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Mobile health: the power of wearables, sensors, and apps to transform clinical trials

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Mobile technology has become a ubiquitous part of everyday life, and the practical utility of mobile devices for improving human health is only now being realized. Wireless medical sensors, or mobile biosensors, are one such technology that is allowing the accumulation of real-time biometric data that may hold valuable clues for treating even some of the most devastating human diseases. From wearable gadgets to sophisticated implantable medical devices, the information retrieved from mobile technology has the potential to revolutionize how clinical research is conducted and how disease therapies are delivered in the coming years. Encompassing the fields of science and engineering, analytics, health care, business, and government, this report explores the promise that wearable biosensors, along with integrated mobile apps, hold for improving the quality of patient care and clinical outcomes. The discussion focuses on groundbreaking device innovation, data optimization and validation, commercial platform integration, clinical implementation and regulation, and the broad societal implications of using mobile health technologies.

Keywords: biosensors; mobile technology; wireless; medical device; health care; data; clinical study

> If [one] thinks about the scientific revolutions that have occurred in history, they've been driven by one thing—the availability of data. From Copernicus to quantum mechanics, it's data that drives innovation.[1]
>
> John Quackenbush

Introduction

Mobile health technology enables the capture of massive amounts of patient-related data—such as physiological, behavioral, environmental, and imaging data—in a way that has never been possible before, and at a relatively trivial cost and high level of convenience that is likely to facilitate its widespread adoption.

The expense of collecting data has always been a key bottleneck of advancing biomedical research, restricting the amount of data collected as well as the number of organizations that could afford the expenses. Easing this choke point will likely usher a massive transformation with far-reaching ramifications. One can predict that, if gathering data becomes substantially less costly, we will ultimately have larger quantities of data. Several very large observational patient cohorts are already enrolling, such as the Precision Medicine Initiative, PCORnet,[2] Human Longevity,[3] 23andMe, the P4 Initiative,[4] and other initiatives internationally.[5] Individuals are increasingly involved in collecting data about themselves. There are 165,000 healthcare apps in Apple

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and Google stores, including approximately 40,000 for disease and treatment management.[6] Crowdsourcing platforms, such as Apple's ResearchKit™ (Ref. 7), and patient advocacy groups are helping to manage this activity and organize data in a way that is easily available to biomedical scientists. The result is a rapidly growing body of fine-grained data about sick and healthy individuals, data that promise to provide unparalleled insights into the etiology of diseases previously difficult to achieve because of the costs and methods of traditional research. The new data will also likely impact the culture of drug research and development (R&D) and the direction of basic and clinical research.

Wanting affordable innovation quickly, patients are embracing principles that they feel will help deliver it, including transparency, data sharing, free open access, and, importantly, control over their own data—which, historically, they have not had. But many patients are not bent on hoarding their data and are open to contributing them to biomedical research, as long as the process upholds the above-mentioned values; increasingly, it looks as if this will be the case.

Mobile health data are valuable; they comprise scores of parameters measured noninvasively, at high frequency, and under real-world conditions, quickly adding up to millions of data points that include signals that otherwise would be imperceptible with the tools of traditional drug R&D. The data can also greatly facilitate the development of disease models and an understanding of the complex behavior of biological networks. Mobile health data can be a valuable tool for drug discovery, as well as clinical research, even though they are unstructured and different from traditional clinical trial data. For example, while the data can inform about the status and performance of tissues and organs monitored, they may not be appropriate to test specific hypotheses. Extracting information embedded in mobile health data calls for mathematical tools such as artificial intelligence, network analysis, and advanced multivariate analysis, which have not previously been core competencies of the drug industry and will likely need to tap the expertise of specific scientific communities that have embraced open science to a far greater extent. This will help shift drug R&D culture from a proprietary mindset to one in which competitive advantage begins with the ability to extract better knowledge from open, shared data. Yet, for all their promise, mobile health data have not been embraced to support drug approval. The U.S. Food and Drug Administration (FDA) has been supportive of the technology,[a] which offers, among other benefits, the potential for real-time monitoring of trials and safety signals; however, skepticism is likely to linger until the data have passed FDA scrutiny.

Other challenges remain, such as the quality of mobile health data, the potential for incorrect use of devices, their reliability and validation, the protection of the data collected, and whether these data can successfully be used in clinical practice. To address these issues, the New York Academy of Sciences, in collaboration with leading clinical trials software firm Medidata Solutions, sponsored the conference "Mobile Health: The Power of Wearables, Sensors, and Apps to Transform Clinical Trials" on September 30 and October 1, 2015 in New York City. The conference brought together professionals from the fields of science and engineering, analytics, health care, business, and government to explore the promise that wearable biosensors, along with integrated mobile apps, hold in improving the quality of patient care and clinical outcomes. The discussion focused on groundbreaking device innovation, data optimization and validation, commercial platform integration, clinical implementation and regulation, and the broad societal implications of using mobile health technologies. The remainder of this report will highlight several of the conference presentations.

Key themes

Glen de Vries (Medidata Solutions) highlighted the importance of mobile health in clinical trials and previewed the key themes. He explained that the process of testing and approving medical therapies has largely remained unchanged for the past 50 years—clinical trial participants are still subjected to outdated tests and methodologies to evaluate the risks and benefits of new treatments, while the costs and complexity of drug development steadily increase. However, the pharmaceutical industry is in the midst of a renaissance. Mobile technology has become ubiquitous in everyday life and is shaping

[a]See, for example, http://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm and http://www.fda.gov/medicaldevices/digitalhealth/.

the way people think about personal health. Smartphones and activity trackers are now loaded with features that enable individuals to count the number of steps they take, monitor how much and how well they sleep, and remind them to take their medications on time. These tools are helping millions of people take a more active role in monitoring their own health and have the potential to make clinical trials safer for patients, while providing new, meaningful data to sponsors and regulatory agencies.

