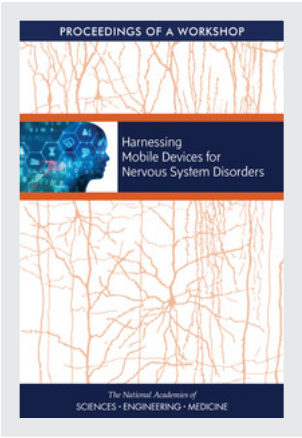

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Harnessing Mobile Devices for Nervous System Disorders

PROCEEDINGS OF A WORKSHOP

Lisa Bain, Daniel Flynn, and Clare Stroud, *Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Health and Medicine Division

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **LESLIE Z. BENET,** University of California, San Francisco. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

Contents

1

Introduction and Background[1]

The critical importance of using mobile technology is obvious to anyone in the health professions, particularly those who treat people with central nervous system disorders, said Steven Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute of Harvard and the Massachusetts Institute of Technology. Whether those conditions are psychiatric or neurologic, he said, "We know remarkably little about the patients we're treating." Even if those patients are enrolled in a clinical trial where they are assessed every three or four weeks, important clinical and regulatory decisions are made on what he called "intermittent, brief, and superficial cross-sectional examinations."

"Digital phenotyping" is one approach to addressing these measurement gaps and methodological problems. Jukka-Pekka ("JP") Onnela, associate professor of biostatistics at Harvard's T.H. Chan School of Public Health defined digital phenotyping as the moment-by-moment quantification of social, behavioral, and cognitive markers in situ using data from personal digital devices (Onnela and Rauch, 2016). Hyman contrasted these digital tools to the types of periodic assessments typically done in clinical trials, which he said provide shallow rather than deep phenotyping of participants. In addition, he said, retrospective bias—the tendency for false reporting if a person has had a particularly good or bad day—may color an individual's responses to even well-administered rating scales.

[1]The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They should not be construed as reflecting any group consensus.

Patient-reported outcomes (PROs) may also be misleading if patients consciously or subconsciously want to demonstrate to their physician either how bad or how well they are doing, said Hyman. Digital technologies offer the potential to do better, he said, if they can be implemented in ways that are meaningful, sensible, and cost effective.

Husseini Manji, global therapeutic head for neuroscience at Janssen Research & Development, LLC, agreed. The twin revolutions in neurobiology and mobile computing have the potential to offer important benefits for people with neurological disorders, he said. There are reasons to think these technologies could be transformational, yet he cautioned against overhyping what they can do. "Let's be thoughtful and systematic about it, so we can really make a difference for some of these complex neuropsychiatric, neurodevelopmental, and neurodegenerative conditions," he said.

To explore current developments and opportunities for using mobile technology to advance research and treatment of central nervous system (CNS) disorders, the National Academies' Forum on Neuroscience and Nervous System Disorders hosted a workshop in June 5–6, 2018. This publication summarizes the presentations and discussions at that workshop.

WORKSHOP OBJECTIVES

The workshop brought together a diverse group from federal research and regulatory agencies, academia, industry, and foundations, along with advocates presenting the patient point of view to discuss how to ensure that technological advances are translated into something meaningful for individuals and society as a whole. The workshop also addressed key concerns that society will have to grapple with regarding digital technologies, including privacy and data ownership, said Manji (see Box 1-1 for the workshop Statement of Task).

BOX 1-1
Statement of Task

An ad hoc committee will plan a 1.5-day public workshop that will bring together experts and key stakeholders from academia, government research and regulatory agencies, the technology and pharmaceutical sectors, and nonprofit organizations

to explore current opportunities afforded by developments in device and mobile health technology to advance research and treatment of central nervous system (CNS) disorders. Invited presentations and discussions will be designed to:

- Explore innovative approaches to using device and mobile health technology to predict, diagnose, monitor, assess adherence to, and develop treatments for CNS disorders, including discussion of methodology, analytical techniques, and the evidence needed to validate the data for use in research and the clinic.
- Share approaches and lessons across efforts to apply device and mobile health technology in different CNS disorders and identify opportunities for collaboration.
- Discuss regulatory, privacy, ethical, security, and practical issues that arise specifically when using devices for CNS disorders, such as collection, analysis, storage, use of behavioral information, and ensuring parity in access to these technologies.

