayofthings.github.io/>).
18. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol* 2008;4:1-32.
19. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological momentary assessment methodology in chronic pain research: a systematic review. *J Pain* 2018; 19:699-716.
20. Walz LC, Nauta MH, Aan Het Rot M. Experience sampling and ecological momentary assessment for studying the daily lives of patients with anxiety disorders: a systematic review. *J Anxiety Disord* 2014;28:925-37.
21. Shiffman S. Ecological momentary assessment. In: Sher KJ, ed. *The Oxford handbook of substance use and substance use disorders*. Vol. 2. New York: Oxford University Press, October 2016:466-512.
22. Brooks GC, Vittinghoff E, Iyer S, et al. Accuracy and usability of a self-administered 6-minute walk test smartphone application. *Circ Heart Fail* 2015;8:905-13.
23. Singh S, Xu W. Robust detection of Parkinson's disease using harvested smartphone voice data: a telemedicine approach. *Telem J E Health* 2019 April 26 (Epub ahead of print).
24. Moore RC, Swendsen J, Depp CA. Applications for self-administered mobile cognitive assessments in clinical research: a systematic review. *Int J Methods Psychiatr Res* 2017;26(4):e1562.
25. Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *NPJ Digit Med* 2019;2(1):14.
26. Noah B, Keller MS, Mosadeghi S, et al. Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials. *NPJ Digit Med* 2018;1:20172.
27. Luik AI, Kyle SD, Espie CA. Digital cognitive behavioral therapy (dCBT) for insomnia: a state-of-the-science review. *Curr Sleep Med Rep* 2017;3:48-56.
28. Pear Therapeutics. Redefining medicine: prescription digital therapeutics for the treatment of serious disease (<https://peartherapeutics.com/>).
29. Akili Interactive. Akili achieves primary efficacy endpoint in pediatric ADHD pivotal trial. December 4, 2017 (<https://www.akiliinteractive.com/news-collection/akili-achieves-primary-efficacy-endpoint-in-pediatric-adhd-pivotal-trial>).
30. Omada Health. Digital therapeutics for chronic disease (<https://www.omadahealth.com/>).
31. Barrett MA, Humblet O, Marcus JE, et al. Effect of a mobile health, sensor-driven asthma management platform on asthma control. *Ann Allergy Asthma Immunol* 2017;119(5):415.e1-421.e1.
32. Pourmand A, Davis S, Marchak A, Whiteside T, Sikka N. Virtual reality as a clinical tool for pain management. *Curr Pain Headache Rep* 2018;22:53.
33. Freespira. A solution for panic attack treatment: FDA-cleared, drug-free (<https://freespira.com/>).
34. FDA clears mobile medical app to help those with opioid use disorder stay in recovery programs. News release of the Food and Drug Administration, Silver Spring, MD, December 10, 2018 (<http://www.fda.gov/news-events/press-announcements/fda-clears-mobile-medical-app-help-those-opioid-use-disorder-stay-recovery-programs>).
35. Teva announces FDA approval of first and only digital inhaler with built-in sensors — ProAir Digihaler (albuterol sulfate 117 mcg) inhalation powder. Press release of Teva Pharmaceutical Industries, Petah Tikva, Israel, December 21, 2018 (<https://ir.tevapharm.com/investors/press-releases/press-release-details/2018/Teva-Announces-FDA-Approval-of-First-and-Only-Digital-Inhaler-with-Built-In-Sensors--ProAir-Digihaler-albuterol-sulfate-117-mcg-Inhalation-Powder/default.aspx>).
36. Sheridan K. Prescription apps are gaining ground — and drug makers' backing — as digital therapeutics. Boston: STAT, July 25, 2018 (<https://www.statnews.com/2018/07/25/phone-apps-digital-therapeutics/>).
37. Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's disease diagnosis and treatment: a systematic review. *Front Neurosci* 2017; 11:555.
38. Vargas-Cuentas NI, Roman-Gonzalez A, Gilman RH, et al. Developing an eye-tracking algorithm as a potential tool for