While traditional measurements, such as patient-reported outcomes (PROs) and the 6-min walk test, were once considered the gold standard, FDA officials have publicly recognized that clinical research processes can be improved by using digital tools that already exist. In fact, the FDA's recent request for stakeholder input on technology that enables remote observation clearly indicated that the agency is looking toward a future that very much includes mobile health tools, such as sensors, wearables, and smartphone apps.

De Vries discussed his examination, over the last 16 years, of the inherent limitations of existing clinical research processes and how he sought out opportunities to use technology to improve the quality of trial data and the experience of participating patients. Working on prostate cancer research at Columbia-Presbyterian Medical Center in 1994, de Vries experienced first-hand delays and inefficiencies of conducting clinical trials on paper. At that time, researchers did not have the wearable sensors or apps now available to capture real-time data and gain more insight into disease trajectory and patient response to therapy.

De Vries stressed that new technologies have enormous potential to improve the quality of clinical research and that researchers have an obligation to bring the best technology to bear for the development of new drugs, devices, and other therapies. To this end, the Medidata and New York Academy of Sciences conference aimed to foster an important dialogue on how the industry can use mobile health technologies to advance the science of drug development. De Vries stated that, although the use of mobile health technology in clinical trials is still in its early stages, the call for action is here and now, loud and clear. With continued support from the FDA and life sciences companies, mobile health and wearable sensors in clinical research will eventually become part of the standard practice in the drug development process. The ability to collect nuanced, meaningful data will ensure that patients—not just their diseases—are at the center of innovation, helping to bring treatments to the market in a way that is faster, less expensive, and addresses the everyday challenges of those who need them most.

Wearables: where we are now and where we are headed

In his keynote address, Ian Ferguson (ARM) discussed the opportunities and challenges in the use of wearable technologies for health care. He pointed out that increasing life expectancy and the rise of chronic diseases are placing significant pressures on healthcare systems across the world. According to a 2015 report[8] prepared for the Association of American Medical Colleges, the United States faces a demand for physicians that will exceed supply by up to 90,000 by 2025. In Japan, the specific healthcare needs of an older population has come into focus, as 26.7% of the population is now over 65 years old, and 40% of the population will be over 65 years by 2050.[9] Furthermore, the International Diabetes Federation estimated in November 2013 that the number of diabetes sufferers will increase nearly 50% from current levels to reach approximately 600 million in 2035, with costs to the healthcare industry estimated to be $630 billion.[10]

Technology has the potential to be a major component in efforts to mitigate these challenges. As of the end of 2014, Pew Research Center reported that 64% of adults in the United States owned a smartphone.[11] Initially used to simply make and receive phone calls, the smartphone is expected to become a gateway that channels a rich set of personal information to and from cloud infrastructure such as servers. Ferguson described an expression used at ARM—"big data starts with little data"—meaning that the smaller sets of data are the information from single sources, which, once aggregated across a large number of users, offers a massive opportunity for medical professionals and researchers to use qualitative data to facilitate research on specific conditions and prescription of treatments tailored to individual patients. According to Ferguson, although the first wave of wearable technology had little impact on the healthcare industry, the technology industry is highly effective at problem solving, and when left in isolation, can develop solutions that are looking for problems. Fundamentally, use cases

should drive the technology and not the other way around.

Ferguson stressed that some substantial challenges remain that still need to be solved. Specifically, (1) one size does not fit all—for example, a medical device for an 80-year-old individual should not require a complex smartphone interface; (2) improvement to technology—continued improvements in energy-efficient integration will, in turn, improve the size, weight, cost, and battery life of future components; (3) security—information must be transmitted securely, which may seem obvious but has implications for cost and battery life; the industry must not compromise on security, which is a non-negotiable functionality; (4) data ownership—Ferguson believes that consumers should be in charge of the data that come from their own body and should control who can be provided access to that information. In certain regions of emerging economies, there can be ratios of 50,000 individuals to one doctor, and in these cases, consumers may accept any terms in order to use a device that provides them with any information about their body vitals. However, in mature economies, consumers are more likely to want to know who is accessing their data and how these data are being used.

Leveraging mobile biosensor device technology to improve clinical trial outcomes and patient health

Lost in translation? A physician's perspective on the mobile health opportunity

The development of sophisticated wearables, biometric sensors, and health-related mobile applications has led many to predict the rapid integration of these technologies into clinical trials and everyday healthcare delivery. Indeed, the potential for these hardware and software products is vast and exciting. However, to successfully achieve this potential, developers and researchers must systematically address a number of practical barriers. In his presentation, John D. Hixson (University of California San Francisco) discussed three critical areas of attention with respect to these barriers, as discussed below.

First, mobile health developers must prioritize and demonstrate data accuracy, reliability, and integrity. In clinical trials, the credibility of the collected data is critically important; medical-grade data are essential, and they may often need to be validated against established gold-standard metrics. Using epilepsy as a chronic condition example, Hixson pointed out that the traditional method of collecting seizure counts is known to be highly inaccurate.[12] Many patients do not know when they have seizures, and yet self-report calendars are the mainstay of clinical trial data. Digital diaries have evolved dramatically over the past decade, but this information is fundamentally still self-reported and has not been systematically validated.[13] As a result, more clinical trial managers are hesitant to use this information for an FDA submission. Next-generation wearable device data offer an intriguing approach but, similarly, have yet to be validated. In the field of epilepsy, the technology goes well beyond simple fitness-based approaches using medical-grade information on body movements, heart rate variability, galvanic skin response, and temperature. To be useful in clinical trials, clinical validation (sensitivity and specificity improvements) and logistical/technical issues (long-term use, battery life, data transmission) will need to be addressed.

