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mHealth: The New Frontier in Healthcare

Carl Bate
Guest Editor

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Opening Statement

by Carl Bate, Guest Editor

In his 1995 book *The Road Ahead*, Bill Gates wrote, "We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten."[1] COVID-19 has inverted this otherwise normally true maxim, especially as it relates to healthcare.

The necessity of providing healthcare even in, and especially during, a global pandemic has meant that pent-up innovations in telehealth, remote patient monitoring (RPM), and remote chronic disease management have gone from "nice to have" to "must have." Simply put, there has been no choice during this past pandemic but to leverage technology to better connect physicians with patients virtually. Such innovations include triage bots, RPM and remote patient management technologies, dedicated healthcare video consultation platforms, and commodity Web call platforms with scheduling integration into electronic health records. The recent US $18.5 billion mega-merger deal between Teladoc Health/Livongo has created what many market commentators believe to be the first true digital health provider, combining RPM and remote patient management with a range of telemedicine services, including virtual consults.[2] Moreover, some major US healthcare systems have seen shifts in telehealth usage across departments from percentages in the low single figures to more than 50%, with some departments as high as 80%.

However, while the opening of the innovation floodgates has produced many benefits — including capabilities for clinicians to diagnose and monitor patients outside of clinical settings, as well as further value for patients in terms of convenience and access — new challenges are emerging, such as the following:

- **Malpractice.** Early data on malpractice claims in telehealth shows more claims, not fewer, than were brought for in-person healthcare.[3] While there is too little data at this point, making it too soon to draw conclusions, it is clear that solving the problem of the patient being remote from the doctor involves much more than solving the problem of the patient and doctor being able to see and talk to each other. Other aspects, including how to perform routine diagnostic tests and how to maintain the personal connection of in-person discussions, will require careful consideration as telemedicine use scales up.

- **Patient trust and access.** Certain demographics are more reluctant to engage with (and trust) telehealth.[4] While the COVID-19 pandemic is changing patient perspectives toward more acceptance of telehealth, recent data indicates that groups facing the greatest risks right now, including older people and those with lower incomes, are not sharing equally in the benefits telehealth offers. Indeed, a Black Book Research and Sage Growth Partners survey found that the majority of respondents (78%) who have used telehealth were satisfied with their experience, although older adults are reluctant to use telehealth, with 81% of respondents age 55 to 64 and 84% of those 65 and older not having had a virtual or telemedicine visit, despite having access to telehealth.[5]

Simply put, there has been no choice during this past pandemic but to leverage technology to better connect physicians with patients virtually.

- **Health economics.** Hospital systems designed for physical care provision that were already under financial strain prior to the emergence of the pandemic are now struggling even more. Elective surgeries have, quite understandably, been significantly impacted. Reimbursement designed for in-person settings, including associated diagnostic testing, is not wholly fit for purpose for mass telehealth. Thus, the post–COVID-19 pandemic world is going to require post–COVID-19 pandemic health economics to ensure long-term viability of healthcare providers. On the positive side, for the duration of the pandemic, the US Centers for Medicare &

Medicaid Services (CMS) has broadened coverage of RPM, making the CPT codes (used for reimbursement purposes to describe the treatment and diagnostic services provided) related to RPM applicable to patients with acute conditions, in addition to those with chronic conditions.[6] These and other changes by CMS to show how providers can utilize RPM will no doubt have benefits going forward. But this is only one component of the virtual health economic model.

- **Post–COVID-19 demand wave.** The sheer scale and tragic impact of COVID-19 on millions of families worldwide since the pandemic commenced may be worsened by "Long COVID," the condition of long-term health effects due to the virus.[7] Long COVID threatens to create an even greater detrimental economic impact. Moreover, pent-up healthcare demand and undetected (non-COVID-19 related) serious conditions may create a second-demand wave for healthcare services that exceeds available capacity and expectations. Exacerbating this situation are the challenges of ongoing clinical knowledge sharing, medical training, and logistical and supply chain issues caused by new physical limitations.

These new challenges, while significant, are opening up further innovation opportunities — especially with mHealth, a subset of telehealth. mHealth uses mobile technology and wireless devices to help achieve healthcare goals both remotely (e.g., via RPM) and within hospital settings. Not only does mHealth have the potential to address fundamental diagnostic challenges caused by the lack of physical engagement necessitated by COVID-19, but innovations from neuroscience to clinical trial operations hold the promise of improving on current in-person-based health outcomes and economics.

For example, if we consider some of the challenges highlighted above, first there is the basic challenge of obtaining vitals data remotely to support the typical consult. In addition to data from smart watches, we are seeing exciting innovations in using visual detection as a proxy for what would otherwise have been done with a medical device in a clinical setting. For example, Binah.ai[8] uses smartphone video images to measure changes in the skin's light absorption properties; information that is reflective of the patient's physiological condition. Such changes are captured within the pixel values of a camera image and converted into various physiological vitals, including variable heart rate, respiration rate, oxygen saturation rate, and blood pressure.

Another example of how to remotely obtain physiological data is from a pioneer in the implantable RPM field, Canary Medical.[9] CEO Bill Hunter and his team are leading in the field of "tweeting devices" — smart medical devices that self-report on function, diagnostic information, patient activity, side effects, and treatment failure, including its "talking" knee.[10]

In This Issue

So how can mHealth support the new challenges and opportunities of telehealth? In this issue of *Cutter Business Technology Journal* (*CBTJ*), we present some stimulating articles that illustrate the impact now, and the future direction, of mHealth.

Sean Lorenz starts us off with a focus on brain health and neuroscience. He describes how technology is helping us better assess our brain health journeys with remote detection, diagnosis, and treatment tools. Given the issues surrounding the current pandemic, Lorenz explores the urgent need that requires the healthcare system to actively look toward telehealth and RPM.

The next article moves us further up the healthcare value chain by highlighting the impact that COVID-19 has had on clinical trials. Cutter Consortium Senior Consultant Ben van der Schaaf and Pan Xi describe the current state of mHealth along with technology innovations that forward-looking R&D leaders in pharmaceuticals are deploying. Knowing that the current shift will not be temporary, the authors urge healthcare organizations "to adapt and be in the right

Upcoming Topics

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place at the right time … to prepare for this imminent change."

Next, Levie Hofstee, cofounder of Neurocast, describes advancements made by his company. Neurocast is a later-stage startup gaining traction in using mHealth to provide real-world data on patients suffering from chronic disease, such as multiple sclerosis, both to aid new discoveries and to support 24/7 data collection during clinical trials. The company has developed an innovative Neurokeys keyboard to gather keystroke dynamics (a great example of the type of proxy data that will be used in the entirely new field of brain-recording technology) combined with noninvasive physical sensors, including those from Kernel.co. (Kernel.co is worth a dedicated mention at this juncture. In Q2 2020, the startup Kernel announced commercial availability of its Neuroscience as a Service [NaaS] platform, enabling noninvasive brain imaging and recording.[11] NaaS neural data acquisition can be used for discovery of biomarkers of cognition and brain health, as well as for other non-health-related applications; for example, insights into the neuroscience driving consumer and social choices.)

Finally, Heléne Spjuth takes a step back to examine the economics of mHealth and the resulting challenges and opportunities for all stakeholders in the healthcare ecosystem. In defining the healthcare ecosystem and its various reimbursement models, she shows the "unique circumstances that will serve either as barriers to, or enablers of, mHealth's efficient implementation."

A key question for health innovators is how long Gates's assertion will remain in reverse: *for how long will we be underestimating rather than overestimating the change that will occur in the next two years?* Which of the most promising mHealth innovations will be adopted to solve today's clear and present challenges?

While healthcare as a practice and an industry has, to date, been notoriously slow to embrace system-wide innovation — though not without some good reasons — healthcare professionals worldwide have again shown their commitment, dedication, and inventiveness when faced with previously unimagined constraints. The best innovators and technologies of mHealth can help these efforts and improve the practice of medicine in the here and now, as well as lay foundations to serve future needs. I hope you find the articles in this issue of *CBTJ* an interesting window into some of this significant potential.

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LISTEN TO YOUR ELDERS

Remote Detection and Treatment for Aging Brains

by Sean Lorenz

How a Global Pandemic Changed Everything

The COVID-19 pandemic fundamentally changed the paradigm in which we deliver care. The need for change existed long before COVID-19, but the pandemic clarified the urgency. You have likely come across news articles (and even promotional emails) discussing the switch to remote check-ins with primary care physicians, specialists, and urgent care nurses. And there's a good chance that by now you've already experienced what a telehealth visit entails. Just as schools have been forced to rapidly assemble remote learning plans for our children, the healthcare system is experiencing an urgent need to finally pivot toward telehealth and remote patient monitoring (RPM).

In the first six months of 2020, digital health shattered funding records, with US $6.3 billion raised so far with no signs of slowing in the second half of the year.[1] The obvious digital health category forerunner is telehealth, with examples such as Amwell's $742 million IPO[2] and the $18.5 billion merger of Teladoc Health and Livongo.[3] In tandem with telehealth growth, Rock Health reported a rise in investment for companies offering remote disease monitoring and behavioral health solutions.[4]

Yet, just a few years ago, investors were slow to invest in digital health products due primarily to lack of reimbursement options. In the US, with healthcare facilities losing revenue during the COVID-19 pandemic due to peoples' fear of entering a hospital or doctor's office, the codes used to obtain reimbursement for remote care needed to change quickly. Changes to CPT codes (used for reimbursement purposes to describe treatment and diagnostic services provided) in 2020 rapidly expanded Medicare and Medicaid RPM reimbursement coverage, as did the passing of the Coronavirus Aid, Relief, and Economic Security (CARES) Act by the US Congress. Moreover, the Centers for Medicare & Medicaid Services (CMS) proposed changes in August 2020 that may make temporary CARES Act reimbursement of telehealth and RPM a permanent addition to the US healthcare system.[5]

RPM reimbursement changes in the US this year have focused heavily on Medicare and Medicaid due to elderly population vulnerabilities and required isolation during the pandemic, yet telehealth adoption among older adults has been a mixed bag. While baby boomers (individuals age 56-74) have almost ubiquitously added smartphones and tablets to their tech repertoire, members of the "Silent Generation" (individuals age 75-91) have adopted these technologies at a far slower rate, making it difficult to deliver remote care to them. However, a recent AARP survey shows that individuals over 75 are starting to use tablets more regularly to connect with family members and access news.[6]

Older adult RPM solutions have been percolating for decades across the health spectrum, primarily finding sanctuary in academic and pharmaceutical research. The holy grail for most RPM startups is clinical data validation, yet digital health trials are unable to move at the pace of other software startup verticals that operate under the "move fast and break things" mantra. Add to this that other players in the elder care ecosystem — home health, skilled nursing facilities, and continuing care retirement communities (CCRCs) — often move at an even slower pace of technological adoption, leaving a long trail of aging tech companies that have closed up shop in the past decade. But this dour story is turning increasingly optimistic. In the US, CPT code updates for RPM, paired with exponential investment in digital health endeavors, mean commercialization of elder care technology is sure to become more palatable to CCRCs looking to provide better care for residents in uncertain times. A key area in which this technology can add value is detecting neurological problems in elderly individuals and aiding with treatment.

