10TH ANNIVERSARY SERIES

A decade of digital medicine innovation

Eric J. Topol

The field of digital medicine has matured over the past decade, but validation will require careful randomized, controlled clinical trials.

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Digital medicine is a new field that got its start around 2007, the time when smartphones were introduced. The connectivity of mobile devices with the internet ushered in technology platforms like telemedicine and wearable sensors, endowing hand-held devices with the ability to acquire images and perform lab assays. This introduced a new path for generating health and medical data—by the individual, in real time, in a real-world environment. Although these features are alluring, the benefits of digital medicine have to be proven through rigorous research, especially validation through randomized, controlled clinical trials. This Focus article, the sixth in a special series celebrating the 10th anniversary of *Science Translational Medicine*, discusses successes and challenges of digital medical devices over the past decade (*1*) and strategies for enabling this key technology to transform medicine.

WEARABLE SENSORS AND SMARTPHONES

Sensors available during the early days of digital health mainly tracked physical activity, namely, step counting. Since then, there has been a proliferation of biosensors, most of which are wearable, that track nearly every physiological system of the human body. The field has progressed rapidly with regulatory clearance or approval by the U.S. Food and Drug Administration (FDA) for continuous heart rate and rhythm detection (the Apple Series 4 Smartwatch), a six-lead electrocardiogram (AliveCor), continuous glucose tracking without fingerstick calibration and with factory calibration (Dexcom G6 and Abbott Libre sensors), oximetry to detect sleep apnea, and smartwatches that measure blood pressure (Omron HeartGuide smartwatch), to name a few. These approvals are an outgrowth of the FDA Digital Health Action Plan, which has the goal of "ensuring all Americans have timely access to high-quality, safe and effective digital health products." Sensors are also digitizing our environment, or human exposome, collecting such metrics as air quality or radiation (*2*).

Besides sensor development and increased interest in telemedicine, the ability to perform imaging using a smartphone is expanding. Smartphone-embedded cameras have remarkable resolution for capturing photos of skin lesions, which are one of the most common conditions for which a person visits a primary-care doctor. Smartphone ultrasound has afforded the ability to go well beyond the skin, imaging every part of the body (except the brain) with quality comparable to that of the expensive imaging machines used in hospitals (*3*). To illustrate this capability, I present a medical selfie (Fig. 1) that I performed using my smartphone connected to an ultrasound probe, one of five currently approved by the FDA. The frontier of smartphone lab assays, with or without wearable sensors [recently reviewed in (*4*)], is also moving forward with the ability to determine transcutaneous hemoglobin concentrations, electrolytes via sweat, nitrite via breath (for asthma), sperm counts for male infertility, quantification of nucleic acids, point-of-care pathogen detection, and sepsis management, among others.

VALIDATING DIGITAL MEDICINE IN RANDOMIZED CONTROLLED TRIALS

These new technologies have enabled site-less, digital clinical trials where suitable participants are identified, consented, and enrolled remotely; wearable sensors are sent by mail, and the data they collect are returned wirelessly without the trial participants and doctors ever having to physically meet (*5*,*6*). By avoiding the classical clinical trial model that requires clinic facilities and intensive human resource support, clinical trial digitization has the ability to revolutionize the way many clinical trials can be performed, with greater efficiency and speed and with less inconvenience for participants.

Several randomized clinical trials and one large population observational study using digital interventions have demonstrated favorable outcomes among diverse and common conditions, such as asthma, heart failure, diabetes, and cancer (*7*, *8*). For example, in a study in Louisville, Kentucky, the use of inhalers that transmit data wirelessly led to a 48% reduction in asthma attacks and a 78% reduction in the need for rescue inhaler use (*7*). In the Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial, there was a 20% reduction in the percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death (*8*). However, these trials were preceded by many small negative studies that left some disillusioned about the role of digital interventions in medicine. In the Medication Adherence Improvement Support App For Engagement—Blood Pressure (MedISAFE-BP) trial, Morawski *et al.* (*9*) found that the use of a smartphone app improved self-reported medication adherence among patients with poorly controlled hypertension; however, app use did not result in lower blood pressure. The expectation for immediate success using digital interventions did not take into account the warm-up phase required to amass experience, plan, execute, and publish clinical trials. There are multiple ways in which digital interventions may prove useful for addressing health conditions. For example, a mobile health system used to screen Kenyan schoolchildren for visual impairment improved follow-up attendance at hospital appointments (*10*), a finding of particular importance for public health. The use of large, randomized, controlled trials will remain the gold standard for validating the benefit of digital medical interventions.