Second, developers must compare these newly available data sets to the existing outcome measures used in traditional clinical trials. In some cases, the value of the mobile- or sensor-based data may need to be justified within a traditional context. In most clinical trials, primary outcome measures have often been perpetuated by historical inertia, even if new approaches are available. As mentioned above, for epilepsy studies, monthly self-report seizure counts are the gold standard, despite the fact that the information is inaccurate.[12,13] However, there may be other pieces of data not currently being captured that would be important.[14] From this perspective, wearables may provide an opportunity to capture both traditional health metrics and novel data points such as daily notifications, medication reminders, adverse-events reporting, educational modules or coaching, and social networking. In particular, the current systems for assessing medication compliance and adverse event reporting are flawed;[15–17] there is opportunity, therefore, for mobile applications in clinical trials to generate superior data for an FDA submission.

Finally, innovators must concurrently experiment with new workflow and economic models for integrating novel data streams into clinical practice.

Although the FDA has not specifically provided clinical trial guidance, the agency has begun to recognize the momentum and value of mobile applications and wearables.[18] If the FDA continues to provide clarity and mobile solutions enter the clinical trial arena, how will this translate into clinical practice? Unfortunately, many of the innovative benefits promised by mobile health solutions do not immediately fit into the historic fee-for-service model, and these data points similarly have not traditionally been available in the daily workflow of doctors and nurses—both of these barriers need to be addressed. Alternative payment models may offer unique opportunities for testing the value of these new health metrics. Novel outcome variables, such as work absenteeism or productivity metrics, should be tested, and mobile health data need to be analyzed by healthcare teams quickly and efficiently. Hixson stated that, overall, an FDA precedent is critical, and simple risk avoidance has largely been to blame. Enterprising companies that directly engage with the FDA, new payor models, and large self-insuring employers may provide fertile areas of opportunity.

Commercial health applications of mobile biosensors and apps for expediting clinical discovery

The role of mobile technologies in innovative healthcare solutions

In his presentation, John J. Mastrototaro (Medtronic PLC) discussed commercial applications of mobile technologies for health care and clinical discovery. The healthcare industry is in the midst of a major transformation necessitated by burgeoning healthcare costs without commensurate improvements in care. In the near future, healthcare providers will be held even more accountable for positive clinical outcomes, and payment will be based on performance, rather than services delivered. Universally, healthcare companies are striving to improve clinical outcomes, expand access of care, and optimize costs and efficiencies. Mastrototaro stated that the challenge is how to best translate novel service models into value. Many experts believe the explosion of clinical data and the new technologies that provide, process, and translate that data will be integral to success.

Regulators and payers are pressing pharmaceutical and medical device companies for real-world clinical evidence, improved postmarket surveillance, and better solutions to assure that optimal clinical outcomes are realized. In order to achieve these goals, new approaches to disease management are being pursued, which include more frequent interactions with patients, typically through additional home-based sensing systems and remote monitoring protocols.

According to Mastrototaro, instead of patient interactions occurring solely at the time of a procedure or sale of a therapy solution, companies will likely need to drive toward a more comprehensive partnership with patients, providers, and payers, extending the scope of services and interactions to provide a continuum of care. Wearables and mobile technologies are facilitating access to real-time sensing parameters and transmission of data to support ongoing monitoring and analytics. Many medical technology companies, including Zephyr and AliveCor, have developed wearable and smartphone-based sensors to provide vital signs and other clinically relevant data. Algorithms can be synthesized to predict when interventions may be necessary, and population data can be used to better understand what therapeutic solutions work best in which cohorts of patients. For example, Cardiocom has successfully used home-based monitoring products with a telehealth system to manage heart failure patients following discharge from the hospital.[19]

Mastrototaro also discussed the potential of wearables, sensors, and mobile apps to revamp clinical trial design and postmarket surveillance. Adding remote surveillance to clinical trial design allows for easier patient recruitment because of lower patient burden, reduced trial costs for home monitoring versus in-clinic visits, and a more real-world design with much of the patient interaction occurring remotely from the patient's home. Ultimately, the goal of new care pathways aims to transition routine care from more costly environments (hospital, specialists) to less burdensome environments (local pharmacy, home), allowing the specialists to focus on patients with genuine need, while using alternative approaches for the management of patients with noncritical issues. Mastrototaro concluded that many opportunities exist to significantly improve healthcare delivery by leveraging the pervasive use of wearables, mobile technologies, and digital data.

The use of mobile sensor device technology in improving clinical trials

Michelle Crouthamel (GlaxoSmithKline) continued with a discussion on the unsustainability of the U.S. healthcare system. Although the United States provides high-quality health care, the current system is heading toward an unsustainable future.[20] The pressure to reduce cost and create affordable care has affected the entire healthcare ecosystem, including not only the healthcare providers but also the pharmaceutical industry. Today, the cost to develop and bring a medicine to approval has increased 10-fold from less than $200 million in the 1970s to now over $2.6 billion.[21] In order to create sustainable R&D, the pharmaceutical industry must transform and innovate to accelerate the clinical development process, reduce timelines and costs, and improve health outcomes.

Crouthamel discussed two opportunities where the pharmaceutical industry should consider using mobile health technology to improve the drug development process, of which the first is related to the recent consumer trend of using the smartphone as the personal health data hub for all electronic-source (eSource) data. Presently, health data are not collected in one centralized location but in many locations, such as electronic health records, personal health apps, and research databases. However, recent consumer trends indicate that many owners of smartphones and wearable sensors are using their devices to automatically track measures of their own health, including sleep, vitals, and exercise, and to easily access their personal electronic medical records through mobile apps, such as Track My Medical Records, iBlueButton® (Humetrix), My Medical™ (Hyrax), and Capzule PHR™ (Webahn). Personal genomic sequence data are also available to be downloaded and reviewed on an iPad,[22] and soon, most routine laboratory tests will likely be obtainable by consumers with smartphone kits.[23] If such trends continue, it is conceivable that mobile devices will become personal health data repositories and shift the data ownership from healthcare providers to patients.[24] A new way to conduct clinical trials will be to ask the study participants to share their data directly through their smartphones. In March 2015, Apple launched ResearchKit, which is an iPhone-based open-source platform that enables researchers to administer app-based research. Since its debut, the kit has demonstrated success of direct data collection from patients, with future potential of standardization and reusability of research apps across the industry. As the platform continues to improve, it may further streamline the data collection process and enable research standardization. Remote monitoring technology also offers similar benefits of speeding up data collection, improving data quality, and reducing trial costs. GlaxoSmithKline, in collaboration with the McLaren Group and Medidata, is working to develop real-time data capture and mobile health trial capability, with encouraging preliminary results.