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. A proceeding of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

ORGANIZATION OF THE PROCEEDINGS

Chapter 2 summarizes opportunities and challenges associated with digital technologies: their potential to elucidate understanding of health and disease, increase the efficiency and productivity of clinical trials, and improve patient care; as well as the challenges associated with gathering and interpreting digital data. Chapter 3 provides a deeper dive into the challenges associated with data collection, validation, standardization, and analysis. Regulatory considerations and steps being undertaken to address regulatory concerns are discussed in Chapter 4. Chapter 5 delves into the promise and challenges associated with incorporating mobile technologies into clinical practice. The importance of addressing consumer attitudes and preferences when developing mobile technologies is addressed in

Chapter 6. The potential to move these technologies forward by building research partnerships is addressed in Chapter 7.

2

Exploring Opportunities Afforded by Mobile Technology

The current state of assessing brain disorders is "exquisitely crude," said William Marks, head of clinical neurology at Verily Life Sciences. The disease-specific scoring schemes used, such as the Unified Parkinson's Disease Rating Scale, the Multiple Sclerosis Functional Composite, and the Alzheimer's Disease Assessment Scale-Cognitive subscale are pseudo-quantitative, limited in scope, and applied in artificial settings, he said. Most importantly, he said, they often fail to consider what matters most to individuals with those conditions and their families.

Digital technologies, however, have the potential to assess objectively, quantitatively, repeatedly, and in a more natural setting the multiple aspects of a disease, including the transition from health to disease, symptom severity, progression, stability, regression, impact on daily life, and response to treatment, said Marks. Moreover, the convergence of increased cloud storage capacity and improved analytical techniques offer the potential to harness these measures for both research and clinical care, he said. If these digital advances can be married to medication development, they might even improve the delivery of different types of therapies, observed Husseini Manji.

For example, neurologists typically assess gait by observing their patients as they walk down a corridor. Digital technologies can provide complementary information about function and context by capturing more quantitative measures of gait parameters as well as other real-world parameters related to walking, such as destination and frequency of walking to a destination, said Marks. Artificial constructs such as tapping one's finger as a measure of dexterity can be replaced by digital monitoring of changes in the ability to eat, write, or perform other daily functions in a natural environment, he said, adding that these more clinically relevant

phenotypes could enable earlier and more definitive diagnoses to guide more personalized treatment as well as a better understanding of treatment responses. In addition to passively collecting information, digital technologies can actively push out surveys and patient-reported outcome measures in a relevant manner, he said.

Although much of the emphasis so far has been on movement monitoring with accelerometers and gyroscopes, these devices are just scratching the surface, said Marks. The technology is reaching the point where gait or other types of movement can be dissected in a much more disease-specific way. Combined with geospatial activity and assessments of falls or use of assistive devices, a more complete picture of motor function can be discerned. Beyond the assessment of motor function, and because neurological and psychiatric disorders are multidimensional, digital devices lend themselves to the measurement of other domains such as sleep, cognition, speech, vision, mood, behavior, cardiovascular and autonomic function, social interactivity, and quality of life—"an amazing wealth of information that could give us insight into these diseases," said Marks.

Currently, digital biomarkers are being incorporated into clinical trials primarily as exploratory measures, running alongside more traditional scales and measures, said Iain Simpson, senior director of digital health at IXICO. IXICO began supporting the pharmaceutical industry in clinical trials as a specialist neuroimaging clinical research organization (CRO), he said, but they have broadened into the digital biomarker field when they saw their potential of wearable devices to be used as clinical research endpoints and realized that many of the issues faced in developing digital biomarkers are similar to those encountered in imaging 5 to 10 years ago. He predicted that while digital biomarkers may eventually supplant some rating scales and other subjective measures of function, it may be more likely that they will provide complementary quantitative input to those scales. He emphasized that implementing biosensors and passive data collection into clinical trials has the potential to capture clinically important information while minimizing patient and site burden (See figure 2-1).

Marks added that in some cases, digital technologies may themselves be therapeutic, for example, by coaching a person through a treatment regimen or healthy brain activity. More granular monitoring of the trajectory of a person's disease and their response to treatment could have the added benefit of democratizing health care, giving people more access to expert care, and facilitating population health management, he said. Indeed, mobile technologies offer the ability to engage more diverse populations, including people who typically do not participate in research either because

