COMMENTARY

Digital medicine's march on chronic disease

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Digital medicine offers the possibility of continuous monitoring, behavior modification and personalized interventions at low cost, potentially easing the burden of chronic disease in cost-constrained healthcare systems.

Chronic disease affects approximately half of all adult Americans, accounting for at least seven of the ten leading causes of death and 86% of all healthcare spending. The US healthcare system is ill-equipped to handle our epidemic of chronic disease. This is because most chronic disorders develop outside healthcare settings, and patients with these conditions require continuous intervention to make the behavioral and lifestyle changes needed to effectively manage disease. Digital medicine, which enables broad scaling of frequent, high-touch, personalized, behavioral interventions at low cost, may thus become an essential component in preventing and managing chronic disorders. Here, we summarize some key research advances, define the marketplace and describe the opportunity for digital medicine in chronic disease.

The mismatch of health system and disease burden

The history of medical progress in the twentieth century was dominated by advancements in the treatment of acute conditions. These developments—which included better medical sanitation, antibiotics, vaccines and surgeries—successfully addressed leading causes of morbidity and mortality of the time (**Table 1**)[1]. In contrast, the most pressing issues facing healthcare in the twenty-first century are chronic diseases (e.g., respiratory disorders, heart disease and diabetes), and many are preventable (e.g., through smoking cessation and diet; **Table 1**; **Fig. 1**)[2]. The increase in the prevalence of chronic disease is the primary contributor to skyrocketing healthcare costs (**Table 2**), which have been such a focal point of discussion in recent months.

An unintended consequence of our twentieth-century success is that our modern healthcare system was born, developed and structured with acute diseases in mind. Our healthcare system is therefore ill-equipped to prevent, manage and contain costs for chronic disease. Why? Acute care is by definition episodic, its solutions are general rather than personalized for each patient, and its interventions happen within healthcare settings. Prevention and management of chronic disease do not fit well into this paradigm. Effective solutions for chronic disease, which often have behavioral components, require frequent, personalized interventions that affect patient actions outside healthcare settings. A 15-minute visit with a physician every few months, general recommendations to lose weight and exercise, and a lifetime of post-diagnosis pharmacologic treatment are not enough to solve our epidemic of chronic disease.

The mismatch between what our current healthcare system can deliver and what it needs to deliver is now of extreme proportions. Today, at least seven of the ten leading causes of death are chronic disease (**Table 2**), and patients with chronic disease account for half of all Americans (117 million people) as well as 86% of healthcare costs[3–5]. The United States has the highest disease burden of any developed country[6]. Trends in the above data are expected to worsen in the near future. The growth in chronic disease prevalence means that, despite increases in average life span, we may be experiencing a decrease in average health span (the period of a person's life spent in generally good health)[7].

Why are we continuing to lose ground on chronic disease? Simply put, the bulk of chronic disease development and management occurs beyond the reach of the healthcare system. Patients need intervention before developing disease, and those with chronic disease need ongoing and consistent support from multiple layers of providers to bring about behavior change. Continuous intervention—in-person provider visits, telemedicine, phone calls, e-mails, texts and apps—has the potential to improve prevention and management efforts.

Continuous intervention has historically been impossible because of financial considerations. Fee-for-service reimbursement, a model suited to acute care, has historically rewarded actions over outcomes, and implicitly encourages volume over value. In-person interventions have received reimbursement preference over digital ones. Reimbursement for preventative care has been spotty. The onus of preventing and managing chronic disease has largely fallen on the patient. And, historically, almost no one has been incentivized to control costs.

It's therefore unlikely that chronic disease will be prevented or effectively managed in twentieth-century fashion with a pill, an injection or surgery. We already know that the most effective and cost-effective strategies for chronic disease are the behaviors that

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Table 1 Leading causes of mortality in 1900 and 2013

1900				2013			
Disease	Chronic or acute	Annual deaths	Percent of total deaths	Disease	Chronic or acute	Annual deaths	Percent of total deaths
Influenza and pneumonia	Acute	40,362	12	Heart disease	Chronic	611,105	24
Tuberculosis	Acute	38,820	11	Cancer	Chronic	584,881	23
Diarrhea and enteritis	Acute	28,491	8	Chronic lower respiratory diseases (COPD)	Chronic	149,205	6
Heart disease	Acute/chronic	27,427	8	Accidents (unintentional injuries)	Acute	130,557	5
Stroke (cerebrovascular diseases)	Chronic	21,353	6	Stroke (cerebrovascular diseases)	Chronic	128,978	5
Nephritis, nephrotic syndrome and nephrosis	Acute/chronic	17,699	5	Alzheimer's disease	Chronic	84,767	3
Accidents (unintentional injuries)	Acute	14,429	4	Diabetes	Chronic	75,578	3
Cancer	Acute/chronic	12,769	4	Influenza and Pneumonia	Acute	56,979	2
Senility[a]	Acute/chronic	10,015	3	Nephritis, nephrotic syndrome and nephrosis	Chronic	47,112	2
Diphtheria	Acute	8,056	2	Intentional self-harm (suicide)	Acute/chronic[b]	41,149	2
All other causes	Acute/chronic	123,796	36	All other causes	Acute/chronic	686,682	26

[a]The disease names used in 1900 records are not the same as those used in 2013. In 1900 records, 'senility' likely referred to Alzheimer's disease. [b]>90% of suicides occur in patients with serious mental illnesses, which are chronic conditions; we believe that describing suicide as an acute condition is misleading (it is most often the end result of a long chronic process).

prevent disease development in the first place, such as weight loss, exercise and smoking cessation. For chronic disease management, these same behaviors play a large role as well, as do other behavioral factors like medication adherence. Although these solutions sound simple, they have proven remarkably difficult for our healthcare system to deliver.