The second opportunity Crouthamel discussed is to use digital technology to develop more quantifiable endpoints that will detect efficacy signals better than some of the patient- or physician-reported outcome questionnaires.[25] One way to increase endpoint sensitivity and potentially reduce study size is to collect objective performance measurements, for example, activity scores, range of motion, and sleep/wake cycles. Many quality-of-life questionnaires often include questions such as Can you walk 50 ft? or Can you climb stairs?. Instead of asking patients to recall what they can or cannot do, accelerometers can precisely measure the distance walked or steps climbed, which eliminates subjective data input. As the data become clearly quantifiable, the ability to differentiate between cohorts could be increased, which may allow reduction of the study size. However, developing an industry-wide and healthcare and regulator-accepted endpoint is not an easy task. As it took many years for the healthcare industry to establish the Unified Parkinson Disease Rating Scale (UPDRS) as the clinical gold standard for Parkinson's disease assessment, new endpoint adoption will likely require similar efforts and multiple trials where technology, pharmaceutical, research, and regulatory professionals collaborate.

The latest in mobile biosensor development and design for emerging clinical and healthcare applications

Mobile imaging, sensing, and medical diagnostics

Aydogan Ozcan (University of California, Los Angeles) discussed some of the emerging applications created by the use of mobile phones for the development of next-generation imaging, sensing, diagnostics, and measurement tools. The large

demand for mobile phones worldwide has driven rapid improvements in hardware, software, and high-end imaging and sensing technologies embedded in mobile phones, transforming the mobile phone into a cost-effective and yet extremely powerful platform to run, for example, biomedical tests and perform scientific measurements that would otherwise require advanced laboratory instruments.

Ozcan discussed the use of computation/algorithms to create new optical microscopy, sensing, and diagnostic techniques, which significantly improve the ability of existing tools to probe micro- and nano-objects, while also simplifying the designs of these analysis tools. For example, he introduced a new set of computational microscopes that use lens-free on-chip imaging and replace traditional lenses with holographic reconstruction algorithms. Basically, 3D images of specimens are reconstructed from their "shadows," providing considerably improved field of view (FOV) and depth of field, thus enabling large sample volumes to be rapidly imaged, even at nanoscale.[26] These new computational microscopes routinely generate more than one to two billion pixels (gigapixels), where even single viruses can be detected with an FOV that is more than 100-fold wider than other techniques.[27] At the heart of this leapfrog performance lies self-assembled liquid nanolenses that are computationally imaged on a chip.[28] These self-assembled nanolenses are stable for over 1 h at room temperature and composed of a biocompatible buffer that prevents nanoparticle aggregation, while also acting as a spatial "phase mask." The FOV of these computational microscopes is equal to the active area of the sensor array, easily reaching, for example, more than 20 mm^2 or 10 cm^2 by employing the state-of-the-art complementary metal-oxide semiconductor (CMOS) or charge-coupled device (CCD) imaging chips, respectively.[26]

In addition to this remarkable increase in throughput, another major benefit of this technology is that it lends itself to field-portable and cost-effective designs, which easily integrate with smartphones to conduct gigapixel tele-pathology and microscopy, even in resource-poor and remote settings where traditional techniques are difficult to implement and sustain, thus opening the door to various telemedicine applications in global health.[29,30] Some other examples of these smartphone-based biomedical tools include imaging flow cytometers, immunochromatographic diagnostic test readers, bacteria/pathogen sensors, blood analyzers for complete blood count, and allergen detectors.[30] These results provide important examples of how biomedical imaging and sensing significantly benefit from emerging computational algorithms/theories, revolutionizing existing tools for observing various micro- and nanoscale phenomena in innovative, high-throughput, and yet cost-effective ways.

Innovative design and development of mobile sensor device technology

Veena Misra (North Carolina State University) discussed recent breakthroughs in mobile sensor platforms that provide health-related activity monitoring and have the potential to provide a significantly more sophisticated understanding of human health. The United States has the highest healthcare costs in the world, with approximately 17% of its GDP dedicated to health care.[31] The majority of the healthcare costs are associated with management of chronic diseases, such as heart disease, asthma, and diabetes, for which effective management depends significantly on environmental, dietary, and lifestyle factors. While it is clear that solutions to fixing the healthcare problem will have to be multifaceted, the use of wearable technologies can play a significant role in managing chronic diseases, provided that the devices are reliable, accurate, long-term/continuous, and hassle free for the user. In recent years, there has been an explosion of wearable products on the market, which has validated the demand for technology by users. In the field of athletics, fitness, and increased productivity and connectivity, wearables are indeed making an impact. However, significant barriers exist for their adoption in health care, including, but not limited to, poor battery life, insufficient information, limited functionality, and low accuracy of sensors.

These challenges are being addressed by the NSF Nanosystems Engineering Research Center (NERC) for Advanced Self-Powered Systems of Integrated Sensors and Technologies (ASSIST) by building wearable, wireless, and comfortable systems that are self-powered by the human body and consist of multimodal health and environment sensors. These systems can provide medically validated information to users and inform lifestyle decisions, enable correlation of personal health

and personal environment, and lead to rapid and effective management of health conditions. ASSIST technologies are enabling continuous or long-term monitoring that can produce long-term health trends for individuals and create a paradigm shift in the understanding of many diseases and elucidate the role of environment on health.