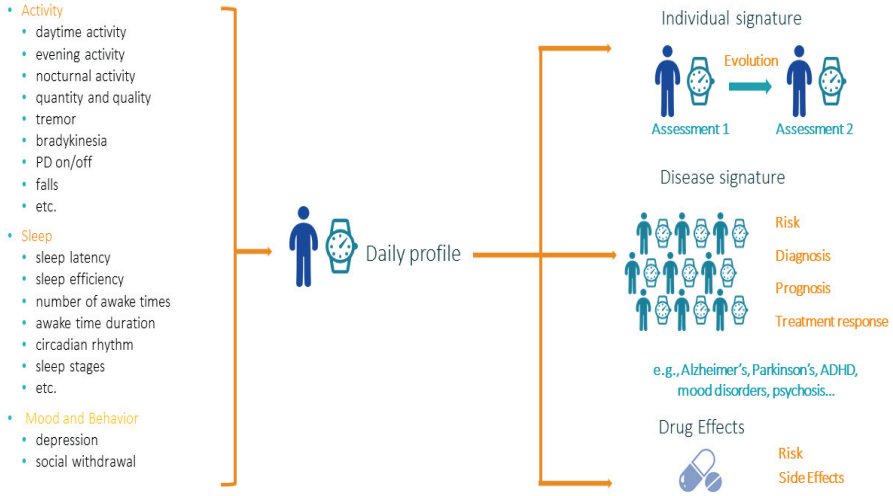

FIGURE 2-1 Extracting clinical value from actigraphy metrics. Wearable actigraphy sensors can provide continuous data on an array of activities and behaviors, which can be translated into information about disease onset, progression, and response to treatment.
NOTE: ADHD = attention deficit hyperactivity disorder; PD = passive device.
SOURCE: Presented by Simpson, June 6, 2018.

they do not live near a clinical site, because they have mobility issues, or because they are too busy working and caring for their families, said Catherine Kopil, senior associate director of research programs at The Michael J. Fox Foundation for Parkinson's Research (MJFF).

Some of the more obvious benefits of digital technologies are likely to be realized in the areas of early identification and objective monitoring of disease progression, with real-world measures for neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), said Manji. For neuropsychiatric disorders that are highly recurrent, such as bipolar disorder, digital technologies may also provide early warning signals of an impending cycle, switch to mania, or suicidal intent, he said. Because these recurrences and relapses may contribute to the pathogenesis of disease, Manji suggested that detecting early warning signs and intervening at that point could potentially impact disease progression (Narayan and Manji, 2016).

Manji noted that digital technologies even have the potential to monitor people when they are healthy but at risk for neurodegenerative diseases, such as people with a family history of certain diseases or those that harbor genetic mutations or genetic risk factors such as the ApoE4 gene, which increases the risk of developing AD (Corder et al., 1993). Being able to detect people in the earliest stages of a disorder not only would enable early intervention, but also the identification of appropriate candidates for clinical trials, said Manji.

Quantitative measures also can supercharge the efficiency of clinical trials through the collection of many high-resolution data points, said Marks. The increased statistical power of this high-density data may result in shorter trials with fewer participants, he said. In addition, because these assessments could be done virtually, a more diverse group of participants could be enrolled in trials.

TECHNICAL, METHODOLOGICAL, AND ETHICAL CHALLENGES

To realize the opportunities just discussed, many technological, methodological, and ethical challenges will need to be addressed, said JP Onnela; these challenges are discussed in more detail in later chapters of these proceedings. These include issues associated with the high dimensionality and noise associated with digital data, which introduce challenges related to data standardization, analytical and statistical methods, and reproducibility, he said (Chapter 3). To make digital data useful in clinical trials will also require multiple levels of validation, as well as novel approaches to organize and synthesize data so that it is useful to different audiences, said Marks (Chapters 3, 5, and 6). Developing such approaches will demand the engagement of participants, clinicians, researchers, data scientists, and regulators, he said. Moreover, a regulatory path for using digital data has yet to be developed, said Onnela, noting that data privacy and security remain substantial concerns for consumers, device developers, and regulators alike (Chapters 4 and 6). Kristen Rosati, an attorney and partner at Coppersmith Brockelman, PLC, added that an evolving web of laws and regulations present challenges to companies trying to incorporate digital measures into clinical trials (Chapter 4).

3

Transforming Digital Data into Insight: Collection, Analysis, Standardization, and Validation