GENOMICS AND MULTIMODAL DATA

Genomics is a useful tool to help understand the medical "essence" of human beings, and at some point, there will likely be general

Scripps Translational Science Institute, La Jolla, CA 92037, USA. Email: etopol@scripps.edu

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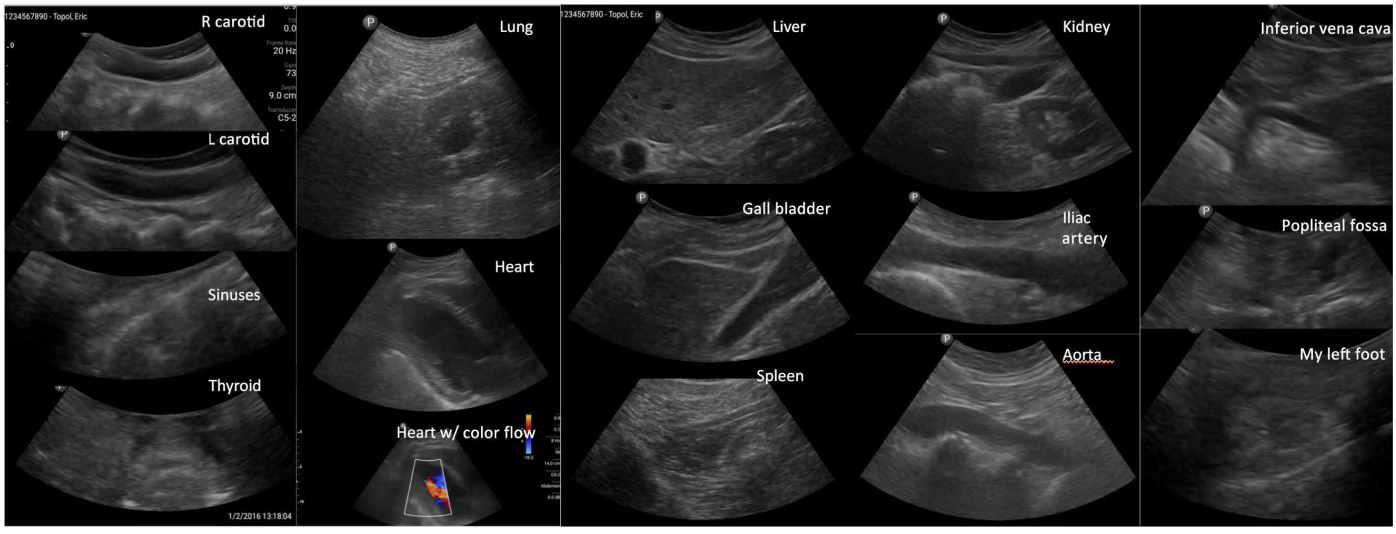

Fig. 1. Medical selfie. Shown is a medical selfie of the author's tissues taken using a smartphone connected to an ultrasound probe. The quality of the images is equivalent to those taken with a hospital ultrasound machine.

acceptance that genomics is integral to digital medicine. A, C, T, and G nucleotides can be considered an extension of the binary 0 and 1 digital code. With millions of people having had high-throughput genotyping, and exome or whole genome sequencing, we are now in a position to provide polygenic risk scores for many common conditions, including heart disease, breast cancer, prostate cancer, colon cancer, inflammatory bowel disease, type 2 diabetes, atrial fibrillation, and more. Individuals in the top decile for a polygenic risk score typically have a high risk that is comparable to that for rare monogenic diseases. Knowledge of heightened risk can be used to implement established preventative strategies, such as lifestyle changes, medications, or screening. With this increased accessibility to genome sequencing data comes the necessity to adequately educate and inform individuals of the implications of their personal risk scores.