One example that illustrates the need for older adult RPM solutions in this area comes from a study exploring the importance of physical exercise and stress reduction to improve motor symptoms and quality of life in individuals with Parkinson's disease (PD).[7] The pandemic has often prevented elderly individuals with

PD from taking daily walks outside, visiting therapists, or attending group fitness classes. Being isolated from the world can increase anxiety and depression, two factors known to exacerbate PD symptoms. The study discusses how self-management strategies that reduce stress, increase coping skills, or increase physical exercise can play important roles in the treatment of PD. Thus, RPM solutions that take advantage of smart health devices and tablet applications designed with aging populations in mind will be able to remotely deliver better tools for increasing mindfulness and individualizing cognitive behavioral therapy interventions and home-based training programs.

Collecting Brain Health Data

Before discussing how we collect data about our brain and behavior, we need to first define what we mean by the term "brain health." As important as it is, brain health is more than meditating or playing *Sudoku* games online. The brain talks with the rest of the body, so if something is wrong with the heart, lungs, or limbs, the brain knows it and attempts to compensate accordingly. Harvard Medical School Neurologist Alvaro Pascual-Leone's "6 Pillars of Brain Health"[8] emphasizes this connection and addresses the role of physical exercise, food and nutrition, overall medical health, sleep and relaxation, mental fitness, and social interaction in keeping your brain fit over a lifetime.

Brain health, then, involves every aspect of our daily lives. Testing how we feel mentally and physically in our natural, everyday environment is the best way to measure brain health. That means the technology that surrounds us and is used by us every day should "know" how our brain health is doing. The first challenge? Engaging technology-averse older adults early on with productized RPM solutions that extract knowledge from data collected across multiple types of devices.

Gathering this data requires a keen awareness of where elderly individuals are physically located. Are they still living at home? And if so, do they receive any in-home geriatric care? Are they living within a CCRC? What are residents' brain health needs as they move from independent living, assisted living, or memory care to skilled nursing? Adoption of Internet of Things (IoT) or screen-based devices for elderly individuals in CCRCs depends on whether: (1) the facility provides these devices; (2) the facility can assist with device setup, use, and charging; (3) individuals grant access consent for the facility to collect data from a device; and (4) individuals are capable of using the device in their current cognitive condition.

For example, independent living communities typically market services that eliminate tedious chores like mowing the lawn, doing laundry, or cooking at every meal. An independent living resident's RPM strategy might focus more on a long-term, preventive brain health smartphone app that adds fitness tracking or sleep analysis. On the other hand, an older resident that lives at home and requires a daily geriatric home care nurse visit may interact only with technology brought to the home by the visiting nurse. Therefore, the RPM strategy for this person might involve giving the home care nurse a tablet and IoT-connected smart health devices, allowing the nurse to directly administer regular brain tests and take vitals during each home visit.

Testing how we feel mentally and physically in our natural, everyday environment is the best way to measure brain health.

Whether individuals are aging in place or in full-time memory care facilities, secure authentication, transmission, storage, analysis, and access are mandated for remote data collection of brain health data. Regardless of whether a brain health application necessitates compliance with the US Health Insurance Portability and Accountability Act (HIPAA), cloud-based platforms such as Amazon Web Services (AWS), Google Cloud, and Microsoft Azure have made significant strides in making it relatively straightforward for software development teams to handle electronic protected health information (ePHI) in the cloud. However, HIPAA compliance regulation for consumer IoT devices such as the Fitbit or Apple Watch can get a bit murky; regardless, healthcare technology should always be designed and developed with the highest HIPAA (or equivalent) security regulations in mind.

What kinds of data can be collected to assess brain health? Below is a non-exhaustive list of devices used to analyze various aspects of older adult cognitive and mental health:

1. **Smartphones.** More ubiquitous among baby boomers than among their parents' generation, the accelerometer in smartphones is a key tool for evaluating gait and balance quality.[9] Other obvious

benefits made possible by smartphones are telehealth, brain-based game apps, and periodic delivery of cognitive assessment questionnaires.

2. **Tablets.** Their larger screen size has made tablets increasingly popular with older adults, who benefit from mental acuity apps and "all in one" family/senior engagement tablets such as the GrandPad.[10] The addition of items such as the Apple Pencil allow brain health companies like Linus Health to digitize common neurocognitive assessments such as the clock drawing test.[11] Brain health tablet apps are able to easily deliver audio- and visual-based assessments, transitioning standard "pen and paper" tests like the Mini-Cog[12] into a simpler, more data-rich tablet version.

3. **Health wearables.** To better understand our own cognitive and mental health, we must also know about our body's response to its environment. The consumer health wearables market has skyrocketed in the past five years, but insights derived from these products are still not perfect. A recent *Washington Post* article comparing the blood oxygen status numbers delivered by Apple Watch Series 6 and Fitbit Sense found wildly varying results.[13] Despite such variances, devices that count steps, measure electrocardiogram signals, track blood pressure, or measure other vitals are continually improving and can provide useful information if tracking and measurement are conducted over long periods of time. The more frequently these overall health measurements are taken outside the clinic, the more they inform us about possible brain health trajectories.

4. **Smart home.** Passive smart home devices such as motion and coming/going sensors can track wandering patterns for dementia patients. Connected mattress sleep monitors assess restlessness, snoring, and sleep quality, all factors that play into long-term mental reserve and resilience. Smart mats measure sudden weight fluctuations that may be indicative of other health issues.

5. **Electroencephalogram (EEG).** Companies like Neuroelectrics[14] have taken great strides in commercialization of medical-grade EEG data collection, making it possible to analyze neural functionality in the home with a simple EEG cap and tablet app.

6. **Deep brain stimulation (DBS).** DBS is now being used outside a clinical setting to assist individuals with movement disorders. A new study[15] used a Bluetooth-enabled DBS electrode system to remotely adjust complex variable frequency stimulation (VFS) for PD patients suffering from freezing of gait.

Remotely Engaging Users

Aggregating data from the latest IoT gadgets and sensors sounds fun to engineers looking for a development challenge, but all those devices are worthless if users don't want or need them. This may seem obvious, but the long line of failed "silver tech" (technology for seniors) digital health startups shows that companies were either not listening to what their users wanted in a product or weren't able to convince buyers their innovative solution was a painkiller and not just a vitamin. Asking elderly users to adopt technology-based solutions can be a very tricky proposition.

There is a great technological divide between the Silent Generation and baby boomers. Parents of boomers are typically far less likely to own smartphones or computers and are especially skeptical of cloud-based services. For example, I spoke with a woman whose mother in assisted living refuses to bank online because she doesn't want the bank to have all her information. When digital health companies bring in a solution that will track mom's movements with cameras and sensors, the answer is often a resounding "no, thank you!" This skepticism is one of the primary reasons many RPM tools for seniors have failed in the past. Mom may already be feeling isolated after moving from home into an assisted living residence with a lot of new faces. Adding cameras and sensors can often make these individuals feel they're being watched under a microscope, instead of being listened to and cared for.

What is the alternative? The best-in-breed RPM solutions listen to their users. They take into account the wide spectrum of technical ability and acceptance that differentiates a 55-year-old from an 85-year-old. These companies also account for this spectrum by giving users a variety of methods to interact with their apps and devices, offering UX/UI functionality that may seem horrible to younger users, but welcoming to an older user. Big buttons, larger text, color choice, and photo accompaniment are a few simple ways to account for failing vision, lack of dexterity, and reduced

accuracy from shaky fingers. Asking older users to perform complicated gestures and swipes on a tablet can also cause confusion and frustration, leaving the tablet to collect dust on a desk. Software developers should consider cognitive and mental decline when designing apps, giving caregivers an option to change the UI setting as their parent is diagnosed with dementia or other neurocognitive issues.

Increasing engagement needs to consider the many people involved in the daily care of elderly individuals — facility nurses, activity directors, home health aides, family members, primary care doctors, specialists, and so on. Each of these roles has its own unique perspective on how to best care for someone; however, building solutions for each of these users is obviously untenable, which is why forming partnerships with like-minded companies is often beneficial.

Another important point on engagement is that timing matters. For example, if you want people to take a quick mental health quiz on a tablet to assess possible signs of depression over time, you should know their habits. Are they a morning or night person? Do they pick up a tablet when hearing an auditory ping? Do they notice the notifications list alerting them to a new quiz? Eighty-year-olds with mild cognitive impairment may not remember that you notified them of a quiz and might be more prone to remember if they see the notification while looking at photos of their grandchildren.

Remote Detection and Diagnosis

Our brains are the most complex object in the known universe. It's no wonder that moving brain-based RPM solutions beyond the classification of "health and wellness" into regulatory approval is no small feat. Remote detection and diagnosis tools for brain health have been slower to show efficacy than other remote diagnostic solutions that can detect more tangible changes over time. Neurologists and neuropsychologists have developed questionnaires and found ways to read MRIs that shed light on what is happening to our brains over time, but in order to make better diagnoses we need more data outside yearly clinical visits.

Understanding how the brain influences behavior, as well as how our lifestyles affect our brain health, requires domain-specific analysis of all the relevant data we can now obtain remotely outside the doctor's office. There is exponential power in the analysis of multimodal data. Speech recordings from a memory recall task, sleep monitor device readings, and a periodic depression scoring question may individually have features that show significance only when combined with other features across multiple data sources. Underlying this assumption is the idea that more frequent testing equates to more data and, thus, more accurate diagnostics.

The arduous path to regulatory approval requires development of scientifically validated metrics that move beyond the health and wellness approaches of displaying cleanly designed charts and graphs gleaned from the raw data. The end goal is to extract meaning from metrics. This is the case for any artificial intelligence and machine learning (ML) application, but deriving brain-based diagnoses from RPM data requires industry expert involvement. Neurologists, neuropsychologists, and other clinicians must be kept in the loop to balance expert-informed rules with appropriately trained ML models.