The time is now to re-examine the twentieth-century paradigms for healthcare, and to develop treatment and prevention paradigms for the twenty-first century. We can leverage technology to expand the parameters of an effective therapeutic. For diseases with behavioral components, interventions such as coaching, cognitive behavioral therapy and support groups can be very effective. Traditionally, these therapies have been difficult to obtain in our healthcare system, they have been difficult to scale, and it has been a struggle to standardize payments and incentives for such services. Now, with the advent of wearable technology, the Internet of Things (IoT), mobile computing platforms, value-based care and new incentives for patients, employers, payers and healthcare systems, we can envision delivering these behavioral interventions to whole populations in the same way we fluorinate our drinking water and deliver vaccines on a large scale. Patients can now be reached before, during and after chronic disease development, interventions can be delivered continuously, and deployment can occur either inside or outside the healthcare system. This is the promise of digital medicine.

Why now?

A combination of three factors has made the time ripe for the development and implementation of digital therapeutics. The first is the enactment of the Affordable Care Act (ACA), which altered reimbursement and patient incentives. Reimbursement incentives are shifting away from volume and toward value, and many healthcare systems are now financially responsible ('at-risk') for delivering quality outcomes at reduced costs. This trend has accelerated rapidly: 40% of private payments are currently value-based and 50% of Medicare payments are anticipated to be value-based by 2018 (refs. 8,9). To better manage at-risk contracts, healthcare systems are looking for ways to prevent and manage chronic disease. Additionally, the ACA's individual mandate has contributed to the growth in high-deductible health insurance plans, which now comprise nearly one quarter of all commercial plans[10]. Patients thus increasingly demand high-quality, low-cost solutions like digital therapeutics.

The second factor is the growing interest of employers in managing employee healthcare costs. In the twenty-first century, premiums for employer-sponsored healthcare, which covers 147 million people, have increased by 123%, whereas wages have increased by only 43%[9]. From an employer's perspective, healthcare is becoming an increasingly large component of the cost of an employee. Employers are now more willing to play an active role in reducing their employees' healthcare costs, which includes preventative therapies and chronic disease management that digital therapeutics can deliver at low cost.

The third factor is the explosion in technological progress, cell phone and smartphone ownership, and broadband Internet penetration. In the twenty-first century, cellphone ownership has increased to 90% from 53%, smartphone ownership has increased to 68% from 0% and broadband internet penetration in American households has increased to 70% from 3% (refs. 11,12). Software applications that are now commonplace on mobile phones—geolocation tracking, SMS and MMS messaging, mobile internet access, streaming video, smartphone apps and connections to IoT devices—were almost inconceivable at the start of the century. Not only do Americans spend more time accessing devices, but they can provide data to and be engaged by digital therapeutics in ways that were unimaginable in the twentieth century.

Below we review how digital medicine is being applied to several important chronic diseases.

The diabetes epidemic

Diabetes is the seventh leading cause of death in the United States[5]. The disease affects 9.5% of the US population—29.1 million Americans—and >95% of diabetic patients have type 2 diabetes, which is strongly associated with behavioral factors such as a high-calorie diet and physical inactivity[13]. Diabetes costs the healthcare system $245 billion annually, $176 billion of which are in direct medical costs[2]. Medical management of diabetic patients includes behavioral change recommendations for diet, exercise and smoking cessation, oral antidiabetic agents, insulin therapy and prevention of complications associated with diabetes, such as cardiovascular risk factor management[14]. To successfully manage diabetes, patients must adopt a number

of other behaviors that take place outside the healthcare setting, such as frequent blood sugar monitoring, medication adherence and the self-injection of insulin. Unfortunately, only 16% of diabetic patients report fully adhering to these behaviors[15].

Compounding the enormous present burden of diabetes in the United States is the even greater potential for diabetes in the future. Prediabetes, a condition in which patients are at high risk for developing diabetes, affects 32% of Americans (86 million people)[13]. Prediabetes is associated with the same behavioral factors as diabetes, and guidelines for preventing diabetes in prediabetic patients include diet and exercise, smoking cessation, and in some cases, the addition of the oral antidiabetic agent metformin (Glucophage)[16].

Multiple digital medicine companies have developed solutions to address the epidemic of diabetes and prediabetes. Below, we examine in more detail the offerings from Partners Connected Health—a Boston-based institution centered on innovation in healthcare delivery where J.C.K. currently serves as vice president—and companies, such as WellDoc (St. Paul, MN, USA), Omada Health (San Francisco), Glooko (Palo Alto, CA, USA) and Podimetrics (Cambridge, MA, USA).

Text2Move. The Text2Move (TTM) study has been one of the most successful programs at Partners Connected Health. The goal of the study was to understand whether automated, personalized, targeted and motivational text messages could boost activity levels among type 2 diabetics to improve outcomes and reduce healthcare spending. To do this, the company developed a machine-learning algorithm, powered by four patient data streams: self-reported motivation, continuous activity data, rudimentary location data and local weather data. Patient readiness to change was periodically assessed, and personalized messages were automatically delivered to each patient.

TTM proved to be a powerful intervention, producing an average 1% drop in hemoglobin A1c (HbA1c) for engaged patients. These results are comparable to the average effect of oral antidiabetic agents like metformin, thiazolidinediones and sulfonylureas, but with zero possibility of adverse events. In addition to producing a drop in HbA1c, TTM produced a noticeable improvement in physical activity, which has additional health benefits. Developing and deploying TTM cost on the order of a few million dollars, not the billions that are standard for a pharmaceutical product, illustrating the power of digital medicine. The Apple Watch has a built-in reminder system that provides a haptic pulse, urging individuals to stand hourly. This and other hardware and software approaches in development could be synergistic with the TTM approach.

BlueStar. Most diabetics manage their blood glucose levels by checking their insulin levels periodically throughout the day, and then self-administering insulin when necessary. However, only 55% of type 2 diabetics report receiving diabetes education, and following their initial diagnosis, their face-time with physicians is typically limited to 15-minute appointments every few months[15].