Highlights

- Collecting data to enable digital phenotyping requires selecting the appropriate device and determining how, where, and from whom to collect data; validating that the sensor is accurately measuring what it was intended to measure; and organizing the data in a way that they can be stored and transformed into knowledge that helps patients (Manji, Marks, Onnela).
- Passive data collection facilitates the inclusion of many participants over a long period of time and may reduce participant burden (Onnela).
- Wearable devices enable the collection of continuous data, which can demonstrate declining function that might not be apparent with infrequent assessments (Arnerić, Marks).
- Data collected from social media platforms may be useful for assessing mental health, and these platforms may also provide a mechanism for intervention (De Choudhury).
- A higher level of data validation involves correlating digital measures to gold-standard measures or to "ground truth" (Brunner, Marks), or demonstrating how they relate to disordered behavior, how they may help select interventions, or how they correspond to what is known about the biology of neuropsychiatric disorders (Choudhury, Estrin, Hyman).
- Integrating, storing, and understanding complex multidimensional data, including digital data, will require data standardization, platforms that enable interoperability, novel approaches to represent the data such as through visual

transformations, and novel statistical approaches to address messy or missing data (Brunner, Manji, Marks, Onnela).
- Ensuring the reproducibility of digital data may pose a substantial problem (Onnela).
- Transforming digital data into insight that can improve people's lives or increase the efficiency of clinical trials requires applying novel analytic approaches (Marks, Matos, Onnela).
- Acquiring reliable and meaningful data will only be possible if individuals, clinicians, and researchers are engaged in the process (Marks).
- Developing an appropriate ethical framework will be necessary to ensure data privacy and security (Manji, Onnela).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Science has nearly always been driven by having better data, said JP Onnela. What has changed in the past 10 years is the volume of data collected and the types of data available about human behavior. Onnela tied this phenomenon to the shrinkage in the size of transistors which, as embodied by Moore's law,[1] has led to smaller and smaller sensors embedded into mobile phones and wearable devices. In parallel with this miniaturization of technology, mobile devices have become ubiquitous, he said, with 77 percent of U.S. adults owning a smartphone in 2017. The widespread application of these technologies has enabled the collection of rich data about the social, cognitive, and behavioral function of individuals, even people with serious mental illnesses, he said.

For digital technologies to have an impact on human health requires not just fancy gadgets but a robust evidence base, said Husseini Manji. He envisioned a kind of learning engine (See figure 3-1) that would transform aggregated digital data into knowledge that would help patients through the development of predictive algorithms. However, Onnela noted that integrating raw data collected from different kinds of devices would be extremely challenging because of the difficulty of convincing device manufacturers and researchers to share their data as well as the complex statistical approaches needed.

[1]Moore's law was named after Intel cofounder Gordon Moore, who predicted in 1965 that the number of transistors that could fit onto a chip would double every year. Moore revised this to every 2 years in 1975, and this rate continued for the next four decades.

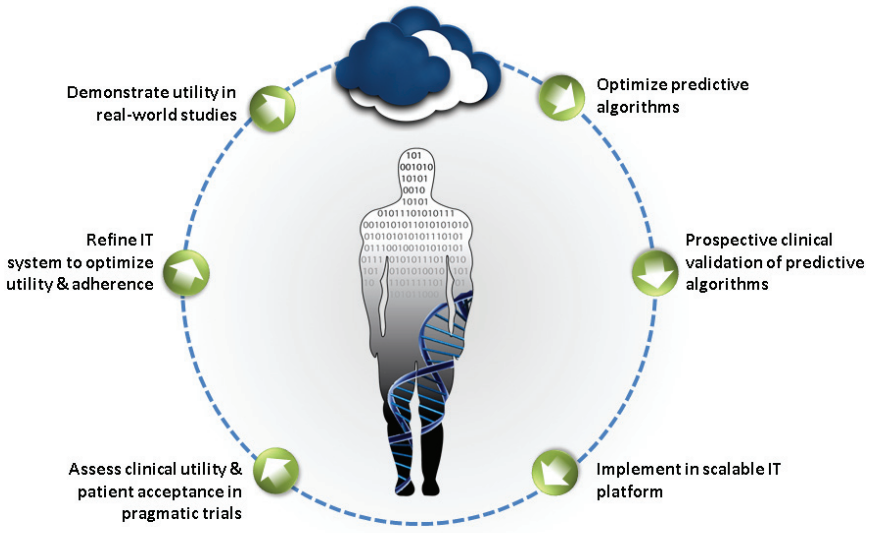

FIGURE 3-1 A data-driven learning engine. It was constructed to ensure a robust evidence base would start with developing, optimizing, and validating predictive algorithms. Once these algorithms have been implemented in a scalable information technology (IT) platform and their utility has been assessed in pragmatic trials, they would be refined and optimized. Finally, their utility would need to be demonstrated in real-world studies.
NOTE: IT = information technology.
SOURCE: Presented by Manji, June 5, 2018. Concepts derived from Manji et al., 2014.

While recognizing the challenges associated with collecting and analyzing digital data, Onnela noted that digital phenotyping has three distinct advantages for research: it facilitates the inclusion of many participants, reduces the burden on participants by enabling the passive collection of data, and enables researchers to conduct large population-level studies with data over a long period of time, including before and after an event or intervention occurs. Box 3-1 describes a project that Onnela has undertaken to transform data collected from digital devices into digital phenotypes.