The arduous path to regulatory approval requires development of scientifically validated metrics that move beyond the health and wellness approaches of displaying cleanly designed charts and graphs gleaned from the raw data.

Remote Treatment

The brain's ability to adapt to environmental constraints and neuronal injury is called *synaptic plasticity*. Exciting research is being done that harnesses neuroplasticity for clinical applications such as stroke recovery, memory improvement, treatment of depression, and so on.[16] Interventions for brain-based disorders can leverage the same RPM devices discussed in this article. Noninvasive brain stimulation, DBS, physical training, exercise, and cognitive training interventions all can be performed remotely without worrying about the physical and monetary cost of transporting elderly individuals to and from therapy offices. Outcomes can also be tracked as new detection and diagnostic data is acquired, creating a closed-loop system for detection and treatment of brain-based disorders.

An inspiring example of this closed-loop approach is the use of transcranial direct current stimulation (tDCS) by Neuroelectrics to help patients with major depression at home amidst COVID-19 restrictions.[17] The technology from Neuroelectrics monitors the brain's electrical activity by EEG and uses transcranial electrical stimulation (tES) to stimulate brain regions or networks with mild electric currents to directly alter brain function. Once daily home stimulation is completed, partnerships with companies such as Linus Health that offer neurocognitive assessments can close the loop by delivering a quick, tablet-based cognitive test to gauge efficacy of the stimulation treatment.

Brain-based remote monitoring tools for aging individuals still have a long road ahead, but recent changes in reimbursement policies (CPT codes), increased investment in aging brain tech companies, smarter home health devices, HIPAA- or other privacy regulation-compliant cloud options, and better understanding of elderly users are making it faster and easier to close the loop from remote detection to alleviation of cognitive and mental disorders.

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STEP IT UP A NOTCH

mHealth in Clinical Trials Has Been a Tease for Years; It's Time to Deliver!

by Ben van der Schaaf and Pan Xi

Healthcare disruption by technology is not a novel idea. Clayton Christensen predicted it in *The Innovator's Prescription: A Disruptive Solution for Health Care* well over a decade ago, when he suggested that technological innovation would propel healthcare toward affordability and accessibility through the decentralization of healthcare delivery services.[1] While Christensen's observations were more focused on medical devices and diagnostic equipment and less on the smartphone apps and wearables explosion, his decentralization concept is exactly what has happened. In recent months, COVID-19 has made the potential of digital in healthcare clear to everyone who had not seen it yet, as pandemic restrictions have forced the wholesale adoption of mobile health (mHealth) in many areas. One of those areas is clinical trials, where sponsors, investigators, and patients have all had to adapt rapidly to a shifting environment. This shift will not be temporary, so now is a good time to take a new look at how mHealth can change many aspects of clinical trials.

mHealth, defined by the World Health Organization (WHO) as "any medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices,"[2] can be seen as part of telehealth and also as a major component in the digital health space. This article provides an overview of the mHealth market and select innovations, benefits, barriers, and challenges of mHealth adoption in clinical trials, as well as what is required for successful mHealth adoption across stakeholders.

Rapid Growth of mHealth App Market

The mHealth market is primarily segmented into mobile apps and wearable devices/biosensors. While adoption of mHealth in clinical development has not been widespread, the general use of wearables and related apps (e.g., Apple Watch, Fitbit, Headspace, or Insight Timer) has exploded, making virtual clinical trials (VCTs) possible. VCTs, also called "remote" or "decentralized trials," are "a relatively new and yet underutilized method of conducting clinical research taking full advantage of technologies such as apps, electronic monitoring devices, and online social engagement platforms."[3]

The global mHealth app market reached US $28.3 billion in 2018 and is forecast to reach $102.4 billion in 2023.[4] Recent studies show that there are 550 million+ global active users (at least once a month),[5] 325,000+ health apps available in the market,[6] and 45,000+ mHealth app developers.[7] The app landscape is rapidly evolving as well. In 2015, only 10% of apps were able to connect to devices and sensors and even fewer could be integrated with provider systems.[8] While the majority of apps still target consumer self-management of overall wellness, diet, and exercise, the number of apps for disease treatment, diagnostics, and remote monitoring has increased (see Figure 1). App connectivity to sensors, data aggregators, and other third parties has improved, too. Currently, the therapeutic areas leading the clinical use of health apps are diabetes, cardiovascular disease (weight management), and certain mental health and behavioral disorders.[9]

In 2015, 300 clinical trials used mHealth apps as part of the study design.[10] Furthermore, a recent study by Kaiser Associates conducted for Intel forecasts that 70% of clinical trials will incorporate sensors by 2025.[11] As Table 1 (a snapshot of a ClinicalTrials.gov search) illustrates, the trend of app and sensor integration into clinical trials is clear. Although mHealth applications have not yet become prominent in trial descriptions on ClinicalTrials.gov, we can expect the number of mentions of mHealth applications to grow rapidly in the near future.

The mHealth Device and Sensor Market

The global healthcare wearable device market is projected to reach $46.6 billion in 2025.[12] Common wearable devices and sensors include fitness trackers,

electrocardiogram monitors, smartwatches, and blood pressure monitors. These devices measure a variety of biological functions (e.g., blood oxygen saturation, heart rate, electrical signals) and can be worn on the body or attached to the skin in the form of a patch, a chip, a watch, wrist/ankle bands, necklaces, or headbands. This market is closely linked to the app market as many of the devices are managed through smartphones.

Significant innovation in devices and sensors has occurred over the past five years. One example is the ingestible wireless sensor Abilify MyCite from Proteus Digital Health.[13] However, although Abilify MyCite gained significant interest and publicity within the digital health space, Proteus Digital Health was forced to file for bankruptcy protection in June 2020.[14] Its assets have since been sold to Otsuka, the marketer of Abilify (the drug used in Abilify MyCite). It is likely that the bankruptcy of Proteus Digital Health was due, at least in part, to the inability of the firm to integrate the operations of its ingestible sensor technology into the workflow of healthcare providers (HCPs). The integration of workflow and data between the device, HCPs, and drug companies is a challenge that many technology innovators will likely face in the commercialization and launch of complex device and sensor products. Integration of workflow and data is often a challenge due to concerns with patient privacy, data integrity,

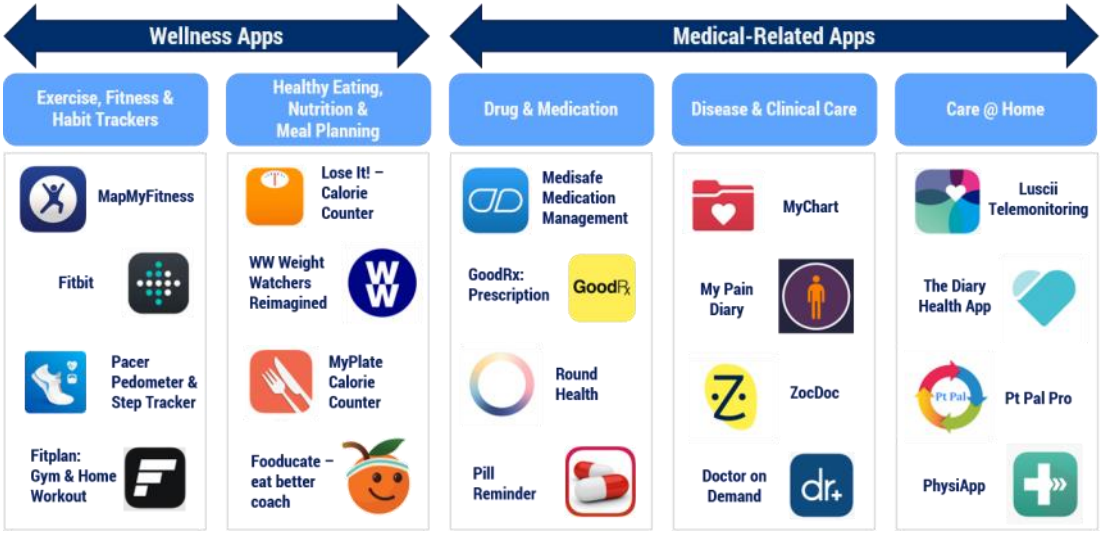

Figure 1 — Popular wellness and medical apps in the healthcare space.

Search Term	All Trials	Percentage	Enlisting/Not Yet Recruiting	Percentage
Wearable	1,004	0.29	430	0.61
mHealth	1,018	0.29	373	0.53
Smartphone	2,086	0.60	717	1.02
Mobile	5,181	1.48	1262	1.80
Remote	4,152	1.19	1511	2.15
iPhone	170	0.05	51	0.07
Smartwatch	64	0.02	27	0.04
Fitbit	552	0.16	209	0.30
Biosensor	156	0.04	55	0.08
IoT	8	0.00	2	0.00
TOTAL Trials Listed	349,708		70,118	

Table 1 — A search on ClinicalTrials.gov for a select set of mHealth terms generates results that point to an increase since 2015 in the number of clinical trials using mHealth apps.

system/IT integration, and data storage. Oftentimes, healthcare and drug companies, the intended customers of device and sensor innovations, are not readily equipped with the internal capability and infrastructure to be able to seamlessly operate and transfer data from the device system to another system.

mHealth in Healthcare

Since the first introduction of the smartphone and wearable device technology, rapid progress has been made in using mobile and wireless technology for healthcare (see Figure 2). Today, COVID-19 has turbocharged the need for companies to be more aggressive and innovative in how they leverage mHealth and other digital applications in clinical trials.

This is becoming visible in various ways. Within the industry, many pharma companies have been forced to adopt mHealth applications in their ongoing trials to ensure patients were treated. Early in the pandemic, some companies delayed or paused trials, but after a few months most companies started adapting to the new situation and introduced different approaches. Examples of this include monitoring, where new approaches to source data verification have been explored; patient assessments (through telehealth rather than in-person visits); and the introduction of apps and wearables to obtain required data, which became much more difficult to obtain as COVID-19 caused site closures and patients simply refused to leave their houses (or government guidelines did not allow them to do so). In the general health field, which is usually a bit in advance of clinical trials in the adoption of mHealth, Evidation Health launched COVID-19 Pulse, a national study that tracks the attitudes and behaviors of the population during the pandemic using Evidation's Achievement app.[15] Similarly, San Diego-based Scripps Research Translational Institute launched DETECT to gather data via the MyDataHelps app on activity, heart rate, and sleep patterns.[16] The Consumer Technology Association (CTA) launched the Public Health Tech Initiative to explore opportunities for using consumer technology to address public health emergencies.[17] These initiatives will not only improve disease tracking and public health surveillance but will also enable better understanding of how to implement mobile technology in future clinical trials.