WellDoc, which was co-founded by University of Maryland endocrinologist Suzanne Sysko Clough, recognized the classic problem of a chronic condition managed by an acute care–focused healthcare system. Diabetic patients are largely left to manage their complex condition on their own, and many of the most important interventions are performed by the patient in their home.

Instead of following the typical protocol of having patients test their blood sugar at regular intervals during the day, the BlueStar smartphone-based app guides each patient in learning the optimal time to test blood sugar. In this way, it provides patients with a more accurate picture of how blood sugar fluctuates throughout the day in response to environmental stimuli. The BlueStar randomized clinical trial demonstrated a statistically significant 1.2 point increase in HbA1c levels compared with the standard of care[17]. On the strength of these results, as well as a successful equivalence claim to predicate devices, BlueStar obtained US Food and Drug Administration (FDA) clearance. Currently, BlueStar is available by physician prescription only and is distributed through pharmacies.

Prevent. Modeled after the Diabetes Prevention Program (DPP)[18], Omada Health (San Francisco) developed Prevent, a 16-week, online, interactive behavioral intervention program designed to reduce the development of diabetes in prediabetic patients through weight loss and increased physical activity.

Peer-reviewed studies conducted by Omada indicate that, across all prediabetic patients who started the program, the average

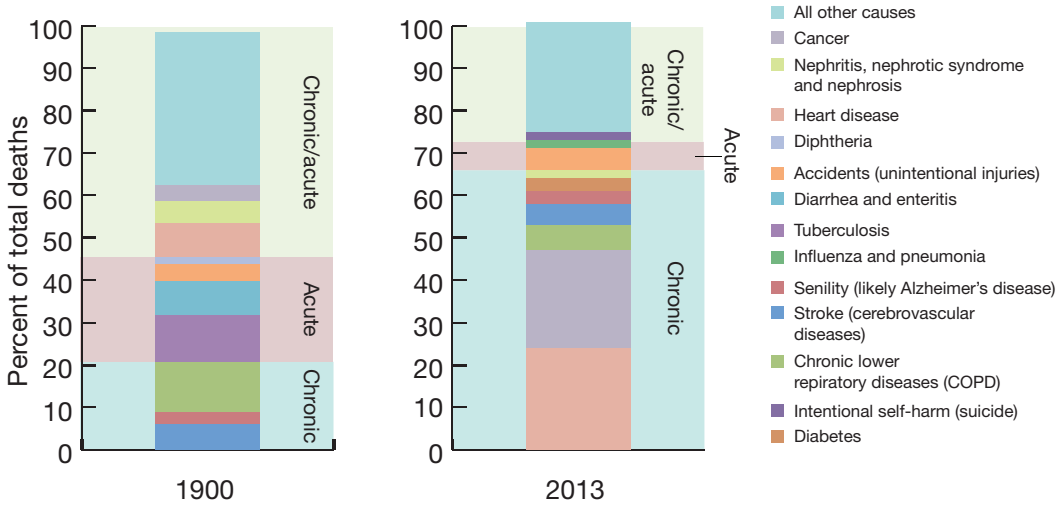

Figure 1 The shift from acute to chronic disease. Leading causes of mortality in 1900 versus 2013 (refs. 1,2). The disease names used in 1900 records are not the same as those used in 2013. For example, in 1900 records, 'senility' likely referred to Alzheimer's disease. In 2013 data, >90% of suicides occur in patients with serious mental illness, which are chronic conditions; we believe that describing suicide as an acute condition is misleading (it is most often the end result of a long chronic process).

participant lost 4.7% and 4.2% of baseline body weight after 1 and 2 years, respectively[19]. Patients also reduced their HbA1c levels by an average of 0.38% and 0.43% after 1 and 2 years, respectively[19]. These results are comparable to the original DPP results, and Omada's programs are now recognized by the Centers for Disease Control (Atlanta)[18,20]. Omada's products are not FDA approved and do not reach patients through the traditional healthcare system. Instead, Omada markets its product to large employers as a means to stimulate employee weight loss, reduce the incidence of chronic disease in the employer's workforce and reduce employee healthcare costs.

Glooko software. Glooko has developed an FDA-cleared software platform that not only can automatically download data from >50 diabetes devices, including insulin pumps, blood glucose meters and wearable devices, but also allows patients to manually download information on diet and other lifestyle factors. Glooko software analyzes trends and provides feedback to optimize treatment. The system can send data to patients through a smartphone app, and data can be automatically shared with providers by a population health management platform. Glooko systems are sold directly to patients and clinics, and can also be distributed by payers and health systems.

RTM System. Podimetrics is developing the RTM System, a solution for early detection of diabetic foot ulcers, which cost the healthcare system $9–13 billion annually[21]. The RTM System is a connected, at-home, temperature-monitoring foot mat that detects local temperature changes in the foot that signal ulcer development. The device can send data to patients and providers, and enables providers to access tools for clinical support and population health management. Podimetrics systems are currently available through payer and provider pilot testing.

Chronic respiratory diseases and smoking cessation

Fourteen percent of the US population suffers from chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD) and asthma. Chronic respiratory diseases cause 150,000 deaths annually, and their economic cost exceeds $105 billion, $80 billion of which is in the form of direct medical care[2,22,23].

Cigarette smoking is a primary contributor to respiratory disorders, such as COPD and asthma. Over all, it is responsible for nearly 500,000 deaths in the United States each year, comprising 20% of all deaths nationwide. It is also a primary contributor to other leading causes of death, including cancer, heart disease, stroke and diabetes. The annual economic costs of smoking are nearly $290 billion, $133 billion of which is in direct medical care[24]. Although efforts to reduce the prevalence of smoking have had success, nearly 18% of the adult population still smokes[2]. However, nearly 70% of smokers report wanting to quit, and >40% of smokers make an attempt to quit each year[24].

Chronic respiratory diseases have behavioral components, both in disease development and in management. Many cases are due to smoking or secondhand smoke, and smoking cessation or avoidance are integral components of treatment plans. Successful management of chronic respiratory diseases also requires behavioral interventions, such as proper inhaler use, medication management, and diet and exercise.