BOX 3-1
The Digital Phenotyping Project

With an NIH (National Institutes of Health) Director's New Innovator Award, JP Onnela launched the digital phenotyping project, which aims to develop tools and methods for collecting and making sense of these very noisy data. His group developed the Beiwe Research Platform for smartphone-based digital phenotyping, which offers both Android and iOS applications to collect active and passive data from individuals and uses cloud computing infrastructure to store and analyze these data (Torous et al., 2016). By building this with open-sourced software, Onnela hoped to encourage other researchers to use and possibly improve the platform.

Onnella described that in a pilot study designed to demonstrate the face validity of the approach, the researchers studied pain in a group of patients after spine surgery. They showed that the patient's subjective rating of pain on a scale of 0 to 10 was significantly associated with reduced mobility assessed using global positioning system summary statistics. In another pilot study, they used wearables to assess sleep; then they went on to show that about 95 percent of the information about sleep patterns collected using wearables could be collected much more cheaply by tracking when a person's smartphone screen was off. For research, the benefits of using smartphones rather than wearables include much lower cost, wide availability, essentially identical measurements across devices, and a high degree of user acceptability, said Onnela.

COLLECTING THE DATA

To build the sorts of algorithms that would enable the digital phenotyping described by Onnela, investigators determine what data will be most useful, what sort of device will enable its collection, and how, where, and from whom to collect this information. This requires consideration not only of the technicalities of data collection, management, and analysis, which are discussed below, but also the perspectives of participants and clinicians involved in studies, which are discussed in Chapters 5 and 6.

Choosing the Device

Many factors must be considered in choosing the device that will best fit the intended purpose, said Daniela Brunner, founder and president of the Early Signal Foundation. She noted that there is an essential tension between research and health care: the devices, data, and algorithms appropriate for research may differ from those used for applied medicine, she said. For either use, both quality of data and sustainability are essential. A fantastic device will prove useless if the company goes out of business, said Brunner. Multidomain sensors that capture as much data as possible are desirable because they can provide the context in which a patient lives and how that context affects the targeted domain.

The device and device manufacturer will also determine what form of data will be available for research studies, said Brunner. Non-aggregated data are essential, but raw sensor data may not be necessary, she said. Two sensors may be used together—what Brunner called "sensor stacking"—to enable interpretation of the data in a meaningful way. For example, if a researcher wants to study various sleep parameters, combining data from a wearable and a bed sensor may provide a solution.

Determining Which Data to Collect and How to Get Them

William Marks noted that one of the advantages of wearable devices is that they enable the unobtrusive collection of continuous or near-continuous digital data at home in a person's normal environment or elsewhere during the normal course of the day. The power of collecting continuous data is illustrated in Figure 3-2, which shows the declining function of two hypothetical patients at points where infrequent assessments can lead to incorrect interpretations, said Stephen Arnerić, executive director of the Critical Path for Alzheimer's Disease. However, Onnela cautioned that continuous monitoring could result in data overload for the person being monitored as well a clinician trying to make sense of the data.

Episodic monitoring also has some advantages, said Marks, including the potential to reduce the burden to the person being monitored and to prevent data overload. For example, to assess response to a new treatment, 1 week of monitoring at baseline before treatment, followed by another week of monitoring after the treatment has been initiated, may be sufficient to detect treatment response. Or to track the progression of PD, it