Misra explained that, in order to achieve the self-powered feature of the wearable platform, power generation has to be maximized while power consumption has to be reduced. In ASSIST wearable platforms, the power is being generated by the human body in the form of body heat and body motion/strain. Power consumption is being reduced by employing subthreshold silicon electronics, ultralow power radios, and low-power sensors for health and the environment, such that the system never requires recharging. Beyond activity monitoring, ASSIST wearable platforms can provide real-time measurements of ozone and volatile organic compounds in the environment and critical corresponding health signals, such as wheezing, heart rate, electrocardiogram (ECG), and pulse oximetry. This functionality can address the needs of asthma management by providing users immediate assessment of respiration burden and environmental triggers, leading to rapid treatment and enabling effective correlation between health and the environment. ASSIST wearable platforms are also capable of noninvasive and minimally invasive biochemical sensing from sweat (glucose and cortisol), which adds to the users' health picture in addition to physiological sensors. ASSIST systems also provide vigilant cardiac monitoring through continuous ECG and motion sensing, with transmission to a smartphone-based aggregator. The body-worn platform is entirely powered by energy harvested from the body in the form of body heat or motion. Lastly, Misra discussed advancements led by NERC in the field of flexible materials, such as textile materials; data analysis, correlation, and causality are critical components of this work.

Managing mobile biosensor–generated data: analysis, infrastructure, and security

The beginnings of an open ecosystem in mobile health

Mobile technologies have the potential to revolutionize both the way in which individuals monitor their health and the way researchers are able to collect frequent, yet sparse, data on participants in clinical studies. However, as pointed out by Brian M. Bot (Sage Bionetworks), in order for data from these mobile devices to have maximal impact in a research setting, the development of systems to collect, manage, and broadly share these data is essential. A recent study[32] showed that over 75% of people surveyed would either probably or definitely share their personal health data with researchers. In possible tension with this finding is the fact that over 90% of this same sample felt that it was somewhat, very, or extremely important to have these data kept anonymous. This tension underscores the importance of the social constructs on which these systems are built in order to allow maximal utility to come from these data while minimizing adverse impact on individual participants. More specifically, the union of these systems and constructs must be an ecosystem built on trust.

Bot discussed Sage Bionetwork's launch in March 2015 of mPower™, a longitudinal observational smartphone-based study developed using Apple's ResearchKit, to evaluate the feasibility of remotely collecting frequent information from Parkinson's disease (PD) patients about daily changes in the severity of their symptoms. The study interrogates aspects of this movement disorder through surveys and frequent sensor-based recordings from participants with and without PD. These measurements provide the ability to explore classification of control participants and those who self-report as having PD, as well as to begin to measure the severity of PD for those with the disease. Benefitting from large enrollment and repeated measurements on many individuals, these data may help establish baseline variability of real-world activity measurement collected through mobile phones and may ultimately lead to quantification of the ebbs and flows of PD symptoms.

The onboarding and consent process of the mPower study focused on placing the participant at the center of the data collection, specifically by acknowledging possible risks both to individual participants and to subpopulations of participants, providing opt-in settings for sharing data collected in the study for secondary research, and by the development of an open research ecosystem built on a social contract between researchers and research participants. When given the option to share their data sparsely (with only study investigators) or more broadly (to qualified researchers worldwide), 78% of participants chose

the latter. The first 6 months of study data from those opting to share broadly has been made available to the research community[33] through the first iteration of a "qualified user" process[34]—a process rooted in trust and transparency. Bot stressed that these are only the first steps in shifting research from the investigator and institution, where disproportional amounts of power and influence are held by few, to a more democratic and transparent research process optimized for the public good.

Mobile health apps transforming medical research and clinical care

Asthma is one of the most common and costly chronic diseases affecting a range of age groups, including both children and adults.[35] The characteristics of asthma as a variable disease necessitating regular medication use, monitoring of symptoms, and avoidance of specific triggers make it particularly amenable to having a mobile health application facilitate active monitoring outside of periodic traditional medical visits.

Pei Wang (Icahn School of Medicine at Mount Sinai) discussed the collaboration between her research group, LifeMap Sciences Inc. (San Francisco, CA), Sage Bionetworks, and Apple Inc. (Cupertino, CA) to develop an asthma health mobile application (AHMA) to facilitate asthma patient education and self-monitoring, promote positive behavioral changes, and reinforce adherence to treatment plans. In March 2015, Wang's group launched the Asthma Health Mobile Study (AHMS) to assess the association between the use of an AHMA and asthma symptom control, quality of life, and healthcare utilization.

During the first 6-month period of the study, the AHMA was downloaded approximately 50,000 times, and over 7000 asthma patients have electronically consented and enrolled in the study. The total number of enrolled users rivals the size of the Centers for Disease Control and Prevention (CDC) National Asthma Survey,[36] although the cost of data collection for the AHMS was only a small fraction of that for the CDC survey. Moreover, the enrolled AHMS users have a very diverse geographic distribution, with people from 48 different U.S. states. Wang pointed out that this is very encouraging, as geographic boundary limitations remain a major concern in most traditional health studies, and mobile apps seem to provide an easy and effective solution to overcome such limitations.

In addition to collecting responses to survey forms, AHMA also collected location and activity information, with user approval, through iPhone location and HealthKit functions. Participants who have personal fitness monitors (such as Nike FuelBand) on their iPhones can also choose to include the data in the study. This rich set of information enables Wang and her colleagues to investigate the association between patients' daily clinical symptoms and their activity profiles or real-time environmental data, such as temperature and pollution levels. These investigations may result in valuable insights into asthma pathophysiology and epidemiology.

Wang concluded that the achievements so far in the AHMS demonstrated the feasibility to conduct large-scale asthma studies using a mobile application, echoing the belief of many other researchers that mobile health research represents a promising new era of clinical research.

Managing biometric big data: the promise and challenges

Pamela C. Baker (FierceBigData) commented that these are exciting times when individuals can access and analyze data from a wide range of injectable, ingestible, implantable, environmental, and wearable devices for new discoveries and better patient, disease, and drug understanding. She stressed that the devices are not simply new tools to assist researchers in doing the same work, they are disruptors—they change how work is done, what work is done, and how researchers think about that work. In her presentation, Baker discussed the promise and challenges of managing data generated from these technologies and her recommendations on how to address these challenges.