- early diagnosis of autism spectrum disorder in children. *PLoS One* 2017;12(11):e0188826.
39. He L, Cao C. Automated depression analysis using convolutional neural networks from speech. *J Biomed Inform* 2018;83:103-11.
40. Simblett S, Greer B, Matcham F, et al. Barriers to and facilitators of engagement with remote measurement technology for managing health: systematic review and content analysis of findings. *J Med Internet Res* 2018;20(7):e10480.
41. Inside wearables: how the science of human behavior change offers the secret to long-term. Endeavour Partners, 2017 (<https://medium.com/@endeavourprtnrs/inside-wearable-how-the-science-of-human-behavior-change-offers-the-secret-to-long-term-engagement-a15b3c7d4cf3>).
42. Whitney RL, Ward DH, Marois MT, Schmid CH, Sim I, Kravitz RL. Patient perceptions of their own data in mHealth technology-enabled N-of-1 trials for chronic pain: qualitative study. *JMIR Mhealth Uhealth* 2018;6(10):e10291.
43. Research 2 Guidance. mHealth economics — how mHealth publishers are monetizing their apps. 2018 (<https://research2guidance.com/product/mhealth-economics-how-mhealth-app-publishers-are-monetizing-their-apps/>).
44. HealthIT.gov. Notice of proposed rulemaking to improve the interoperability of health information. 2019 (<https://www.healthit.gov/topic/laws-regulation-and-policy/notice-proposed-rulemaking-improve-interoperability-health>).
45. Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. *J Am Med Inform Assoc* 2016;23:899-908.
46. Milani RV, Bober RM, Lavie CJ. The role of technology in chronic disease care. *Prog Cardiovasc Dis* 2016;58:579-83.
47. Adler-Milstein J, Nong P. Early experiences with patient generated health data: health system and patient perspectives. *J Am Med Inform Assoc* 2019 April 22 (Epub ahead of print).
48. FDA Center for Devices and Radiological Health. 510(k) Clearances. October 2018 (<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm>).
49. FDA Center for Devices and Radiological Health. Digital health software pre-certification (Pre-Cert) program. October 2018 (<https://www.fda.gov/medicaldevices/digitalhealth/digitalhealthprecertprogram/default.htm>).
50. Wen D, Zhang X, Liu X, Lei J. Evaluating the consistency of current mainstream wearable devices in health monitoring: a comparison under free-living conditions. *J Med Internet Res* 2017;19(3):e68.
51. Perry B, Herrington W, Goldsack JC, et al. Use of mobile devices to measure outcomes in clinical research, 2010-2016: a systematic literature review. *Digit Biomark* 2018;2:11-30.
52. Open mHealth. Open source data integration tools (<http://www.openmhealth.org>).
53. Sage Bionetworks. Parkinson's disease digital biomarker DREAM challenge. 2017 (<https://www.synapse.org/#!/Synapse:syn8717496/wiki/422884>).
54. Express Scripts. Express Scripts simplifies digital health technology marketplace for consumers and payers. May 16, 2019 (<https://www.prnewswire.com/news-releases/express-scripts-simplifies-digital-health-technology-marketplace-for-consumers-and-payers-300851128.html>).
55. Xcertia. mHealth app guidelines (<https://www.xcertia.org/>).
56. NODE.Health home page (<http://nodehealth.org/>).
57. Day S, Zweig M. 2018 Year end funding report: is digital health in a bubble? Rock Health, 2019 (<https://rockhealth.com/reports/2018-year-end-funding-report-is-digital-health-in-a-bubble/>).
58. Centers for Medicare & Medicaid Services. Medicare program: revisions to payment policies under the physician fee schedule and other revisions to Part B for CY 2018: Medicare Shared Savings Program requirements: and Medicare Diabetes Prevention Program. *Fed Regist* 2017; 82(219):52976 (<https://www.federalregister.gov/documents/2017/11/15/2017-23953/medicare-program-revisions-to-payment-policies-under-the-physician-fee-schedule-and-other-revisions>).
59. Richman B. Health regulation for the digital age — correcting the mismatch. *N Engl J Med* 2018;379:1694-5.