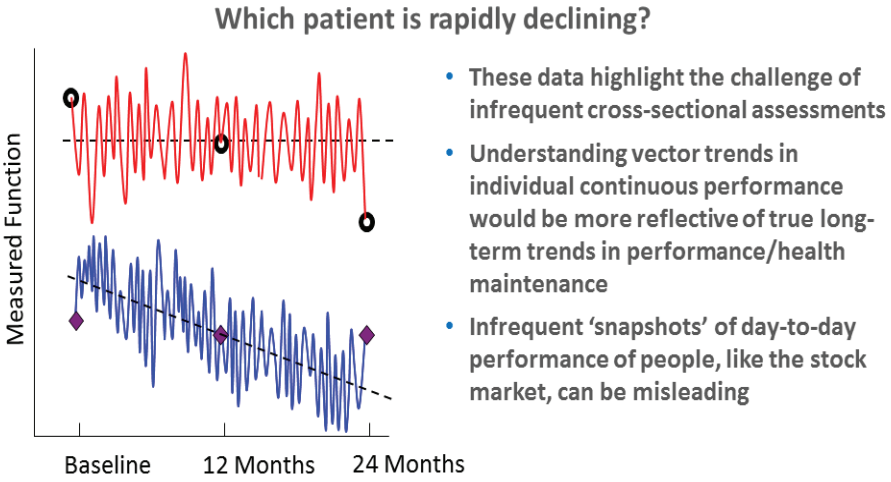

FIGURE 3-2 Why continuous measurement is relevant and critical. These hypothetical data illustrate how infrequent measurement of function may be interpreted as decline in a stable patient (upper graph) or stability in a rapidly declining patient (lower graph). By contrast, vector analysis based on continuous measurement in the patient depicted in the lower graph clearly shows rapid functional decline.
SOURCE: Presented by Arnerić, June 6, 2018.

might make sense to monitor once per month for 24 hours and then take 24-hour measurements at regular intervals.

In addition to free-living continuous or episodic monitoring, collecting data during structured activities also can be valuable because predictable aspects of the activity can be labeled and correlated with the signals being measured, said Marks.

Sensors are not the only tools that provide access to digital data. Social media platforms such as Facebook, YouTube, Instagram, Snapchat, and Twitter are digital tools that are used by a majority of Americans, according to a recent report from the Pew Research Center (Pew Research Center, 2018). While these platforms are designed to enable people to stay connected with others, build new connections, and share information about their lives, Munmun De Choudhury, assistant professor in the School of Interactive Computing at Georgia Tech, said they also provide rich data about people's behaviors and moods, and thus may be helpful in assessing mental health, identifying early warning signals and risk factors, and even may enable early diagnosis. She added that social media platforms may

also be useful as a mechanism for intervening in the care of people with mental illnesses.

De Choudhury described a study she led in which she examined the Twitter archives of women before and after the birth of a child. For about 15 percent of the new mothers, the researchers saw a pattern of change that differed markedly from the other mothers, with reduced activity, more negative affect, reduced emotional intensity and social interactivity, and greater focus on self (De Choudhury et al., 2013). To attempt to understand this further, De Choudhury and colleagues recruited new mothers through Facebook ads. These women consented to have the researchers access all of their Facebook time line data and completed a survey designed to assess depressive symptoms. Using these data, they built models that predicted with reasonable accuracy (explaining more than 48 percent of the variance) the risk of postpartum depression based on social media–derived behavioral and affective markers identified in the prepartum period (De Choudhury et al., 2014). This study indicated that meaningful and clinically relevant signals could be accessed through social media, said De Choudhury. She went on to show evidence from one study suggesting that social media data could be used to efficiently develop an index for depression at the population level.

In a subsequent study, De Choudhury and colleagues mined data from the social media platform Reddit to identify markers of suicidal ideation (De Choudhury et al., 2016). They identified many different words and phrases that are causally linked to an increased or decreased likelihood of suicidal ideation. She suggested that these approaches could be incorporated into suicide prevention efforts going forward.

She cited challenges specific to the use of social media data. First, platforms have different terms of service that may compromise individual privacy; thus, researchers must be very sensitive to how they are using these data. Second, every platform is different and the demographics of people using those platforms differs, which could introduce bias. Usage of different platforms may also change very quickly, so machine learning models must adapt to these evolving changes, said De Choudhury.

VALIDATING DIGITAL DATA

Marks described the different types and levels of validation that are needed when capturing digital data for a research study. The first question to be answered, he said, is whether the sensor is faithfully capturing the

physiological or environmental signal in question. For example, is the photoplethysmography (PPG) sensor in a wearable device measuring pulse as intended? The next level of validation, said Marks, is confirming the accuracy of the feature extraction and activity classification. An example of how a device may misclassify an activity was described by attendee John Gardinier, who said that his smartphone translates vibrations from riding in a golf cart as steps taken.

Next, said Marks, to provide face validity the signals being measured either individually or in aggregate should correlate with other measures of the disorder, such as imaging findings, clinical exam, or molecular endophenotype. They should provide some useful information about the disease, its progression, or its response to treatment, he said. This level of validation involves comparing data from sensors or other novel digital tools to the gold standard measures or "ground truth," said Brunner. However, Steven Hyman commented that while validated and widely accepted behavioral measures may be interpreted as ground truth for many neurological conditions, the same cannot be said for many neuropsychiatric disorders. He expressed concern about overinterpreting phenotypic measures that are disconnected from any kind of ground truth. Alternatives to tying these measures to ground truth may be to look at how they relate to some disordered behavior or diagnosable illness, said Hyman, or how they may help select interventions or make decisions regarding incremental care, said Deborah Estrin, professor of computer science at Cornell Tech.