Major Benefits of Leveraging mHealth in Clinical Trials

Figure 3 outlines potential usage and applications of mHealth across the lifecycle of a trial. When used effectively, mHealth can provide significant advantages in clinical trial execution. These benefits include: (1) improved data quality and availability, (2) better patient engagement and adherence, and (3) more effective

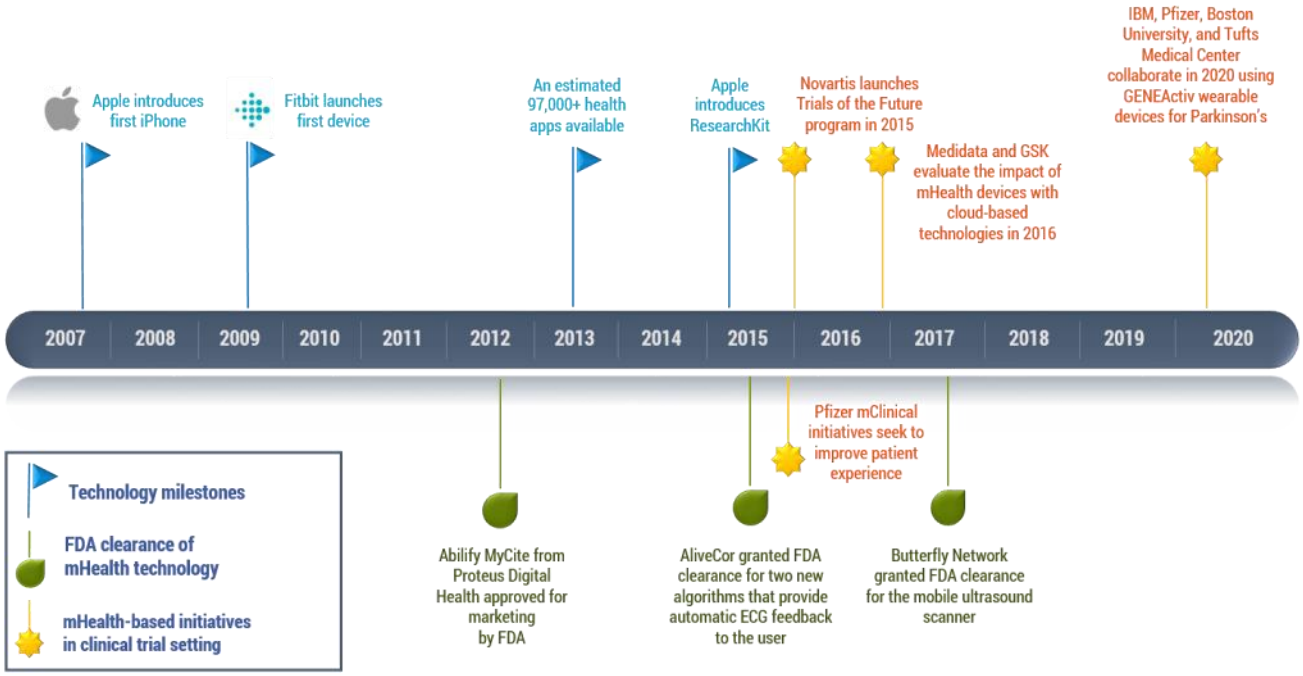

Figure 2 — Timeline of mobile technology and mHealth milestones and events.

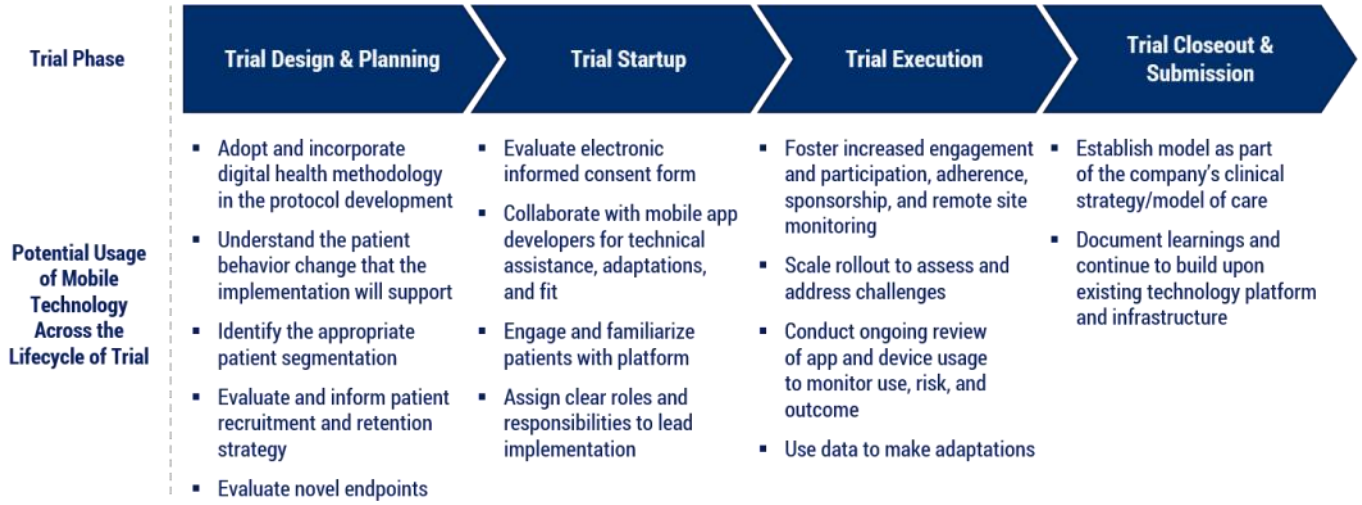

Figure 3 — Potential usage and applications of mHealth across the lifecycle of a trial.

execution, which overall will lead to a more robust trial and faster time to market.

Improved Data Quality and Availability

mHealth, in the form of apps, sensors, wearables, and so forth, enables the collection of a significantly higher (in some cases, continuous) data volume. By reducing human involvement in data collection and documentation, one can expect the quality to improve. The increased volume improves robustness, especially if data collection is in real time, continuous, and passive. Another key advantage is that because mHealth allows for a better understanding of a patient's normal, everyday behavior, it becomes easier to differentiate the effects of treatment. The use of real-world data in combination with trial data, obtained through mobile technology and by engaging patients and HCPs, is another avenue to strengthen the data overall.

Better Patient Engagement and Adherence

The use of mHealth with patients can start early, in the study design process, and continue in recruitment. Using an app or other feedback mechanisms during the enrollment process can provide valuable input into the protocol early in the trial. Moreover, making mHealth an important component in the protocol design with the patient in mind can reduce patient burden by limiting the number of clinic visits for treatment and assessments. mHealth is already being successfully used in the informed consent process; rather than having the patient meet in person with the HCP, informed consent can, in some situations, be obtained from patients through apps and video, live remote video meetings, or other "mobile" applications. In many cases, patients' own smartphones can be used for data collection without the need for additional devices. Many devices use passive data collection and cause minimal disruption to a patient's daily routine. Reducing patient burden is becoming more and more important as patients become better informed and look for clinical trials that meet their needs. Being able to respond to patient needs provides sponsors with a competitive advantage in enrolling studies. Effective application of mHealth results in more engaged patients, making it easier/quicker to recruit and enroll patients, which has a positive impact on costs. An additional benefit may be increased trial participation by members of underrepresented groups (e.g., rural, elderly, low income) with historically low participation rates.

More Effective Trial Execution

Mobile technology can be a major factor in effectively managing data obtained throughout the study. Clinical trials involve many people, many locations in multiple countries, and, often, multiple companies and partners. Despite significant variation among sponsors, contract research organizations (CROs), sites, and patient populations, the processes to capture, check, correct, analyze, and file the relevant data remain inefficient and error-prone due to frequent human interaction points. The use of mobile tools, while increasing, is still in its early stages and offers significant upside for companies: more data (volume), higher-quality data (fewer human touchpoints), and faster processing of data (quicker time to submission may mean faster time to market).

Realizing this upside will require appropriate systems, appropriate data governance, appropriate processes, and appropriate ways of effectively and securely working and sharing with all relevant parties.

Successful Adoption Requires Alignment of Multiple Stakeholders

The adoption, integration, and implementation of an mHealth model in clinical trials require significant efforts from various stakeholders in the healthcare ecosystem. Patients may need to expend less effort, but other stakeholders will need to put systems, processes, and governance in place to share, receive, interpret, analyze, and protect data and information, as well as develop the capability in their workforce to work with the data and information.

Patients

Patients are important stakeholders if mHealth is to become a major factor in delivering clinical trials. Technological solutions (e.g., apps, wearables) need to be designed with the patient in mind, whether the technology is used for any type of data capture or to limit the number of patient visits to the clinic. Mobile equipment may mean that instead of patients visiting the clinic, the clinic is visiting them. In addition to patients' benefiting from the mobility afforded by mHealth, the technology must offer patients ease of operation and provide security measures. A wearable that records data passively is, of course, different from electronic patient-reported outcomes (ePRO) solutions, where patients actively provide data (which introduces a subjective element), and from having an HCP visit the patient with mobile equipment to perform dosing or assessment.

Sponsors and CROs

We treat sponsors and CROs as a single stakeholder category because both can potentially perform all activities involved in an end-to-end trial. The following describes the major phases of a clinical trial (with no intention of being exhaustive):

- **Study design.** Developing the appropriate protocol to integrate the selected mHealth aspects into a study is key. This requires a deep understanding of what the patient will need, what data will be captured, how the data will be processed and analyzed, and how the regulator will react. One pharmaceutical executive recently noted that the volume of data generated from wearables in one trial was so high that a major upgrade in capacity and capability would be required to be able to process and use all the data.
- **Study startup.** Many components are in play at this trial stage. Can mHealth be a component in site activation; for example, in the training of site staff? Can we deploy mHealth tools to manage informed consent in a more effective way? Can patients find and register for clinical trials on their phones?
- **Study conduct.** Clinical monitoring, both remote and virtual variants, obviously comes to mind here. Patient interactions may occur offsite, whether patients interact through their phones, are constantly monitored through a smart patch or wearable, or have an HCP visit to do assessments using mobile equipment.