Digital medicine for the epidemic of chronic respiratory disease is now emerging. Below, we describe in detail four companies, Propeller Health (Madison, WI, USA), 2Morrow (Kirkland, WA, USA), LifeMap Solutions (San Jose, CA, USA) and Claritas Mindsciences (Worcester, MA, USA), that have applied digital medicine tools to such disorders.

Propeller. Propeller Health has designed the Propeller system for COPD and asthma patients with the goals of increasing medication adherence, predicting disease exacerbations, and reducing the frequency and severity of symptoms. Propeller's solution combines sensors attached to patients' inhalers, a patient-facing smartphone app, a physician-facing website and data from a network of air-quality sensors, such as those used by the Environmental Protection Agency. Propeller monitors the use of both controller and rescue inhalers, and tracks patient trends over time. By combining these data streams, Propeller aims to provide patients and providers with frequent, personalized feedback on the connections between environmental factors and patient behavioral factors in chronic respiratory disease.

The Propeller system has four FDA clearances, which include FDA-granted claims that its system can be used to increase medication adherence, predict exacerbations, and reduce the frequency of symptoms and exacerbations in asthma and COPD. It has been cleared for use with GlaxoSmithKline's (London) Diskus dry powder inhaler, Boehringer Ingelheim's (Ingelheim, Germany) Respimat and other medications using pressurized metered-dose inhalers. Although Propeller Health has yet to publish results on efficacy and cost in peer-reviewed medical journals, the company has indicated that it is conducting randomized trials.

To date, the Propeller system has been deployed with commercial partners, which include payers, employers and healthcare systems. Additionally, Propeller has developed a public-private partnership with the city of Louisville, Kentucky, which has a high prevalence of chronic respiratory diseases.

SmartQuit. 2Morrow developed and clinically validated the SmartQuit smartphone app for smoking cessation. To date, of the >400 smoking cessation apps, SmartQuit is the only app-based smoking cessation therapy that has demonstrated effectiveness in randomized clinical trials.

The company provides an eight-day pre-quit program followed by 6 months of automated support, which includes video tutorials and in-app rewards, such as badges. Patients track their progress and receive automated feedback, with encouragement and reminders. Patients can also customize their program to be used in conjunction with nicotine replacement therapy.

SmartQuit is based on the Acceptance and Commitment Theory of behavior change, which has been shown to outperform other smoking cessation approaches, such as cognitive behavioral therapy and the US Clinical Practice Guidelines, across multiple digital and in-person platforms[25]. The app has been found to be two to three times more effective than unaided smoking cessation, with pilot trials demonstrating a 13% overall quit rate and a 15% quit rate in some subgroups[25]. It also increased quit rates by 62–88% compared with the National Cancer Institute's QuitGuide smartphone app[25].

A lite version of the SmartQuit app is freely available on iOS and Android devices, and the full version is available through employers, health insurance plans, some state-level departments of public health or through an in-app purchase.

COPD Navigator and Asthma Health. LifeMap Solutions has developed smartphone apps for COPD and asthma management that combine patient data, care guidelines and behavioral science techniques in an effort to improve outcomes and reduce cost. The goals of the apps are to log patient symptoms and events, provide medication reminders and identify patterns in environmental factors and patient behaviors that correspond with exacerbations. LifeMap apps are freely available to patients, and can be obtained through partnerships with employers, payers and healthcare systems.

CravingToQuit. Claritas MindSciences developed CravingToQuit, a digital smoking

Table 2 Selected chronic diseases and their digital medicines[2–5,14,22,23,25,28–31,35,36,45,46]

Disease	Prevalence (%)	Annual deaths	Total cost (direct, indirect; $ billions)	Digital medicine product
Obesity	34.9	300,000	147 (142.1, 4.9)	Omada, Noom, Rise, Canary Health, Lantern, RecoveryRecord, EcoFusion, MedTep, Zipongo
Prediabetes	32.0	NA	NA (44, NA)	Omada, Noom, Canary Health, Blue Mesa Health, Personal Medicine Plus
Hypertension	26.7	61,762	118.6 (91.4, 27.2)	Omada, Noom, Personal Medicine Plus, Withings
Hyperlipidemia	21.9	NA	38.5 (NA,NA)	Omada, Noom
Smoking-related diseases	17.8	480,000	300 (170, 156)	SmartQuit, QuitGuide, Chrono Therapeutics, Click Therapeutics, Quit Genius, Claritas MindSciences
Chronic pain (includes arthritis)	15.0[a]	NA	592 (280.5, 311.5)[b]	Jojnts, Reflexion Health, Canary Health, RespondWell
COPD and asthma	13.7	149,205	105.9 (79.5, 26.4)	Propeller Health, LifeMap, MedTep
Diabetes	9.5	75,578	245 (176, 69)	Omada, Noom, Canary Health, EcoFusion, Podimetrics, WellDoc, Glooko, Dexcom
Alcoholism	7.0	88,000	223.5 (24.6, 198.9)	Pear Therapeutics, The Alcohol Tracker, A-CHESS
Coronary artery disease	5.3	NA	129.6 (46.8, 82.8)	EcoFusion, MedTep
Serious mental illness	4.2	41,149[c]	317.6 (100.1, 217.5)	Ginger.io, Lantern, Recovery Record, MedTep

Digital medicine matched with diseases only if specifically mentioned by the product or company. NA, not available. [a]Median of range estimates. [b]Mean of range estimate. [c]The vast majority of suicide deaths are due to serious mental illness

cessation program delivered through a smartphone app in conjunction with an online community and video support groups. CravingToQuit is a digitally delivered version of the Mindfulness Training approach, an in-person version of which was found by one study to be more than twice as effective for smoking cessation as another leading smoking cessation approach[26]. The program is delivered over the course of three weeks, and can be purchased either directly by patients or through employers.