In Baker's view, more data are not always better, as some can be distracting, unusable data that can either confuse findings or interfere with work; instead, data quality and relevance may matter more. She suggested deciding from the beginning what data are actually needed and using that as a guide in selecting wearables, sensors, and apps, rather than the other way around. Furthermore, she recommended, for the moment, disregarding traditional processes in conducting clinical research; she considers attempts to shoehorn data from new

devices into traditional processes as generally the wrong approach. A better approach may be to discern what these traditional processes were designed to accomplish, determine the reasoning for the process, and then look for better ways to reach that end goal. According to Baker, using machine learning should be a given, as it can find patterns in the data much sooner than can human researchers.

Certainly, there are steps that must be followed to ensure compliance with regulatory, ethical, and scientific rules, but how the work moves from one step to the next—the processes—are often more flexible than first presumed. Baker considers this flexibility to be crucial not only to doing better, faster, and more efficient research but also in staving off industry disruptors, such as citizen scientists, nontraditional researchers, and biohackers, who are not working in the traditional way. Already, individuals from these groups have developed, tested, and brought to market a number of new innovations in quick-fire progression. Baker stressed that, although disregarding available resources is unwise, unchaining researchers' thinking from them can be a helpful exercise. In particular, considering how the work could be accomplished if those resources were unavailable could help the research team rethink processes, as would observing a biohacker community laboratory or maker's space to learn how they think.

Research is now framed by a new data economy wherein data and insights have value. In order to stretch budgets and save time and effort, Baker suggested looking for ways to collect and share data with other researchers, for example, by sharing costs of data collections, sensor purchasing or leasing, tool costs, security products, and data storage. She recommended that researchers start by thinking similarly to companies in the sharing economy, such as Uber, the ride-sharing company, and Airbnb, the home-sharing company. While the term *sharing* is widely misused in this context, the point is to evaluate the redistribution of assets and sharing versus ownership. Examples such as these may help traditional researchers think in terms of sharing data assets in a way that reduces costs of ownership and also renders more data in the process.

Another example of a sharing or collaborative economy approach can be found in the way that teachers are now selling lesson plans to other teachers on the site TeachersPayTeachers.com. Baker suggested that clinical researchers can similarly sell algorithms, models, redesigned processes, lessons learned, and other steps and shortcuts to innovation. Such sales could help fund the next project or at least supplement researchers' income.

Using open data, which are freely available to qualified researchers, is another excellent way to quickly and efficiently find some of the data needed. Baker also urged researchers to consider using data from older clinical research projects, in order to avoid the expense and effort of collecting data that already exist and are free to use.

Following Baker's discussion on some of the ways that wearables, sensors, and apps should be changing how researchers think about clinical research, the processes used, and the knowledge that can be extracted and traded, she suggested that, while making these changes, researchers be very careful about data security and protecting patient privacy. In particular, researchers were urged to be aware that using cloud services does not typically discharge them from the duty to comply with regulations, even if the cloud provider proves Health Insurance Portability and Accountability Act (HIPAA) and other regulatory compliance. In the end, the law will likely hold the user legally responsible. Also, many apps and devices are already showing sizable security flaws; it is therefore important to exercise due diligence in choosing and using tools, apps, and data storage accordingly.

Baker also discussed other commonly overlooked liability issues that researchers should be cognizant of. For example, if implantable or ingestible sensors are used, she recommended being diligent in removing the sensor and/or ensuring the sensors dissolve or are expelled as intended. There could be substantial legal liabilities in allowing sensors to remain, or even accumulate, in patients' bodies. In addition, multiple sensors should not interfere with each other. For example, it is already known that a smart pacemaker interferes with a standard heart monitor. Potential interference among new devices is not necessarily already known.

Baker concluded her presentation by emphasizing that, most importantly, the deciding factor in realizing the promise of these new biometric data

sources is the human researcher. It is the researchers' creativity, imagination, skills, and knowledge that make all the difference, not the data or the tools themselves. Baker urged researchers to think differently, but think carefully.

Regulation, compliance, and standards of emerging mobile biosensor technologies for clinical applications

Regulatory considerations regarding the use of biosensors in clinical trials

Leonard Sacks (U.S. Food and Drug Administration) discussed regulatory considerations surrounding the mobile sensors and wearables that are increasingly penetrating the healthcare environment and how they can be harnessed for clinical trials. Small devices that can unobtrusively measure physiological performance (e.g., sleep, arrhythmias, seizures, movement, breathing, heartbeat) may enhance the ability of researchers to understand the effects of new drugs. They may also permit measurement in real-life situations. Since data from mobile devices can be electronically transmitted, the use of these technologies will allow off-site trials, for example, trials that can be partially or wholly conducted from patients' homes.

Sacks discussed the unique opportunities that wearable sensors offer for continuous monitoring, potentially providing a more complete understanding of drug effects, drug dosing, and pharmacodynamics than was previously possible. Their data can be gathered from widely dispersed patients, including from those with rare diseases, improving access to patients in distant locations and patients for whom mobility is limited. The ability to collect data from patients in their homes makes trial participation more convenient and may reduce the amount of missing information and losses to follow-up. Wearable sensors provide objective data in real time and may overcome the challenges of recall bias that occur with traditional data capture. In addition, they may hasten the approval of products by rapid acquisition of data in potentially large numbers of patients and may be particularly helpful in diseases, which to date, suffer from a lack of adequate response measurements. The benefits that drugs offer in many chronic neurological, cardiac, and respiratory diseases have been difficult to characterize. Using mobile sensors, such as accelerometers, pedometers, and global positioning system devices, it is now possible to measure how well patients move and function in daily life, both on and off investigational treatment.