Connecting digital measures with what is known about the biology of neuropsychiatric disorders is key to making these technologies useful, said Tanzeem Choudhury, associate professor in computing and information sciences at Cornell University. Many continuous signals—such as physical activity, sleep, social activity, speech, and even food intake—can be automatically measured to monitor behavioral health, she said. Choudhury's company, HealthRhythms, Inc., has developed a platform that captures data automatically from smartphones on people's sleep–wake and active–rest rhythms because disruptions in circadian rhythms have been linked to disruptions in behavioral health. They have used these sensor measures, for example, to model social rhythms in people with bipolar disorder, and have demonstrated that these models predict stable and unstable states with high accuracy (Abdullah et al., 2016).

ORGANIZING, MANAGING, AND INTERPRETING DIGITAL DATA

Having access to high-resolution data is not sufficient, said Marks. Organizing the data collection system in a way that makes it easy for an individual to contribute data, that allows for secure, high-fidelity storage, that provides easy access to data miners and analysts, and that stores the data in a form that can be brought together with other data types in a multidimensional way is equally important.

Integrating data from multiple sources would require the creation of data standards and the establishment of platforms that enable interoperability of data, said Manji. He cited two organizations as exemplars—One Mind and Cohen Veterans Bioscience—that have attempted to do this by encouraging the use of open source approaches. Even companies developing proprietary interventions can benefit from shared data, he said.

Representing complex multidimensional data—for example, data from sensors, clinical assessments, and other outcome measures—in a format that is easy to understand may be accomplished using visual approaches that transform group data using dimensionality reduction and identifying clusters that represent certain features of a population (e.g., persons with a certain condition), said Brunner. Once these clusters have been identified, interactions among clusters may be explored to generate new hypotheses that deserve further investigation. In addition, individual outliers that do not follow said patterns may be identifiable to enable more accurate diagnoses and more individualized care, said Brunner.

Onnela noted that in a research setting, continuous monitoring can produce very high-grade data; however, it can be very consuming on the device's battery, making this approach non-scalable. The Beiwe platform created by Onnela and colleagues records global positioning data intermittently, leading to large amounts of missing data. Therefore, they developed a statistical method that allows them to impute missing data. By collecting continuous data for one person, they were able to demonstrate that in comparison to linear interpolation, where one simply connects the dots between data points with straight lines, this imputation method provides a measure much closer to ground truth (i.e., empirical measurement), said Onnela. Although improvements in the imputation method are needed to improve its precision, Onnela described how his lab has demonstrated its utility in a study using gyroscope data to monitor when and for how long a person is walking, standing, sitting, and climbing up or down stairs. Such statistical methods, he said, allow researchers to "propagate uncertainty,"

and thus draw more reliable conclusions from incomplete data. They also have the potential to improve in-clinic measures, he said.

Approaches are also needed to manage the high variability of free-form digital data acquired in different contexts and environments. These data are both high dimensional and extremely noisy, with substantial variability and strange patterns of messiness, said Onnela. All of these factors will likely impact the ability to reproduce digital findings across multiple studies, he said, noting that insufficient reproducibility of data has plagued biomedical research studies across multiple fields (NASEM, 2016; Prinz et al., 2011). This variability highlights the importance of developing new methods specifically designed to tackle these kinds of problems, he said.

ACTIVATING THE DATA

The final piece of this process is what Marks called "activation" of the data—using analytics to transform the data into insights that can improve the lives of the people who were monitored by modifying behavior, identifying new clinical endpoints, and accelerating drug development.

Marks noted that digital technologies are starting to creep into the clinical world, largely from individuals who share data from wearable devices with their physicians, hoping that the physician may be able to answer questions about the data. The problem, said Marks, is that the data being fed back to consumers are not always reliable or actionable. Although miniaturized technologies have provided useful data in fields such as diabetes and cardiovascular disease management, neuropsychiatry has lagged far behind in terms of accessing useful and believable data, said Marks. Furthermore, Tanzeem Choudhury suggested that being aware of every single aspect of one's behavior by itself can be overwhelming and stress inducing.