Chronic neurological and psychiatric conditions

Chronic neurological and psychiatric conditions represent some of the most challenging and costly problems facing the healthcare system today. Alzheimer's disease affects 5.3 million people in the United States alone and is responsible for nearly 85,000 deaths each year[5,27]. Chronic pediatric neurological conditions include attention deficit hyperactivity disorder (ADHD), which has been diagnosed in up to 11% of US children aged 4–17 and autism spectrum disorder, which is estimated to affect up to 1.5% of children in the United States[28,29]. Furthermore, ~800,000 individuals in the United States will suffer from stroke each year[30]. Current treatment options, including medications, often have limited efficacy and/or problematic adverse events. Other current alternatives include interventions that are more costly and time-intensive interactions with a therapist (e.g., applied behavioral analysis for autism).

Apple's (Cupertino, CA, USA) Research Kit set of apps for the iPhone is already being tested as a tool for gathering information and monitoring patients with chronic conditions, one of which is the mPower app for Parkinson's disease. But in terms of clinical practice, it seems likely that digital medicine tools will have their most immediate benefits in psychiatric conditions, where social stigma or lack of access to skilled therapists represent barriers to patient care. Below, we describe two companies, Jintronix (Seattle) and Akili Interactive Labs (Boston), that are applying digital medicine approaches to chronic neurological disease, and MoodGYM, which is a program developed in Australia.

Jintronix. Requiring a computer fitted with Microsoft Kinect for Windows, the Jintronix package provides physical and occupational therapy at home for patients undergoing rehabilitation for stroke and other conditions. The system uses motion tracking and visual feedback to reinforce physical rehabilitation exercises, which are presented in the forms of games designed to be enjoyable. This is the first time that Microsoft's Kinect, which was originally designed purely as an entertainment games platform, used a product that received FDA clearance for a healthcare-related use. Injecting a gaming component to make the exercise enjoyable engenders compliance, which is particularly important for an at-home therapy.

Cognitive Engine and Project EVO. Akili Interactive Labs is developing therapeutic and cognitive monitoring tools delivered through a mobile action video game-like interface for several chronic disorders where cognition is negatively affected. The company's goal is to get FDA clearance for its therapeutic products after completion of the required pivotal clinical studies. The company's main product, Project EVO, is based on measuring and improving a new functional neurological target for intervention: cognitive interference (efficiently managing two or more information streams real-time). In addition to evidence that measuring a patient's cognitive interference susceptibility has the potential to provide a sensitive biomarker of neurological function, there is clinical evidence that directly improving the ability to process cognitive interference results in more general improvement in cognitive domains, which has been demonstrated in elderly subjects in a sham-controlled study[31]. In a pilot study, Akili showed that Project EVO improved attention and other aspects of cognition (e.g., working memory) in children with ADHD, as measured by objective tests[32]. The company plans on carrying out a pivotal study for pediatric ADHD in 2016 and currently has clinical trials in several chronic neurological and psychiatric illnesses, including autism, Alzheimer's disease and depression.

MoodGYM. A software program developed by Australian National University (Canberra, Australia), MoodGym is one example of digitally delivered cognitive behavioral therapy (CBT) programs. CBT is a mainstay of psychiatry and has been used to treat depression, anxiety and other conditions. The technique involves changing a patient's thought processes and behaviors, and has historically been delivered in person by a skilled psychologist. The techniques used in CBT can be delivered digitally and a meta-study has suggested that Internet-delivered CBT may be as effective as in-person therapy[33]. A challenge that online CBT faces is compliance and motivating the patient to engage with the exercise, particularly given that lack of motivation is often a characteristic of depression. Including a degree of human contact and

encouragement of the user could increase compliance.

Chronic cardiovascular conditions

Cardiovascular disease is one of the leading causes of death in the United States, and is often associated with other chronic diseases (e.g., obesity). The sequelae of cardiovascular disease can include debilitating events, such as stroke, that then lead to other chronic problems. Being able to monitor a patient on a frequent or continuous basis to alert him or her of a change in a key physiological parameter (e.g., blood pressure or heart rate) could help prevent an acute cardiovascular event. Recording a patient's data over time with a granular data set will also allow a physician to understand if a treatment intervention is effective. As artificial intelligence approaches become more sophisticated, it could be possible to start to automate sifting through the data to make a conclusion, which will be key to making the data actionable from the viewpoint of a physician who only has a short amount of time to spend with a patient. Several different sensors are available for measuring physiology, and a subset are useful for heart-rate monitoring.

Below, focusing on medical applications, we discuss three examples of companies producing digital tools for blood pressure and heart monitoring. What the companies have in common is the use of a physical device in conjunction with an app.

AliveCor Mobile ECG. AliveCor (San Francisco) is marketing a mobile electrocardiography (ECG) device that works with an app. The company's product has received clearance from the FDA. The app has the ability to detect atrial fibrillation, which can significantly increase the risk of stroke. To help physicians better examine the data obtained from the recordings, the company has established a provider dashboard, which a physician can access online. AliveCor has also started to try to integrate patient data into electronic health records (e.g., for Practice Fusion).

Wireless blood pressure monitor. Withings (Cambridge, MA, USA) is focused on making digital products for physiological monitoring. The company developed and obtained FDA clearance for a wireless blood pressure cuff used in conjunction with an app to display blood pressure data. Historic readings are saved and can be stored in the cloud, allowing either the patient or physician to note changes from previous readings.

Similar to Withings, iHealth Lab (Mountain View, CA, USA) sells a number of wireless products to measure physiology. The company has produced a blood pressure monitor that is placed on the wrist as well as one that is placed on the arm. In both cases, the data are sent to an app and displayed using an app on a mobile device such as a phone. The data can also be stored so that a patient can later share it with a physician. Both blood pressure monitoring devices have received FDA clearance.