Sacks emphasized, however, that it is critical that the data provided by these devices are sufficiently sensitive and specific to capture the physiological phenomenon of interest. False signals and signal artifacts may present challenges that do not occur in face-to-face encounters. The measurements made by these devices must be clinically meaningful and relevant to the patient community. When used as clinical trial endpoints, validation of the measurements may rely on a comparison with clinical outcomes, such as those reported by patients or with other traditional endpoints known to be clinically relevant.

Offsite conduct of clinical trials raises considerations regarding patient safety. When trial participants do not have access to a traditional study site, alternative arrangements may be necessary to provide urgent care and advice when adverse events occur, and there are obviously situations where off-site technologies are not appropriate. Sacks concluded that, given the power of these devices to acquire novel data, judicious introduction into the clinical trial enterprise has the potential to revolutionize the development for many new drugs.

Data privacy, cybersecurity, and health IT legal issues in emerging mobile health technologies

Linda A. Malek (Moses & Singer, LLP) offered a legal perspective on the use of emerging health technologies. Wearable biosensors and mobile applications are changing the way health care is delivered to millions of people. Activity and heart rate trackers, smart clothing that provides vital-sign monitoring, smart patches, and even smart pills, are being used to help individuals (and often their physicians) with medication compliance, disease management, and pain management. App and device developers must be aware that certain federal and state agencies, particularly those charged with protecting the privacy of individuals' health information, may have oversight authority over their technology, as well as the data that they may be collecting.

Malek explained that, in the United States, biosensors and apps as devices may be subject to regulation by the Federal Communications Commission (FCC) if they depend on radio technology, including Bluetooth, to collect or transmit

information.[b,37,38] The FCC's regulatory authority often overlaps with FDA medical device regulations.[c] The FDA recently indicated that certain mobile medical apps will be regulated as medical devices if they are "intended to be used as an accessory" to a medical device or "to transform a mobile platform into a regulated medical device."[d] While much of the data collected may not be protected health information under the HIPAA, (in part because app and device developers are not covered entities under the rule),[e] collection of personal information may be subject to general data privacy rules. Even where healthcare apps, such as personal health record apps, may fall outside the purview of the FDA or the U.S. Department of Health and Human Services Office of Civil Rights, in the event a user's identifiable health information[f] is breached, an entity may be subject to the Federal Trade Commission (FTC) breach notification rule,[g] which requires the entity to notify users of a breach within 60 days. Violation of this rule will be "treated as an unfair and deceptive practice" under the FTC Act, which also grants the FTC authority to oversee cybersecurity practices of any commercial entity.[h] Developers or manufacturers who use their technology in the conduct of research may be subject to regulation under the Common Rule for the protection of human subjects.[i] Finally, several states, including California, New York, and Texas,[j] have privacy laws that may be more stringent than certain federal privacy laws and may cover a broader category of entities and activities than HIPAA.

Malek stressed that it is the responsibility of the developers, designers, and marketers to know the federal and state requirements and to abide by them, and to be aware that state privacy and security laws may be more stringent than federal laws and regulations. Responsible development should include data security and privacy at every step, from concept to deployment. She recommended considering intended future use, testing security often, and having a robust breach reporting plan in place in the event unauthorized access occurs.

Societal impact for the use of mobile biosensor technologies on human health

Bernard Munos (FasterCures, Milken Institute) discussed the impact of mobile biosensor technologies on pharmaceutical R&D, human health, and ultimately, society. As asserted by Munos, business disruptions happen[39]—they are a by-product of human ingenuity. Science and technology provide new tools and ways of doing things that change—sometimes abruptly—what used to be done, and in the process, create winners and losers; the latter often agitate to delay, regulate, or even ban innovation. But societies that heed their call pay a stiff price: ossification, limited social mobility, and economic underperformance. In the last 20 years, many industries have been disrupted (e.g., music, publishing, taxis, photography, retailing, and oil drilling). Although these disruptions have made some jobs obsolete, they have also generated new ones. More importantly, few people are ready to give up their smart phones, iPads, or streaming music.

In the next decade, more disruptions are expected, such as self-driving cars, the widespread "uberization" of services—including medicine, and mobile applications for many things. In biomedical research, gene editing, RNA therapeutics, and cell therapy will lead to new treatments, while biosensors and wearables will transform clinical research. These innovations arrive at a critical time, as the cost of biomedical research has soared.

Public companies spend about $140 billion annually in drug R&D—roughly $40 billion for drug discovery and $100 billion for clinical trials. For these amounts, only 35 to 45 new drugs are produced per year. Munos stressed that, regardless of

[b] 47 Code of Federal Regulations (CFR) Parts 2 and 15.
[c] FDA defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . . " (21 United States Code (USC) § 321(h)).
[d] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf.
[e] 45 CFR Parts 160 and 164.
[f] 16 CFR § 318.2(e).
[g] 16 CFR § 318.
[h] Federal Trade Commission (FTC) Act § 5, 15 USC §57a(a)(1)(B) (1914); FTC vs. Wyndham Worldwide Corp., No. 14-3514, 2015 WL 4998121 (3d cir. August 24, 2015); 16 CFR § 318.7.
[i] 45 CFR Part 46.
[j] See, for example, California Civil Code § 56 et seq.; N.Y. Civil Rights L. § 79-l; Texas Health and Safety Code Chapter 181.

how one calculates the costs, the R&D expense per drug approved is enormous, in some cases leading to drugs that cost $100,000. While many people, including industry executives, consider this as evidence that the model is broken, attempts to reform the model have foundered. Fear of change is one concern; yet, history indicates that, while reforms can be delayed or stymied, disruption cannot be avoided and is a way to rejuvenate aging industries that misallocate resources (i.e., overspend massively for what they deliver).

What does it mean for the pharmaceutical industry? According to Munos, contrary to fears, it is good news. Mobile biosensor technologies address a key bottleneck of drug R&D, namely, the enormous costs of collecting patient data,[40] which has traditionally been carried out in hospitals at great expense. Wearables allow at-home collection at near-zero cost beyond that of the devices, which is typically very low. Initial estimates suggest savings of up to 80%. If the cost of innovation is decreased, there will be more of it, both in developed and developing countries. Wearables also allow the collection of much richer and diverse data; for example, up to 1 gigabyte/patient/h has been collected. Regulators have been very receptive, as the technology offers the promise of real-time trial monitoring and early detection of safety signals.