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Investigators and Sites

The impact of mHealth on clinical sites and investigators will vary. Sites that struggle with resources may welcome mHealth as it may reduce resource needs. On the other hand, a perceived limitation of interaction with patients might be resisted. mHealth provides the potential for improved patient and investigator interaction and may allow real-time remote patient monitoring. However, concerns exist that investigators are now more removed from patients and cannot be in full control of the study procedure and patient safety. What is certain is that sponsors will need to invest in bringing sites along with them on their journey toward implementing mHealth in their clinical trials.

Technology/Digital Health Players

The pandemic has put telehealth firmly on many agendas, and mHealth is very much part of the discussion. While healthcare systems, pharmaceutical companies, and patient organizations are obvious participants in these discussions, the big technology companies are also significant players. Apple, Google,

and Amazon all produce wearables. These companies control the app environment through their operating platforms and are very active in developing capabilities (mostly through M&As) in this space. Apple and Microsoft have acted as the lead sponsors for a few trials, but, in general, they seek to work in partnership with pharmaceutical companies to deploy their technology and other capabilities into clinical trials.

Continued innovation in mobile app, sensor, and device functionalities will enable full adoption of mHealth into clinical trials. While connectivity between devices and apps and the Internet of (medical) Things continues to improve, there is much progress still to be made in seamless connectivity with, and integration into, provider healthcare systems and sponsor systems. The ability to connect with HCPs is important for clinical trials because it makes the use of real-world data possible. The integration of mHealth with electronic medical records (EMRs) is complex and presents many implementation challenges.

Although there has been significant innovation in trial design, companies have been reluctant and risk averse in innovating in operations.

Regulatory Agencies

The first thing to consider when we talk about the regulatory environment for mHealth is that mHealth is not just the purview of the health authorities. Taking the US as an example, in addition to the Food and Drug Administration (FDA), other federal agencies that have a stake in the regulation of mHealth are the Federal Communications Commission (FCC) and the Federal Trade Commission (FTC). The Office for Civil Rights (OCR), within the US Department of Health & Human Services (HHS), governs the Health Insurance Portability and Accountability Act (HIPAA) and will also be involved. Still other agencies and committees have mandates that give them a seat at the table for any mHealth discussion. The involvement of so many regulatory agencies does not make the governance of mHealth easy, and, at this point, one reason why companies are reluctant to get out in front and invest heavily is that many questions remain unanswered, meaning that the goalposts are still moving.

This fluid landscape poses risks to developers, providers, patients, and the public. Creating regulatory standards for mobile apps, wearables, and cloud adoption will be challenging but is not optional. Regulators must ensure strict and robust regulatory oversight but in a way that is both conducive to technological advancement and the protection of patient data.

Barriers and Challenges

Organizations face many barriers and challenges in bringing mHealth into their clinical trials. The main challenges are: (1) data integrity, privacy, and security; (2) changing company culture in a fairly traditional space; (3) an evolving regulatory environment; and (4) lack of empirical evidence to support the value-add of mHealth for the various stakeholders involved.

Data Integrity, Privacy, and Security

Significant challenges exist for health data privacy, security, validation, and governance. This is partly because data policies of most mHealth apps are not clear and the mechanisms to protect data integrity and privacy have not kept pace with advances in mHealth technology. A report by UC San Diego[18] outlined examples of malicious attacks associated with wireless connectivity and communication in mHealth applications, including resource depletion, replay,[19] and external device mis-bonding attacks. These threats interfere with the operating system of the device, which may lead to data manipulation and fraud.

Company Culture Shift and Change Management

The operation of clinical trials is a traditional space in many ways. Although there has been significant innovation in trial design, companies have been reluctant and risk averse in innovating in operations. For example, despite statements of interest in new approaches to recruitment or monitoring, few people want to apply those new approaches to their trial. Failing while using the tried-and-tested approach is perceived as not being as bad as failing while trying something innovative. The pandemic (again) has shifted this perception, as companies have been forced to move outside their normal processes because external

circumstances have put trials and patients at risk. The pandemic has effectively given companies a free pass to try something new. While not all changes will stick, innovations in patient enrollment, monitoring, and home visits (a major component of the virtual trial) are here to stay.

This forced change will reverberate across the clinical development space, including sponsors, CROs, hospital systems, regulators, investigators, patient organizations, and, of course, the technology and mHealth companies that have shifted their innovation into high gear. The ramifications of change will, in turn, require new capabilities in terms of data handling and analysis, governance, processes, and systems infrastructure. Forced change does not mean that everyone will automatically adapt, so organizations will need to make the effort to have change seriously stick. It means that companies will need to deliberately manage change, involve key stakeholders and impacted people so that they can understand what will change and why, and adapt accordingly, to ensure any change is lasting and perceived as positive.

Lack of Regulatory Clarity and Support

In 2017, the FDA introduced the "Digital Health Innovation Action Plan"[20] to foster digital health innovation. In April 2018, the agency outlined its guidance and plan for digital health, and in September 2019 updated its guidance and launched its digital health software precertification pilot program ("Pre-Cert").[21] Other health authorities have similar ongoing initiatives. As mentioned, health authorities are not the only interested regulatory agencies, which complicates the prediction of outcomes. Another complicating factor is that the US, EU, and China, while quite collaborative where health authorities are concerned, are not necessarily on the same page regarding data privacy, mobile technology, and intellectual property. This makes for a fascinating, yet difficult to navigate, landscape.

Lack of Empirical Evidence to Support Value-Add of mHealth

Rigorous investigation is needed to understand the full spectrum of mHealth value-add across clinical trials. To date, few studies have assessed mHealth from a quality and value-add perspective. Health app functionality and consumer/patient adoption, behavior, and usage are some of the critical aspects not yet well understood.

How Companies Can Best Use mHealth in the Future

There is no doubt that mHealth will be an important enabler for clinical trial design and delivery. Innovation is accelerating and while the regulatory landscape is fluid, it seems certain that mHealth will be a major factor in clinical development. Organizations need to adapt and be in the right place at the right time. To prepare for this imminent change, companies must:

- **Develop capabilities** to take advantage of opportunities by:
  - Partnering with mHealth and digital health players.
  - Building data capabilities and infrastructure.
  - Recruiting people with multiple skill sets and domains of experience and expertise (e.g., in both a digital environment and the clinical operations space).
  - Investing in resources to identify trends and intersections with respect to regulations, data and technology, and clinical trial innovation.
- **Understand how attitudes to risk** across the organization impact innovation.
- **Develop the infrastructure** to prepare for a dynamic future:
  - Cloud-based solutions are gaining prominence for easy access and storage of data and the upload of EHRs directly from sensors.
  - 5G will bring more extensive computing capabilities and enable a health-specific Internet of Things.
- Last but not least, **focus on the patient.** Patients are at the center of the drive for more accessible trials, with the aim of lowering the patient burden and making the trials about them, rather than focusing on commercial or scientific interests.

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WE'RE ALL IN THIS TOGETHER

The Need for Truly Passive Patient Monitoring to Change Healthcare

by Levie Hofstee

The chance of winning the lottery during a lifetime is 1 in 13,983,816.[1] The possibility of getting diagnosed with a chronic illness during that same lifetime is 60%.[2] Let that sink in for a moment. More worrisome still is that 40% of adults will get two or more chronic diseases,[3] and 20% of all chronic diseases relate to the central nervous system (CNS).[4] CNS diseases include multiple sclerosis (MS), Alzheimer's disease (AD), depression, and Parkinson's disease, to name a few. In the US alone, such chronic diseases are the leading cause of death and disability as well as the leading driver of US $3.5 trillion in annual healthcare costs.[5]

To face this immense problem, many different areas of healthcare require reorganization. One key aspect that must be addressed as a priority is how we assess patients. Being able to properly assess a patient's health and disease status is important as it allows us, among many other things, to develop new and better treatments and medications more quickly.

Given the fast progression of current technologies, assessing patients would seem to be a simple affair, but that is not yet the case. If obstacles to the process were only technical, that might be so. However, ultimately, optimal patient assessment depends on people's willingness to change, as not all people support innovation. Not everyone wants to fully embrace new possibilities and available technologies to improve assessment of a patient's condition. This lack of support results in cumbersome regulations and makes for slow adoption.

For those who see the need for better assessment tools, my company is building a solution. Neurocast is working on a platform that enables remote monitoring of patients, without the need for active patient involvement. By turning everyday digital interactions into medically approved outcomes, the platform enables physicians and researchers to unobtrusively measure the effect of the disease on an individual patient's daily life.

Assessing Patients

Accurate patient assessment in CNS diseases is not an easy task. Many of the tests available have not changed much since the 1980s and have serious shortcomings. For example, if neurologists, within their clinic or within a clinical trial, want to measure an MS patient's disease progression, they will, in addition to relying on their expertise as a specialist, use a number of long-accepted "gold standards" to obtain a scientifically verified picture of the patient.

Accurate patient assessment in CNS diseases is not an easy task. Many of the tests available have not changed much since the 1980s.

In the case of MS, neurologists primarily use the Expanded Disability Status Scale (EDSS),[6] developed by John Kurtzke in 1983, a method intended to quantify disability due to MS and monitor changes in the level of disability over time (see Figure 1). The EDSS ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Scoring is based on the neurologist's structured examination of eight functional systems. Similar scales, of similar age, are used in the assessment of other CNS disorders.

Another common (and more objective) way of determining patient status and disease progression within the field of MS is the use of magnetic resonance imaging (MRI) data.[7] The images produced allow doctors to see lesions and the lesion load in patients' brains. Lesions show up as light or dark spots, depending on the type of damage and the MRI settings. Analyzing the visible changes in the brain and spinal cord may help assess whether the disease is active and can confirm current treatment and drive future options.

Figure 1 — Expanded Disability Status Scale example.