No-burden monitoring

One intriguing direction of monitoring for cardiovascular and other chronic conditions is 'no-burden' monitoring that is used passively by smartphone or other devices. An ideal no-burden application is compatible with devices a patient already owns and uses regularly, and once downloaded, is ready to function without any further action by the patient. Although putting on a wearable or opening an app every day requires minimal effort, even a small amount of required effort can be burdensome enough that many patients use them less consistently over time or discontinue their use altogether. Furthermore, sensor diversity, data quality, data format, device cost and limited durability of wearable devices each represent substantial obstacles to large-scale adoption and routine use of meaningful longitudinal health monitoring.

There are some early examples of no-burden monitoring approaches including some academic work around an app that is downloaded to a phone and could potentially accurately measure heart rate passively without the need for a separate device. Another example, Sonde Health (Boston) is a digital medicine company developing technology for computational analysis of nonlinguistic features in voice and other sounds that are correlated with subtle changes in neurological and physiological function. Sonde's technology enables longitudinal monitoring of mental, emotional and physical health conditions in the background on devices that most people already own and use every day, and without requiring that the content of their speech be stored or analyzed. This approach has potential advantages of being both no-burden and privacy preserving. No-burden approaches could be crucial when longer-term compliance for meaningful longitudinal monitoring is required in patients with difficult care regimens. A clear example is the case in lifelong chronic conditions, such as heart disease, where objective early indications of new complications have the potential to allow earlier and less costly interventions.

Medication adherence and compliance

Medication adherence and compliance—a patient's following of providers' recommendations for medication taking, which includes prescription fulfillment, dosage, timing, duration and other relevant factors—are of major concern in chronic disease, as 83% of all prescriptions are filled by patients with chronic conditions, and the average patient with one or more chronic diseases fills >20 prescriptions per year[7]. Multiple studies have demonstrated that 50% of medications prescribed for chronic disease are not taken as directed, and between 20% and 30% of all prescriptions are never filled[34]. Annually, medication nonadherence is responsible for 125,000 deaths, 10% of all hospitalizations and $100–289 billion in healthcare costs[34–36].

Nondigital approaches to increase medication adherence are generally resource intensive or ineffective. The most reliable method is directly observed therapy, in which healthcare providers watch patients take each dose of medication. The method is time and resource intensive, and virtually impossible to scale up to address the epidemic of chronic disease. Indirect methods include patient surveys, monitoring of patient pill diaries, pill counts and monitoring prescription refill rates. Historically, indirect methods have been reactive, and they do not proactively attempt to increase adherence.

Now, digital medicines are working to increase adherence and compliance in chronic disease. Below, we discuss in more detail the offerings from Proteus Health (Redwood City, CA, USA), MediSafe (Boston), Mango Health (San Francisco) and Memotext (Bethesda, MD, USA).

Proteus Discover. Proteus Digital Health is working to address medication adherence through a system that can determine whether patients have ingested medications. The Proteus system consists of an Ingestible Event Marker, which is a digital sensor embedded in a pill, and the Proteus Personal Monitor, which is an externally worn adhesive monitor. The Proteus Discover system can report when medication is taken, how medication is taken and information related to activities of daily living such as steps, heart rate and resting time. Data are sent to patients through a smartphone app and can also be shared with providers and researchers with patient consent. Studies have indicated that the Proteus system is an efficacious and cost-effective alternative to directly observed therapy[37,38].

The Proteus system has received FDA clearance, and is currently the only cleared device with a claim for general medication adherence. Proteus is also 'CE-marked' for use in Europe. The company recently announced a new FDA application for integration of the

Proteus system with Otsuka Pharmaceutical's (Chiyoda-Ku, Japan) Abilify (aripiprazole) for the measurement of compliance and physiologic response in serious mental illness.

MediSafe. MediSafe has developed a cloud-synced smartphone app to improve medication adherence. The app allows patients to manually enter medication schedules, medication doses, measurements, provider appointments, diary entries and a social support network. MediSafe sends patients reminders of their schedules, and allows patients to send medication alerts and summaries to providers and designated members of their social support network. The app creates a 'virtual pillbox' for patients that includes images of the size and shape of pills. MediSafe also provides multimedia content relevant to patient disease management and education. The app is freely available to patients on iOS and Android platforms, and MediSafe creates customized versions of the app for corporate partners, such as healthcare systems, payers, employers and pharmacies.

Although MediSafe has yet to publish findings in peer-reviewed medical journals, it does present results of internally conducted research on its website. The company reports that its 2.5 million users are 86% adherent to prescribed medications, a substantial improvement over the 50% national adherence rate (http://bit.ly/1om8W35). Compared with control groups, MediSafe patients with hyperlipidemia, hypertension and diabetes achieve statistically significant increases in medication adherence of 10.7%, 5.4% and 7.7%, respectively.

Mango Health. Mango Health has developed a 'gamified' smartphone app for medication adherence. The app combines medication adherence-promoting features, such as schedules, reminders, information and alerts, with features of video games that encourage adherence and healthy behaviors. Patients who adhere to their medication regimen and lifestyle goals earn badges and points, which can then be redeemed for gift cards or charitable donations. The Mango Health app is available for free to patients, and is also available through payers and employers.

Memotext. Memotext has built a digital communication platform to increase medication adherence. The platform uses a combination of interventions, including text messages, pre-recorded phone calls, e-mails, and app-based and web-based reminders to encourage medication adherence. One study found that the Memotext system resulted in a statistically significant increase in adherence of 31% (ref. 39). The Memotext system can integrate data from electronic medical records, patient wearables and monitors, and payer claims data. Memotext is available through pilot programs, employers and payers, and is used in conjunction with pharmaceutical companies.

Initial success, but challenges remain

Despite initial success in multiple digital medicine approaches to chronic disease, challenges remain in the areas of patient engagement, regulation and privacy.

Patient engagement and motivating patients to use the digital medicine products can be a challenge. One obstacle is that older patients and underserved patients—those with the highest rates of chronic disease—are the least technologically savvy members of the population, and therefore the least likely to be able to use digital medicine products. This is why a new breed of 'no-burden' approaches may be beneficial.