Wearables will transform research in other ways.[41] For example, collecting big data on presymptomatic patients will allow scientists to understand disease etiology at a much deeper level and thus to develop earlier interventions. But since patients will control much of data collection, their influence over drug R&D will likely increase on such issues as data sharing, open access, and affordability. Munos concluded that as a result there will be more, cheaper, and better drugs and massive savings from the current $3 trillion annual U.S. healthcare spending.

Concluding remarks

The above discussion suggests that mobile health has the potential to markedly transform health care in that it (1) offers enormous savings in capturing biomedical data, which is both the bottleneck and lifeblood of biomedical research; (2) greatly enhances the value of the data captured by allowing simultaneous, high-frequency data collection under real-world conditions; (3) is flexible enough to meet (and exceed) the diverse and growing data capture needs of biomedical scientists; and (4) is noninvasive and convenient, which is essential to win the support of patients and healthy users (many of whom are presymptomatic patients).

But the benefits of mobile health have been extended even further—what began as a better way to capture data is evolving into a smarter way to conduct scientific research, as well as to regulate it and manage health and diseases. By collecting data on healthy patients, mobile health can help unravel the etiology of disease before clinical symptoms manifest. Today, the practice of medicine starts with the signs of sickness; there is little known about the processes developing in presymptomatic patients. By the time a disease can be diagnosed, it can be too late for effective intervention, as in the case of pancreatic cancer or Alzheimer's disease. Mobile health can change this situation by allowing earlier disease discovery, which leads to better outcomes and, ultimately, less costly health care. Mobile health can also provide baseline data on thousands of diseases on which researchers currently have none—a major obstacle to developing treatments for which effectiveness cannot be assessed without such data.

Mobile health can also broaden the range of diseases for which new therapies are being developed. Historically, illnesses that affect few patients have not attracted a lot of research dollars. But with mobile health, modest research funding—the kind that can be raised from philanthropy—is often sufficient to start viable programs, and many patient groups are taking advantage of this as they organize, collect, and curate vast amounts of data, and offer them for open access. Drug R&D, which only the pharmaceutical industry was able to afford, is now attracting patient groups, academia, venture philanthropists, successful entrepreneurs from other industries, and citizen scientists.

Mobile health could also change drug development—not only by making it cheaper, faster, and more patient friendly but also by transforming the process itself. The large volume of high-frequency data that mobile health generates can allow scientists to detect signals with much greater precision. And the ability to put these signals on a timeline will facilitate understanding of the events that occur inside each patient following drug administration. Subpopulations of responders would be easier to identify, and scientists and

regulators would eventually be able to follow each clinical trial—and perhaps even each patient—in real time. Safety signals could also be detected sooner than can be done using traditional study designs with periodic study visits. In effect, mobile health will not only enable smarter R&D but also give regulators tools to make better and faster decisions.

Furthermore, a new, powerful industry is taking shape that develops smart objects—everyday devices embedded with biosensors that collect biomedical data upon contact (or proximity). A dizzying collection of smart objects has already been marketed or will be soon, such as smart clothes, underwear, watches, eye glasses, seats, beds, bed sheets, toilets, and thermostats. These smart objects can monitor fitness, health, the environment, and lifestyle and behavior; send alerts or nudge individuals toward behavior modification; and can already track hundreds of biological parameters, including vital signs, sleep, emotions, stress, breathing, movement, efforts, posture, gait, body shape, lesions, mental acuity, toxins, blood glucose, ECGs, and drug adherence. Simultaneously, breakthrough technological advances are enabling low-cost, smartphone-based, lens-free microscopy with performance that dwarfs that of the microscopes found in most laboratories. One can easily imagine a not-so-distant future when the data streams from all of these devices will automatically be scanned by a Watson supercomputer-like system that possesses all of the biomedical knowledge ever generated. Its ability to detect signals and match them to patterns characteristic of diseases could create an early warning system that could transform medicine.

Mobile health could also spawn other forces that will influence medicine. For example, having more data leads to enhanced ability to measure health, as well as outcomes from therapies, which will add to the pressure to shift health care from fee-for-service to performance-based systems. It may also result in a repricing of drugs to align with their benefits. Innovators will be rewarded; but less innovative companies may be challenged.

The benefits from mobile health may also accrue globally, with the largest ones likely seen in developing countries that lack a modern—but high-cost—medical infrastructure. Smart phones are ubiquitous, with 1.5 billion being sold in 2015 alone. Mobile health, which relies on smart phones to collect, process, store, and transmit data, could bring affordable, high-quality telehealth applications—including medicine, disease surveillance, diagnostic, imaging, and pathology—to countries that can afford little else.

Challenges

While the above discussion presents a compelling vision of mobile health, there are hurdles that must be overcome, including those related to the reliability of the data generated by biosensors and the validation of devices; data encryption; patient privacy; data ownership; colocation of each patient's data in a single place where it can be accessed for analysis; the intellectual property that might be derived from such data; potential incorrect use of devices, which could impair data quality; and the performance of the technology, including device size, weight, battery life, and cost. While none of these hurdles is a show stopper, each one can lead to protracted discussions, pitting entrenched interests. Yet, the benefits of mobile health are so significant, and the pressure on healthcare costs so great, that consumer acceptance is likely. Apple, with its software platform for biomedical research (ResearchKit), is already using its brand power to reassure customers that it will overcome these hurdles; others are likely to follow.

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presentations from this conference at www.nyas.org/MobileHealth2015-eb. The related podcast, "Improving Clinical Trials Through Mobile Technology," is also available at www.nyas.org/MobileHealth2015-Podcast.

Conflicts of interest

A.O. is the cofounder of a company that commercializes mobile diagnostic technologies.

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