In conjunction with these tests, to obtain a more complete picture of a patient with MS, secondary outcome measures, such as the degree of fatigue, level of depression, problems with fine motor skills, walking ability, and changes in cognition, have become increasingly more important. Various gold standards, often in the form of questionnaires or physical or mental tests, are used for these assessments.[8]

The Shortcomings of Traditional Methods

Traditional methods do not usually provide an accurate reflection of patients' real-life experiences. After all, patients visit a doctor only once or twice a year. Moreover, the limited time (10-15 mins) that the specialist has with the patient is insufficient to employ many of these traditional methods. Similarly, within clinical studies, the number of patient visits during the runtime of the trial is limited and collecting patient data this way is a costly affair. A trial costs a median of $41,117 per patient and $3,562 per patient visit. During a clinical trial, numerous visits are needed. A substantial portion of these costs relate to data collection and data management.[9]

Besides these quantitative shortcomings, there are also many qualitative shortcomings. To take MS as an example once more, the EDSS score is considered too subjective, not sensitive to subtle changes, and with too heavy a focus on ambulation. As for MRIs, the number of lesions shown on an MRI scan doesn't always correspond to the severity of symptoms, or even whether a person has MS. Not all CNS lesions are due to MS, and not all people with MS have visible lesions.[10] The need to complete a number of tests to gain a full patient picture to understand a complex story and overcome the potential unreliability of subjective tests is burdensome to patients, clinicians, and researchers.

The overall shortcomings of EDSS (and other scoring scales), MRIs, and other secondary outcome measures are similar: the methods used are obtrusive for patients, require the patient's physical presence, are labor-intensive and costly, and provide potentially biased data, often with large data intervals, due to the infrequency of clinical visits.

The Need for Real-World Evidence

Given the conceptual and physical pitfalls of utilizing traditional methods, there is a great need for more objective, less obtrusive, and more granular data. Data collected from the daily lives of patients, called "real-world evidence" (RWE),[11] enables obtaining a more holistic picture of patients' status with regards to their disease progression. This more complete picture could eventually enable prediction of the course of chronic diseases. Furthermore, RWE offers all parties involved endless opportunities for innovation, including:

- **Pharmaceutical companies.** RWE enables the identification of unmet needs, utilizes novel data streams, uncovers underlying disease mechanisms, and can optimize clinical trials. It can also improve market access because it can enhance understanding of the patient journey through the disease course, potentially improving overall outcome for patients.
- **Healthcare providers.** RWE enables better and more informed clinical decision making, through data-driven and evidence-based methods and systems.

- **Payers.** RWE enables improved management of cost of care and makes possible insights for personalized reimbursements driven by the actual value that the therapy delivers to the patient.
- **Regulators** (e.g., US Food & Drug Administration [FDA] and European Medicines Agency). RWE helps improve post-market authorization, safety, and risk mitigation assessments.
- **Patients.** RWE is tremendously beneficial to patients because it enables next-generation healthcare, such as optimized monitoring, personalized medicine, and precision interventions.

Gathering validated data from the daily lives of patients enables a focus on patient care pathways and the development of integrated solutions. For the business stakeholder (usually a pharmaceutical company), the popular phrase "moving beyond the pill"[12] will be within reach for the first time. RWE also helps in building new value propositions. It sparks partnerships between life science companies and companies embedded in people's daily routines (e.g., Apple, Tesla, Facebook) and provides the potential for the latter to move toward healthcare.

A Changing "Real World"

Given the abundance of opportunities afforded by RWE, it is no surprise that many life science companies are pivoting in this direction. An obvious first step is to digitize the current gold standards, by, for example, creating a digital version of medical questionnaires or by having patients do a walking test at home with an activity app.

However, it is not as simple as it seems. We are living in a world that is moving toward becoming completely digital, not merely one that is digitizing. "Digitizing" implies the translation of current approaches to digital technologies, while "going digital" requires a complete rethink of the status quo. Thus, we need to reimagine value chains and drive innovation before deploying innovative digital technologies.

Much has changed technically, but also socioeconomically since the adoption of many of the so-called gold standards. As perfectly described in Eric Topol's bestseller, *The Patient Will See You Now*, the idea that healthcare providers are in control of the patient journey has long been outdated.[13] The concept of customer centricity is finally finding its way to healthcare.

Truly Passive Patient Monitoring

As mentioned, my company is working on a truly passive patient-monitoring platform. We are accomplishing this by turning everyday digital interactions into medically approved outcomes, enabling physicians and researchers to unobtrusively measure individual patients' performance in daily life.

Today, we are focusing on data collected via smartphone, smartwatch, and computer usage (e.g., the way you type tells a lot about how you feel). In the future, such digital interactions can take place anywhere. After all, we may assume that the repetitive pressing of an elevator button is not an expression of joy, but rather one of stress, anger, or fatigue.

And, clearly, technology is now inseparable from how we live our lives. For example, we use our smartphones 80-100 times per day, and if we accidentally leave home without our phone, we go back to pick it up.

Our clinical research shows that everyday smartphone interactions hold valuable and novel information. After all, smartphone use requires a myriad of mental and physical functions likely to be affected by MS or other neurological disorders. Consider, for example, the steps required for sensing, interpreting, planning, moving, and executing. To access and analyze this data in a nonintrusive, safe, and effective way, we have developed the Neurocast RWE platform, which includes the Neurokeys smartphone app.

Neurokeys replaces the native smartphone keyboard with our intelligent Neurokeys keyboard. This enables us to analyze typing behavior along with profile, sensor, and activity data (see Figure 2). Altogether, millions of data points per patient, timestamped by the millisecond, are gathered in a real-world setting, ready to be analyzed.

With our statistical and artificial intelligence models and algorithms, we provide our healthcare industry partners with insight into the *mental, physical, and social performance* of patients suffering from chronic disease.

Patient Centricity: A Chance to Do Better

Frequent engagement with patients has strengthened our belief that even though we spend all day developing innovative technology, our focus, above all, should be on the *people who use that technology*. These people

Figure 2 — Neurocast's Neurokeys app.

happen to suffer from a life-changing chronic illness but are also just a father or a mother, a colleague, or a friend. And while they are forced to live with a life-changing chronic disease, this shouldn't mean they needlessly have to be confronted with it every day, that they have to compromise their privacy, or that they have to accept technical or economic barriers.

It is vital to know precisely how patients are doing for research purposes, but this can also be accomplished in a way that guarantees patient privacy. Our privacy model is based on patient consent; patients own their data, and they decide with whom they want to share it, for how long, and under which circumstances.

For example, Neurocast does not collect data that can be traced back to a person's identity. Our systems are set up to make it impossible for us to collect data that can be used to identify a particular individual, such as name, birthday, or precise GPS location. Importantly, we look at how people type and never what they are typing.

Privacy and security are often linked in a single phrase, but they are really two different concepts. In addition to our philosophy on user privacy and the technical implementation to make that philosophy reality, we do everything we can to provide the best possible security infrastructure. Both the databases themselves and all traffic between these databases are heavily encrypted on multiple layers. Besides that, we have carefully examined the processes for handling this data. Access to data is limited to a select number of employees, all of whom are frequently trained in security protocols and abide by ISO 27001 guidelines.[14] With all these privacy and security measures, Neurocast not only meets requirements such as the EU's GDRP and the US's HIPAA, but also passes strict standards set by the pharmaceutical industry.

The real customers of any healthcare innovation designed to help manage a chronic illness should be those suffering from a chronic illness. Measuring a chronic illness should be, and can be, done completely unobtrusively, with privacy and security embedded by design — and this technology should be available to everyone.

The Validation Challenge

Developing innovative products in close consultation with customers is sufficient for most markets. That is not the case in the medical world, which requires reliable and valid tests and products. After all, it is difficult to treat a patient if you can't trust that the thermometer is giving you the right temperature every time you use it.

Traditional standards have been interpreted and implemented for years. However, many new solutions have not yet been medically validated. In fact, more than 300,000 health apps have been developed thus far, but only a small percentage has been studied, and evidence tends to be low quality for those that have been studied.[15] For example, a recent study of mental health apps shows that only 1.3% of new applications actually have medical validation.[16] In general, the lack of medical validation of health apps makes it difficult to reliably implement them in a clinical setting.

Because validation is necessary for proper substantiation and affects the speed with which new technology can be accepted and implemented, we have defined the Neurocast validation pathway (see Figure 3).

The pathway has four types of validation: customer, technical, real-world, and medical. For each type of validation, relevant questions can be posed to ensure that a new technology satisfies that validation. For example, questions might include:

- Is the technology technically feasible and reliable?
- Is it useable and accessible?
- Does it adapt to/respond to real-world variations?
- Is it reliable, valid, and responsive to change over time?

Let's take a closer look via the four types of validation:

1. **Customer validation: do we meet customer requirements?** For example:
    - *Patients.* Is user experience up to par, and are patient interests safeguarded?
    - *Companies.* Are outcomes validated, and is the technology reliable in large patient groups?
    - *Healthcare providers.* Do physicians agree on the interpretation and implementation?
    - *Regulators.* Will the technology meet regulatory and industry standards?
    - *Payers.* Can we provide sufficient proof for reimbursement, without disclosing unnecessary information?
2. **Technical validation: how do we guarantee that the infrastructure and incoming data are reliable?** For example:
    - Is the infrastructure working properly?
    - Is the data coming in properly?
    - Is the data coming in as expected?
    - If anything is wrong, are the escalation procedures working properly?
3. **Real-world validation: does it matter that there is no doctor present during data collection?** For example:
    - Can we assure the right person provides the data?
    - Is the user walking or in a car? Do we need to make adjustments depending on the answer?
    - What kind of device is being used? Do we need to make adjustments on a device level (e.g., due to differences in makes or models)?
    - What are the settings of the device in question? Do we need to make adjustments on a device settings level (e.g., due to personal preferences of the user)?
4. **Medical validation: can we match and outperform the traditional methods?** For example:
    - Can we differentiate healthy individuals from persons with a specific disease, such as MS?

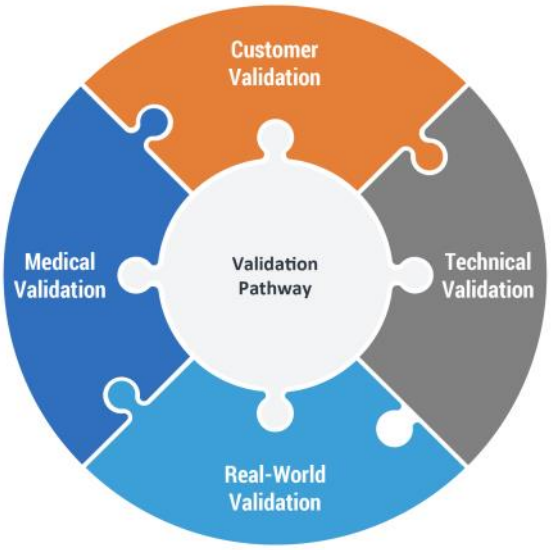

Figure 3 — Neurocast validation pathway.