Given that 60% of patients with chronic disease have more than one chronic disease[7], another issue is that digital medicine solutions are not available across the board for all chronic conditions; this may complicate the development of strategies for driving patient engagement. What's more, although most chronic diseases have a behavioral component, there may be limits to how much behavior can change, and how many behaviors can change at once. Can we use digital medicines to get patients to stop smoking, lose weight and better monitor their blood glucose, all at the same time? Also, most clinical validation and deployment of digital medicines designed to affect chronic disease is done with self-selected, volunteer patients. It remains to be seen how well digital medicines work in patients who have some resistance to using them. Finally, it remains to be seen whether the use of digital medicines can be sustained over long periods. Digital medicine products have at most a few years' track record, and details about total patient retention and long-term outcomes are sparse.

Regulation is also an issue that will need to be addressed, as discussed previously in this series[40]. Because apps that make claims about the diagnosis or treatment of the disease are subject to FDA enforcement discretion, apps aimed at chronic disease that don't make direct disease claims (e.g., greater medication compliance) may find that they are not subject to FDA regulation. Depending on the exact claim that is being made (e.g., 'aids in weight loss' verses 'treats obesity'), developers of digital medicine interventions can choose whether or not to be subject to FDA regulation. Those interventions that do not go through the FDA approval process will still be subject to regulation by the Federal Trade Commission (FTC) whose goal is to protect consumers from unfair and deceitful practices. Recently, the FTC reprimanded and levied a large fine against one company for making unsubstantiated claims regarding the ability of its main product to improve cognition and fend off age-related cognitive decline[41]. Likewise, the FTC reprimanded another company for making unsubstantiated claims for improving cognition, including in ADHD[42]. However, given the enormous number of health-related apps available, the FTC will not be able to police all of them. For those digital interventions aimed at chronic disease that do not seek FDA approval, there will be a question of how to judge the quality of the intervention, especially for consumers who are not familiar with science.

Privacy and security are also a major concern for digital medicine interventions particularly for those that affect behavior change through intensive monitoring of personal data, such as location data, movement data and purchase data. Large amounts of aggregated health data could be valuable to third parties, which could incentivize digital medicine companies to sell the data to third parties. Individuals may simply push 'accept conditions' when downloading an app that includes a provision for use of the patients' data, but few people will read the details of the agreement or realize how their data are being used. Digital interventions may be subject to the Health Information Portability and Accountability Act (HIPAA) and interventions may need to build in safeguards to be HIPAA compliant. Hacking of financial institutions that have built highly secure systems shows the complexity of guarding against the release of sensitive information. If a series of high-profile hacking incidents were to occur in the digital health space, it could fundamentally undermine trust in the system. That said, the value of an individual's health data to a hacker is much less clear than that of their bank account details, which is probably why there have been fewer large-scale hacking incidents in healthcare (even so, over 100 million patient health records were stolen in the first six months of 2015 alone[43]).

On the surface, digital medicine for chronic disease seems low risk, particularly compared to traditional drug therapy. However, there are differences in the safety risk posed by different digital medicine applications. A game to treat a cognitive disorder or to gamify taking medication to increase compliance is relatively low risk. On the other hand, apps that are involved in monitoring physiological function or whose output can result in a patient or physician taking life-saving action are much higher risk.

For instance, an app directly tied to a heart monitor that malfunctions could have devastating sequelae. Another example is an app that purports to determine if a skin growth is potentially malignant, which could cause a patient to delay critical treatment in the case of a false negative. In fact, the FTC has reprimanded a company for making false claims about the ability of its app to detect melanoma[44].

Although attitudes by payers and employers are changing in ways that will help drive the adoption of digital medicine in chronic disease, gaining reimbursement will remain an issue particularly for those areas where there is no immediate financial incentive (e.g., stroke recovery). Digital medicines are a new category of products, and may not be easily classifiable under existing reimbursement structures. Additionally, the much-discussed concept of incentivizing patients to use digital products for chronic disease management also poses challenges. Should insurance companies be allowed to offer premium discounts to patients who enroll in a digital medicine program? Should employers be allowed to pay employees for enrollment or even make enrollment in a program to improve health part of an employee's performance review?

Conclusions

The epidemic of chronic disease we face in the twenty-first century necessitates approaches different from those delivered by our twentieth-century healthcare systems. Unlike the acute healthcare problems we solved in the past, chronic disease requires prevention and continual intervention that effectuates patient behavior change on a massive scale. And given the unsustainably high cost of our healthcare system, efforts to combat chronic disease will need to reduce, rather than add to, overall healthcare spending. These forces, along with substantial technological progress and advances in computer and behavioral science, have created the opportunity for digital medicine to be used as a major tool to address our twenty-first-century healthcare problems.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.3495).