To date, most efforts in digital medicine have been pursued in one dimension—one sensor, one type of image, or solely genomics—with little convergence. This approach captures a very narrow, constrained view of a person and, in general, is grossly insufficient. For example, in June 2000 when the human genome draft was first announced, it was naïve to expect that having a map of the genome alone would transform the future of medicine. Rather, multimodal data are needed to understand the uniqueness of human beings and to personalize medicine. This requires an aggregation of anatomical, physiological, biological, environmental, and demographic data, where the biological layers include DNA, RNA, protein, and the microbiome, metabolome, immunome, and epigenome.

Just as the genomics field embraced bioinformatics strategies to address the large datasets generated by sequencing, digital medicine will need to incorporate advanced computational analytics, specifically the use of machine and deep learning artificial intelligence tools, to parse the overwhelming amount of multimodal data that will be generated. For example, continuous glucose sensors for individuals with diabetes can alert a person if their glucose is trending up or down. But, we need a smart algorithm that integrates the person's physical activity, stress, sleep, food and beverage intake, gut microbiome, and possibly other relevant layers of data. For an individual with diabetes, deep learning algorithms can enable greater understanding of the drivers of their glucose regulation and management of their condition. A smart algorithm has potential to be useful for prevention in people with a high risk of developing type 2 diabetes. As voice assistants have become popular recently, it would not be surprising to witness the emergence of the voice medical coach, delivering health-related feedback to the person via the voice assistant platform. Although such coaches will likely be initiated for specific conditions, over time a virtual medical coach, with deep learning of all of a person's relevant data, has the potential to promote the general health of individuals.

WHERE ARE WE HEADED?

The next phase of digital medicine will greatly impact clinicians across disciplines. Much has been written about anticipated impact for radiologists and pathologists, whose primary role is interpreting images that can be improved—both in accuracy and in speed—by deep learning algorithms. However, every discipline in medicine stands to benefit. Digital medicine can incorporate natural language processing of voice during clinic visits to eliminate tedious keyboard use, or use machine vision in the hospital to improve patient safety by monitoring patients to prevent falls or to avoid removal of endotracheal tubes by patients in the intensive care unit. Many of the back-office functions of health systems, such as coding charts, billing, and administrative functions, will likely be supplanted by machines. Overall, there is potential for a marked enhancement of efficiency and productivity. Digital medicine will continue to increase accessibility to personalized medicine, placing tools to monitor personal health in the hands of the individual.

The next decade of digital medicine will need to confront the challenges of processing massive, multimodal datasets. It will also need to fully address potential liabilities in order for the best interests of patients to be advanced. Many serious concerns loom, including algorithmic bias, black box issues defying explainability and transparency, worsening of health inequities, and compromise of privacy and security. Just like any new drug or device, the implementation of digital medical technologies will require rigorous validation with randomized, controlled clinical trials. Digital medicine has considerable promise for improving the accuracy and efficiency of medical practice

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and for fostering a greater degree of empowerment for patients.

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Competing interests: E.J.T. holds editorial board positions for multiple medical publications and is editor-in-chief of Medscape (WebMD). He is on the Dexcom board of directors and serves as an adviser to Illumina, Walgreens, Blue Cross Blue Shield, MyoKardia, Tempus Labs, Trice Imaging, Whole Biome, and HÙYÀ Bioscience. He was a founding board member of the Gary and Mary West Wireless Health Institute and cofounded Molecular Stethoscope.

10.1126/scitranslmed.aaw7610

Citation: E. J. Topol, A decade of digital medicine innovation. *Sci. Transl. Med.* **11**, eaaw7610 (2019).

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Sci Transl Med **11**, eaaw7610.
DOI: 10.1126/scitranslmed.aaw7610

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