- Can we correlate with the existing gold standards at a single point in time? That is, can we correlate by comparing our keystroke dynamic features to data collected from an outcome measure at a single point in time, rather than matching changes in our data to changing outcome measurements over time?
- Can we show agreement with a clinically valid change as measured by change detected by the gold standards?
- Can we outperform the gold standards and predict changes in disease course early by identifying early warning signs?

Companies developing innovative healthcare technology must proceed thoroughly and with dedication if they are to convince healthcare stakeholders to implement new ways of measuring disease progression. The Neurocast validation pathway provides a controlled and four-dimensional approach.

A Medically Validated Solution

The Neurocast RWE platform is medically validated in collaboration with Amsterdam UMC, a leading medical institute. Currently, Neurocast's technology matches most known gold standards for MS outcome measures, such as cognition, hand-eye coordination, fatigue,[17] and overall disease status. For examples of keystroke measurement analysis, see Figure 4.

In Figure 4, Plot A compares the keystroke data between healthy subjects (HC) and MS patients. One

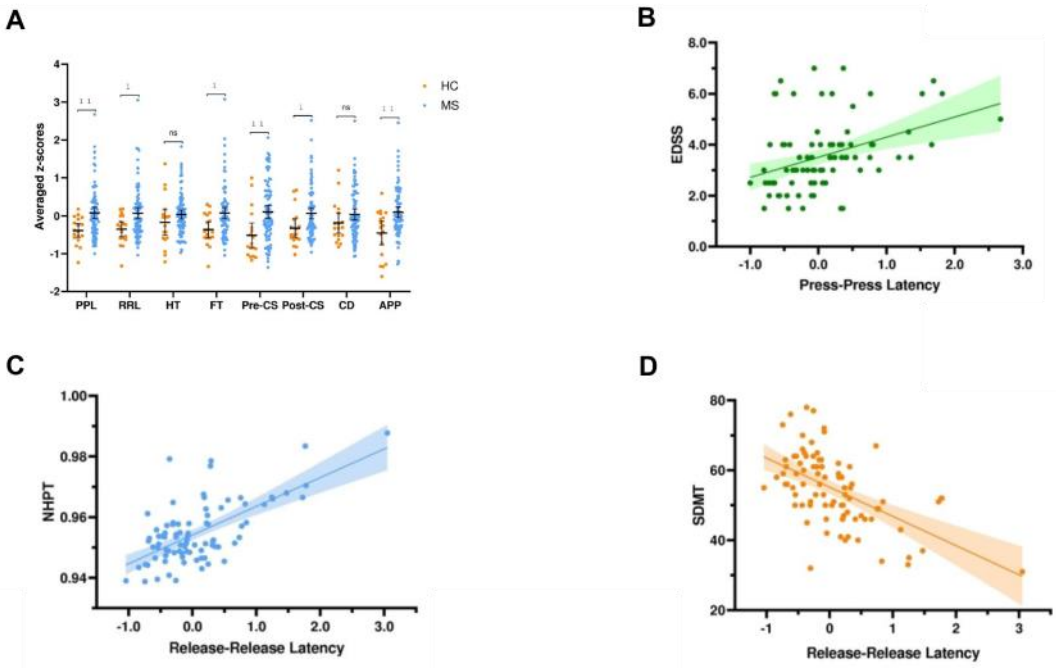

Figure 4 — Statistical analysis of keystroke dynamics performed on people affected by MS using the Neurokeys keyboard.

can observe that healthy subjects have a faster typing rhythm with respect to the MS group. Plots B, C, and D show a linear correlation, or relationship, between features engineered from the typing behavior with the gold standard currently used by clinicians to assess the degree of disease.

Being medically validated in one disease doesn't automatically mean that a technology is reliable and valid for others. Cognitive decline, for instance, should be interpreted differently in people suffering from MS than in those who have AD. It is only logical, then, that a technology must demonstrate that it matches disease-specific standards. Therefore, medical validation per therapeutic area is needed.

Neurocast does not randomly expand to new therapeutic areas. The primary focus is on areas related to the CNS and ones where a patient's mental, physical, and emotional state can be measured. By limiting our focus, we assure a good technological fit. In addition to MS, we are currently expanding into dementia, where AD is the most prominent condition. There is a large unmet need for early detection and diagnostic identification to facilitate research and clinical trials focusing on developing further understanding of, and potential treatments for, this disease. Not only is AD a good technological fit, it is also hugely impactful. Consider that one in three people reading this article will fall prey to AD during their lifetime.[18]

The future of disease assessment is one that utilizes change in an individual's behavior as the new (and very personalized) standards. If healthcare really aims to put patients first, it needs to stop putting patients in boxes of syndromes, in effect, using a one-size-fits-all yardstick, where each box comes with its own methodologies and measures. Instead, healthcare should consider the patient's perspective and how each individual is doing mentally, emotionally, and physically, and then translate that information to disease evaluation.

Changing the Status Quo Demands Joint Effort

We believe that by translating everyday digital actions into medically relevant values, we can monitor many aspects of people's health completely unobtrusively, with privacy and security in mind.

By doing our work with respect for patients, without losing sight of other stakeholders' interests, we hope to be able to make a positive contribution to a much-needed transformation. This transformation is neither about our company nor about technology. It's about

change and the need for all stakeholders to work together to improve an essential aspect of our lives: being able to live in good health. Ideally, all before there is even any need to start labeling people as patients.

But before we get there, we will have to jointly create a world in which we shape healthcare around people instead of forcing people into a funneled system. Fortunately, many people and organizations are dedicated to turning these challenges into opportunities. For example, companies such as IQVIA,[19] a leading global provider of health information, are innovating the way we look at health data and how we manage and exchange that data; people within regulatory bodies are trying to accelerate the adoption of new technology by setting up special task forces; futuristic hospitals such as Mercy Virtual Care Center,[20] the world's first hospital without beds, are seeking new solutions to care; companies such as Byteflies[21] are dedicated to transforming the way we unobtrusively gather medical-grade health data by using wearable sensors; and pharmaceutical companies are investing heavily to move "beyond the pill."

If the COVID-19 pandemic has taught us anything, it has shown us that it's time to do things differently. We need to change the system from reactive to proactive and work together to find a solution. Being able to measure disease indicators well enough to determine patient status is an essential part of that turnaround. Or, as we say in Dutch: "Meten is weten." ("Measuring is knowing.")

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IT TAKES A VILLAGE

While the Health Economics May Look Compelling, Who Pays for mHealth, and Why?

by Heléne Spjuth

The World Health Organization (WHO) has defined mHealth as the "use of mobile and wireless technologies to support the achievement of health objectives"; in this article, mHealth refers specifically as the practice of medicine and public health supported by mobile devices, such as mobile phones, tablets, personal digital assistants, and wireless infrastructure. mHealth encompasses all applications of telecommunications and multimedia technologies for the delivery of healthcare and health information. As such, mHealth is a subset of eHealth (telehealth is another subset, which focuses on remote access to care functionality; there are some overlaps among these subsets). mHealth also covers the use of mobile interfaces for patient self-care outside a care setting and within a hospital setting (e.g., by care personnel), allowing patients to benefit from mobile technology as well. Note here, however, that we distinguish mHealth from health/wellness apps, such as sports and fitness activity tracking, diet and nutrition, weight loss coaching, hospital selection, and appointment tracking, which are not covered in this article.

There is consensus among healthcare stakeholders that mHealth interventions may reduce the cost of healthcare delivery by decreasing time to diagnosis, addressing inefficient practices, limiting the need to transport patients and healthcare workers, reducing the length of hospital stays, maintaining patients at home instead of in a costly healthcare facility, and so on. But despite optimism about mHealth as a cost-effective solution to deliver care, especially for chronic diseases such as diabetes, respiratory and cardiac diseases, and dementia, the incorporation of mHealth into established healthcare systems (i.e., healthcare providers reimbursed and financed by taxes or insurance premiums) has been slow. Many meta-analyses cite mHealth implementation constraints in reimbursement regimes as one of the top barriers, alongside a lack of evidence for mHealth's having a more scalable, sustainable impact on health indicators.

New players entering the healthcare market are soon made aware that healthcare is a rather slow adopter of new technologies, which can be a frustrating awakening, especially for those that come from fast-moving sectors like the mobile industry. Technology in healthcare is often a matter of life and death. Hence, long and complex regulatory processes are involved in getting new treatments, drugs, and medtech products and solutions approved as efficient, reliable, and safe. The relatively slow adoption is due not only to the need for proof of safety, efficiency, and value but also to healthcare's conservative approach to providing medical treatment. Moreover, complex political decision making and funding regimes affect healthcare governance.

In the current world environment, the COVID-19 pandemic has driven people, organizations, and governments to increasing digitalization as everyone tries to find alternatives to face-to-face interaction in their day-to-day lives and businesses. This increasing digitalization also applies to healthcare. Telemedicine and mHealth have played important roles in keeping patients who do not need critical care out of healthcare facilities in order to minimize the risk of unnecessary exposure to the coronavirus. During the pandemic, policy makers in many countries have relaxed obstacles to the increasing use of mHealth, such as long-standing healthcare regulations, including reimbursement constraints. In fact, in the US, Medicare has granted waivers to provide more flexibility in using telehealth services. We will likely continue to see wider use of mHealth in established healthcare post-pandemic.

Despite a lack of solid evidence, most stakeholders agree that the health economics of mHealth look compelling. If, however, mHealth implementation expands post-pandemic as an integral part of established healthcare over the long term, the question then becomes who should pay for mHealth. The answer relies primarily on two parameters: who benefits economically from mHealth and who bears the risks of healthcare costs.

Understanding the Healthcare Ecosystem

The ecosystem of any healthcare system is large and complex, encompassing many different stakeholders that vary widely among regions and between healthcare systems. A simplified analysis of this ecosystem identifies its stakeholders as consumers/patients, policy makers, research centers, payers, providers, and the industry (i.e., vendors supplying pharmaceuticals, healthcare devices, and medical equipment). All these stakeholders, in different ways, benefit economically from mHealth services and, hence, play a role in the funding and implementation of mHealth. To incorporate mHealth into established healthcare systems, it is essential to understand the perspectives of all stakeholders and to secure their collaboration and support.