1. Centers for Disease Control and Prevention, National Center for Health Statistics. Leading causes of death, 1900–1998. http://www.cdc.gov/nchs/data/dvs/lead1900_98.pdf (Accessed November 28, 2015).
2. Centers for Disease Control and Prevention. Chronic disease overview. http://www.cdc.gov/chronicdisease/overview/ (Accessed November 28, 2015).
3. Elenko, E., Underwood, L. & Zohar, D. *Nat. Biotechnol.* **33**, 456–461 (2015).
4. Ward, B.W., Schiller, J.S. & Goodman, R.A. *Prev. Chronic Dis.* **11**, E62 (2014).
5. Centers for Disease Control and Prevention. Deaths and mortality. http://www.cdc.gov/nchs/fastats/deaths.htm (Accessed November 24, 2015).
6. Crimmins, E.M. *Gerontologist* **55**, 901–911 (2015).
7. Gerteis, J. *et al. Multiple Chronic Conditions Chartbook*. http://www.ahrq.gov/sites/default/files/wysiwyg/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf (Agency for Healthcare Research and Quality, April 2014).
8. US Department of Health & Human Services. Better, smarter, healthier. http://www.hhs.gov/about/news/2015/01/26/better-smarter-healthier-in-historic-announcement-hhs-sets-clear-goals-and-timeline-for-shifting-medicare-reimbursements-from-volume-to-value.html (26 January 2015).
9. Delbanco, S. The Payment Reform Landscape. *Health Affairs Blog*. http://healthaffairs.org/blog/2014/09/30/the-payment-reform-landscape-value-oriented-payment-jumps-and-yet/ (30 September 2014).
10. The Henry J. Kaiser Family Foundation. 2015 employer health benefits survey. http://kff.org/report-section/ehbs-2015-summary-of-findings/ (22 September 2015; accessed 28 November 2015).
11. Pew Research Center. Mobile technology fact sheet. http://www.pewinternet.org/fact-sheets/mobile-technology-fact-sheet/ (October, 2014; accessed 28 November 2015).
12. Pew Research Center. Broadband technology fact sheet. http://www.pewinternet.org/fact-sheets/broadband-technology-fact-sheet/ (September 2013; accessed 28 November 2015).
13. Centers for Disease Control and Prevention. 2014 national diabetes statistics report. http://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html (Accessed 28 November 2015).
14. American Diabetes Association Standards of Medical Care in Diabetes—2016 (ADA, Washington, DC, 2016). http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf
15. Renders, C.M. *et al. Cochrane Database Syst. Rev.* **2001**, CD001481 (2001).
16. Nathan, D.M. *et al. Diabetes Care* **30**, 753–759 (2007).
17. Quinn, C.C. *et al. Diabetes Care* **34**, 1934–1942 (2011).
18. Knowler, W.C. *et al. N. Engl. J. Med.* **346**, 393–403 (2002).
19. Sepah, S.C., Jiang, L. & Peters, A.L. *J. Med. Internet Res.* **17**, e92 (2015).
20. Centers for Disease Control and Prevention. Diabetes Prevention Recognition Program: registry of recognized programs. https://nccd.cdc.gov/DDT_DPRP/Registry.aspx (Accessed November 28, 2015).
21. Rice, J.B. *et al. Diabetes Care* **37**, 651–658 (2014).
22. Centers for Disease Control and Prevention. Asthma. http://www.cdc.gov/asthma/ (Accessed 28 November 2015)
23. Centers for Disease Control and Prevention. Smoking and tobacco use. http://www.cdc.gov/tobacco/ (Accessed 28 November 2015)
24. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). http://www.cdc.gov/copd/index.html (Accessed 28 November 2015).
25. Bricker, J.B. *et al. Drug Alcohol Depend.* **143**, 87–94 (2014).
26. Brewer, J.A. *et al. Drug Alcohol Depend.* **119**, 72–80 (2011).
27. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. http://www.alz.org/facts/ (Accessed 13 January 2016).
28. Centers for Disease Control and Prevention. Attention-deficit/hyperactivity disorder (ADHD) data & statistics. http://www.cdc.gov/ncbddd/adhd/data.html (Accessed 13 January 2016).
29. Centers for Disease Control and Prevention. Autism spectrum disorder (ASD). Facts About ASD. http://www.cdc.gov/ncbddd/autism/facts.html (Accessed 13 January 2016).
30. Centers for Disease Control and Prevention. Stroke facts. http://www.cdc.gov/stroke/facts.htm (24 March 2015).
31. Anguera, J.A. *et al. Nature* **501**, 97–101 (2013).
32. Cutler, A. *et al.* Game-Based Digital Intervention Improves Attention & Memory in Pediatric ADHD. Poster session presented at the American Academy of Child and Adolescent Psychiatry 62nd Annual Meeting, San Antonio, TX, USA, October 26–31, 2015.
33. Andersson, G., Cuijpers, P., Carlbring, P., Riper, H. & Hedman, E. *World Psychiatry* **13**, 288–295 (2014).
34. Viswanathan, M. *et al. Ann. Intern. Med.* **157**, 785–795 (2012).
35. Osterberg, L. & Blaschke, T. *N. Engl. J. Med.* **353**, 487–497 (2005).
36. Iuga, A.O. & McGuire, M.J. *Risk Manag. Healthc. Policy* **7**, 35–44 (2014).
37. Au-Yeung, K.Y. & DiCarlo, L. *Int. J. Tuberc. Lung Dis.* **16**, 1498–1504 (2012).
38. Belknap, R. *et al. PLoS One* **8**, e53373 (2013).
39. Boland, M.V. *et al. JAMA Ophthalmol.* **132**, 845–850 (2014).
40. Elenko, E., Speier, A. & Zohar, D. *Nat. Biotechnol.* **33**, 697–702 (2015).
41. Federal Trade Commission. Lumosity to pay $2 million to settle FTC deceptive advertising charges for Its "Brain Training" program. https://www.ftc.gov/news-events/press-releases/2016/01/lumosity-pay-2-million-settle-ftc-deceptive-advertising-charges (5 January 2016).
42. Federal Trade Commission. FTC approves final order barring company from making unsubstantiated claims related to products' "Brain Training" capabilities. https://www.ftc.gov/news-events/press-releases/2015/04/ftc-approves-final-order-barring-company-making-unsubstantiated (9 April 2015; accessed 13 January 2016).
43. Kish, L.J. & Topol, E.J. *Nat. Biotechnol.* **33**, 921–924 (2015).
44. Federal Trade Commission. FTC cracks down on marketers of "Melanoma Detection" apps. http://www.ftc.gov/news-events/press-releases/2015/02/ftc-cracks-down-marketers-melanoma-detection-apps (23 February 2015).
45. National Institute of Mental Health. Annual total direct and indirect costs of serious mental illness. http://www.nimh.nih.gov/health/statistics/cost/index.shtml (Accessed 28 November 2015).
46. Gaskin, D.J. & Richard, P. *J. Pain* **13**, 715–724 (2012).