60. Clinical Trials Transformation Initiative. CTTI recommendations: decentralized clinical trials. 2018 (https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/dct_recommendations_final.pdf).
61. ResearchKit. Introducing ResearchKit (<http://researchkit.org/>).
62. ResearchStack: an SDK for building research study apps on Android (<http://researchstack.org/>).
63. Tidepool. The place for your diabetes data (<https://www.tidepool.org/users>).
64. Rosenbaum L. Swallowing a spy — the potential uses of digital adherence monitoring. *N Engl J Med* 2018;378:101-3.
65. Baron KG, Abbott S, Jao N, Manalo N, Mullen R. Orthosomnia: are some patients taking the quantified self too far? *J Clin Sleep Med* 2017;13:351-4.
66. Korinek EV, Phatak SS, Martin CA, et al. Adaptive step goals and rewards: a longitudinal growth model of daily steps for a smartphone-based walking intervention. *J Behav Med* 2018;41:74-86.
67. Rainie L. Digital divides — feeding America. Washington, DC: Pew Research Center, February 9, 2017 (<http://www.pewinternet.org/2017/02/09/digital-divides-feeding-america/>).
68. StatCounter. Mobile operating system market share in United States of America: June 2018-June 2019. Global Stats. 2019 (<http://gs.statcounter.com/os-market-share/mobile/united-states-of-america>).
69. Comscore. iPhone users earn higher income, engage more on apps than Android users. August 14, 2014 (<http://www.comscore.com/Insights/Infographics/iPhone-Users-Earn-Higher-Income-Engage-More-on-Apps-than-Android-Users>).
70. Centers for Disease Control and Prevention. Health Literacy: understanding literacy & numeracy. 2018 (<https://www.cdc.gov/healthliteracy/learn/UnderstandingLiteracy.html>).
71. Rampey BD, Finnegan R, Goodman M, et al. Skills of U.S. unemployed, young, and older adults in sharper focus: results from the Program for the International Assessment of Adult Competencies (PIAAC) 2012/2014: first look (NCES 2016-039rev). Washington, DC: Department of Education, March 2016 (<https://nces.ed.gov/pubs2016/2016039rev.pdf>).
72. Pasquale F. The black box society: the secret algorithms that control money and information. Cambridge, MA: Harvard University Press, 2015.
73. Consumer Reports. Guide to digital security & privacy. 2019 (<https://www.consumerreports.org/digital-security/online-security-and-privacy-guide/>).
74. Hill D. Project HealthDesign: rethinking the power and potential of personal health records. Princeton, NJ: Robert Wood Johnson Foundation, 2015 (<https://www.rwjf.org/en/library/research/2010/10/project-healthdesign--rethinking-the-power-and-potential-of-pers.html>).
75. Toscos T, Drouin M, Pater J, Flanagan M, Pfafman R, Mirro MJ. Selection biases in technology-based intervention research: patients' technology use relates to both demographic and health-related inequities. *J Am Med Inform Assoc* 2019 June 7 (Epub ahead of print).
76. Kumar S, Nilsen WJ, Abernethy A, et al. Mobile health technology evaluation: the mHealth evidence workshop. *Am J Prev Med* 2013;45:228-36.
77. Zhang X, Hailu B, Tabor DC, et al. Role of health information technology in

addressing health disparities: patient, clinician, and system perspectives. *Med Care* 2019;57:Suppl 2:S115-S120.

78. Sheon AR, Van Winkle B, Solad Y, Atreja A. An algorithm for digital medicine testing: a NODE.Health perspective intended to help emerging technology companies and healthcare systems navigate the trial and testing period prior to

full-scale adoption. *Digit Biomark* 2018;2:139-54.

79. Makhni S, Atreja A, Sheon A, Van Winkle B, Sharp J, Carpenter N. The broken health information technology innovation pipeline: a perspective from the NODE health consortium. *Digit Biomark* 2017;1:64-72 (<https://www.karger.com/Article/FullText/479017>).

80. Pauwels E, Denton SW. Searching for privacy in the Internet of Bodies. *Wilson Quarterly*. Spring 2018 (<https://www.wilsonquarterly.com/quarterly/living-with-artificial-intelligence/searching-for-privacy-in-the-internet-of-bodies/>).

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