Consumers/Patients

Although mHealth will benefit consumers' health and well-being, consumers entitled to established healthcare don't bear the risk of healthcare costs and will most likely not be willing to pay for mHealth solutions that exceed the cost for affordable wellness apps and wearables. Consumers will instead expect mHealth solutions, such as remote monitoring devices, diagnostic and treatment support, and telemedicine-enabling solutions, to be incorporated into the established healthcare system without any additional charges. Even though it could be argued that consumers would benefit economically by improved health and reduced loss of income due to illness, their willingness to pay for mHealth services will be limited. However, to be able to meet the rising costs of healthcare in the future, this situation must change, and consumers must take more accountability for their own health and, thus, health expenditures.

Policy Makers

Policy makers are, among other things, responsible for public health and enabling cost-effective healthcare. Therefore, they have an economic interest in creating optimal conditions for the implementation of mHealth in terms of both infrastructure and regulatory frameworks. In tax-funded healthcare systems, policy makers also bear the economic risk of healthcare costs. Moreover, policy makers play an important role in enabling reimbursement for mHealth. As an example, some countries still have regulations defining a medical act as occurring only when both the patient and a physician are present in the same physical location; reimbursement is obviously possible only if a medical act, as defined, took place. With advancing technology solutions, policy makers must work to change such regulations.

Research Centers

In addition to taking part in the development of mHealth solutions and services, and in the evaluation of their long-term efficiency and safety, research and academic centers may benefit from, and have an interest in, using the data collected through mHealth apps and devices. As a result, research centers might be willing to pay for the data. However, given that this stakeholder group depends on funding from others and, typically, does not generate its own revenues, its financial capability will be limited.

Payers

Healthcare funding regimes are complex and differ greatly among countries and between healthcare systems. In more developed countries, governments (through taxes imposed on citizens) or private insurers (through premiums from their policyholders) provide most of the financing for healthcare. Limited elements of cofinancing through patient fees and, in some countries, a degree of funding by employers are variations of this funding regime. In emerging countries, healthcare for much of the population is funded out of the pockets of the patients, although wealthier citizens usually have some form of healthcare insurance.

Governments and health insurance companies could benefit significantly from increasing use of mHealth solutions, as the faster diagnostics, personalized care, reduced length of hospital stays, and improved clinical outcomes that these solutions would likely make possible may both reduce patients' need for care and total healthcare costs, as well as improve public health.

Providers

When it comes to healthcare providers, the economic benefits of mHealth depend on how the healthcare system where they operate is reimbursed and what risk they bear for the cost of care. Most current reimbursement models are designed with traditional healthcare in mind (i.e., face-to-face interactions between healthcare providers and patients) and are based on the interactions (services) between the provider and the patient.

Providers are reimbursed when a service has taken place, either by the funding government or by patients through their insurers.

The most common reimbursement model is fee-for-service. In this model, payers reimburse providers based on the services (tests, procedures, visits, hospital days, etc.) carried out on behalf of a patient over a defined period. Usually, the fee is set based on an estimated but generalized cost for a service. Determining the actual cost of every different service would necessitate an overwhelmingly complex model, and, given all the different factors that affect the cost of any healthcare service, calculating the real cost would be almost impossible. Some critics argue that the fee-for-service model, in which providers (and patients in government-funded systems or with insurance) bear little financial risk or accountability, incentivizes physicians to order more tests and procedures, as this will generate more income. Consequently, this model can encourage overutilization by both patients and providers and, therefore, lead to increasing overall healthcare costs over time for the payer. In addition, in a fee-for-service model, the economic incentives for healthcare providers to order only necessary services or to recommend mobile solutions that don't include a reimbursable interaction with a provider are limited, as such actions will decrease their revenue.

To incorporate mHealth into established healthcare systems, it is essential to understand the perspectives of all stakeholders and to secure their collaboration and support.

At the other extreme is the capitation or global budgeting model, in which healthcare providers are reimbursed a fixed fee for every patient for whom they are responsible (per capita) within a set time frame, whether or not the patient receives care and regardless of the cost of any treatment that the patient receives. Capitation, a quality-based payment model, is intended to create a system that fosters efficiency and cost control, while providing incentives for better healthcare. The counter argument is that capitation models may encourage undertreatment.

Between the fee-for-service and the capitation or global budgeting models are a vast variety of reimbursement models, with various degrees of passing the financial risk burden from payers to providers. Some other examples of quality-based reimbursement models, in which the risk is passed on to the provider, are:

- **Pay-for-coordination.** To manage a unified care plan for patients and to ensure efficiency and quality, a primary care physician leads and coordinates care between multiple providers and specialists.
- **Pay-for-performance.** Healthcare providers are incentivized to meet certain quality and efficiency indicators, and reimbursement is based on the achievement of these performance measures.
- **Episode-of-care payment.** Healthcare providers are reimbursed a set amount to pay for a specific episode of care. Providers keep any realized net savings but are accountable and bear the financial risk of any complications within a set period.
- **Shared savings program.** A group of physicians (e.g., accountable care organizations) provides population health management through coordinated team care and any realized net savings are returned to the provider.

In countries and systems where established healthcare is reimbursed, in whole or in part, through any of the quality-based reimbursement models, the incentives for providers to pay for mHealth will most likely be higher, as providers under these models bear the financial risk. As such, the providers are the economic beneficiaries of the more cost-effective mHealth solutions, which may lower their cost of delivering healthcare.

The reimbursement models mentioned here constitute just a fraction of the innumerable types of existing reimbursement models, and the way in which healthcare cost risks are distributed between providers and payers varies from one model type to the next.

Industry

Vendors that supply medicines and medical devices and equipment could benefit economically from mHealth services. For example, a quicker diagnosis could mean that patients receive medicine or an

implanted device sooner. mHealth apps that provide medical reminders would be beneficial to pharmaceutical companies, as they would encourage patients to stick to their medication regimens. The industry stakeholder group is a financially strong player, willing to invest to increase the value of its products and to offer added value free of charge or as a bundled deal in exchange for the promise of higher market share in a given segment. In recent years, partnerships and innovation agreements between industry and established healthcare have become more and more common, with products being bundled with services and solutions. The industry has taken a role in the co-funding implementation of mHealth services in established healthcare systems.

Conclusion

This article has defined the healthcare ecosystem and the various reimbursement models in their simplest forms; there are many variations and combinations of each that result in unique circumstances that will serve either as barriers to, or enablers of, mHealth's efficient implementation. To be successful, mHealth vendors entering the market must do their homework to understand the needs and drivers of key stakeholders in the healthcare ecosystem and which entities bear financial risk. Next, they must evaluate which country, region, or healthcare system they want to approach. The US, the UK, Germany, Denmark, Canada, and the Netherlands are generally perceived as attractive markets for implementing mHealth services, some due at least in part to market size, but collectively because of access to investors and clinicians' acceptance of apps. However, these markets vary greatly both in how healthcare is governed as well as in how it is financed, so the approach will have to be adjusted accordingly.

In countries or systems with fee-for-service reimbursement models, the payer will most likely be the government or insurance companies, but with capitation or other quality-based models, the payer is more likely to be the providers. The trend of moving from fee-for-service to reimbursement for quality and value means that mHealth providers must aspire to prove the long-term value, even post-pandemic, of mHealth's being incorporated into reimbursable healthcare services.

The bundled agreements, in recent years, between industry stakeholders and established healthcare systems can also play a role in incorporating mHealth services into the established healthcare system, meaning that mHealth vendors should aspire to also enter partnerships with industry stakeholders. An upside for industry stakeholders is that they already have a strong and established network with important healthcare ecosystem stakeholders and have existing sales channels.

Integration of mHealth services into the established healthcare system will not depend on only one stakeholder group but will be a team effort involving the entire ecosystem. This integration effort will require regulatory and operational changes, partnerships, patience, and perseverance. Research centers will play an important role by conducting studies to provide policy makers with evidence of the long-term efficiency and benefits of mHealth. Policy makers, in turn, will have to bring about regulatory changes to enable market access for mHealth services by minimizing barriers in infrastructure and reimbursement regimes. They will also have a key responsibility to inform and educate citizens about how to be more accountable for their own health and well-being. Otherwise, patients' contribution to the funding of mHealth services will continue to be limited to low-cost wellness apps. Payers must secure flexible reimbursement models that incentivize preventive and remote healthcare. Providers will have to make operational changes, with a shift away from traditional, reactive healthcare based on treating patients in face-to-face interactions. Finally, if the ecosystem collaborates, even post-pandemic, the integration of mHealth into established and reimbursed healthcare services will continue and expand.

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— Doug Mikaelian
VP Business Technology,
Dairy Farmers of America

"The information technology revolution continues to change how businesses work and how people work in and with them. Today's demands on software to provide useful, usable, secure, and scalable services stress all aspects of systems development. These include architecture, technology selection, product development, and lifecycle management. Cutter provides comprehensive coverage for these crucial topics — through research reports and customized virtual training delivered globally — helping us to understand needs and solutions that span traditional silos."

— Eric Schoen
Director of Engineering, i2k Connect LLC
Former Chief Software Architect,
Schlumberger

"Thanks to Cutter´s experts, in a short time we have been able to:

- Improve our capabilities, using the contract scorecard for outsourcing
- Gain key insights and practical strategies for responding to challenges we face in building trust and partnerships within the organization and outside our institutional borders.
- Improve our methods for working with people and anticipating the challenges of cultural transformation within our organization.
- Have immediate access to key 'experts' at critical times, who spend quality time with our teams, provide state-of-the-art orientation, and help us implement projects.
- Implement agile, effective, and articulated innovation around a common vision for achieving quality education in Mexico."

— Arturo Cervantes
Director General of Information Systems
for Evaluation Results, National Institute for
Educational Evaluation, Mexico

CUTTER Business Technology Journal

About Cutter Consortium

Cutter Consortium is a unique, global business technology advisory firm dedicated to helping organizations leverage emerging technologies and the latest business management thinking to achieve competitive advantage and mission success. Through its research, training, executive education, and consulting, Cutter Consortium enables digital transformation.

Cutter Consortium helps clients address the spectrum of challenges technology change brings — from disruption of business models and the sustainable innovation, change management, and leadership a new order demands, to the creation, implementation, and optimization of software and systems that power newly holistic enterprise and business unit strategies.

Cutter Consortium pushes the thinking in the field by fostering debate and collaboration among its global community of thought leaders. Coupled with its famously objective "no ties to vendors" policy, Cutter Consortium's *Access to the Experts* approach delivers cutting-edge, objective information and innovative solutions to its clients worldwide.

For more information, visit www.cutter.com or call us at +1 781 648 8700.