Digital tools have also been used in recent years to increase operational efficiency in clinical development and as new clinical endpoints, said Luís Matos, deployment lead digital biomarkers at Roche. Smartphones, for example, combine multiple integrated sensors that detect light, touch, movement, position, connectivity, sound, and other data that may be relevant to an individual's health status, said Matos. At Roche, they are conducting the FLOODLIGHT trial[2] using a mobile smartphone app that aims to use passive remote monitoring combined with active tests

[2]For more information, see https://floodlightopen.com (accessed July 2, 2018).

to monitor disease activity for 1 year in 60 patients with multiple sclerosis and 20 controls. The active tests available on the app—which take about 5 to 10 minutes per day—have been designed to correlate closely with standard clinical assessments. For example, the pinching test "Squeeze a Shape" asks participants to pinch a shape on the screen for 30 seconds as a way to evaluate fine motor control and hand-to-eye coordination, which are typically assessed in the clinic using the Nine-Hole Peg Test. Another test asks participants to make at least five U-turns while walking between two points. During the performance of this task, the smartphone uses movement and inertial sensors to capture data on the number of steps, the symmetry of U-turns, and several aspects of balance. Matos said they have found that these metrics correlate well with performance on the Timed 25-Foot Walk, a standard clinical test used as a functional measure of walking ability.

Figure 3-3 illustrates how smartphone data can improve adherence and enable the collection of high-quality data on a daily basis. These data are also combined with passive data, questionnaires, and symptom trackers to provide a rich view of disease progression, said Matos.

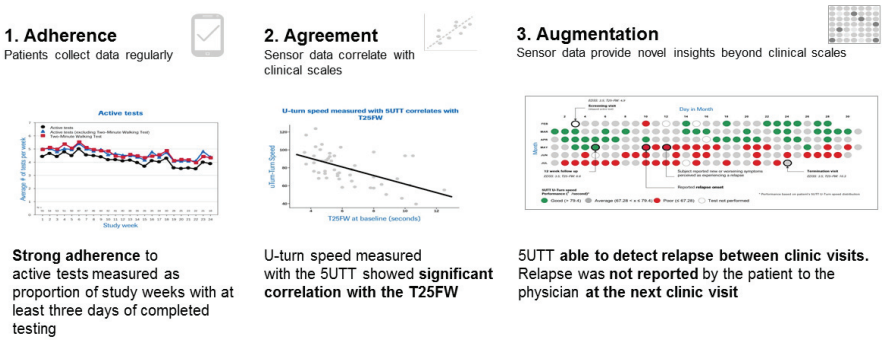

FIGURE 3-3 FLOODLIGHT Digital Biomarker analysis from adherence to augmentation. Smartphone data collected in the FLOODLIGHT trial have been shown to improve adherence, correlate with standard clinical scales, and provide a much more complete view of the progression of multiple sclerosis symptoms in comparison to assessments conducted only at sporadic clinic visits.
SOURCE: Presented by Matos, June 5, 2018.

4

Regulatory Considerations and Pathways

Highlights

- Regulators should be at the table early in the process of developing digital health technologies, including through the use of the Food and Drug Administration's free presubmission process (Manji, Peña).
- Developing and implementing digital technologies in clinical trials will require novel trial designs and regulatory pathways (Narayan).
- Digital technologies facilitate patient-centric drug development through the use of remote and continuous measurements
(Corrigan-Curay).
- To gain regulatory acceptance, both interactive and unobtrusive monitoring devices need to be evaluated for reliability, reproducibility, sensitivity, specificity, and clinical meaningfulness (Corrigan-Curay).
- Organizations working to advance the use of digital and mobile technologies in clinical trials include the Clinical Trial Transformation Initiative and the Critical Path for Alzheimer's Disease (Arnerić, Corrigan-Curay).
- Biometric and other digital assessments may enable regulators and developers to model presymptomatic stages of neurologic disorders by capturing subtle, real-time functional changes (Arnerić).
- Incorporating digital measures into clinical trials, particularly collaborative studies, requires compliance with an evolving array of laws and regulations (Rosati).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Regulatory agencies have taken a keen interest in the development of digital devices to ensure that data acquired in clinical trials are collected systematically and rigorously, and with a focus on providing real benefits to patients while not compromising privacy or introducing other ethical problems, said Husseini Manji. Thus, he said, regulators need to be at the table early in the evolution of the technologies to avoid downstream roadblocks, and clinicians need to be engaged in the process to ensure that these devices will be successfully integrated into clinical practice.

Vaibhav Narayan, vice president of Research Information Technology at Janssen Pharmaceuticals, noted that although mobile computing devices and biosensors are evolving more rapidly than drugs and biologics evolve, the regulatory pathways for digital biomarkers and other diagnostic and monitoring solutions have the same need for accuracy, validity, utility, and value. What has changed, he said, is the speed at which the technology itself changes. Thus, when these technologies are used to provide digital readouts in clinical trials, in the time it takes to design a study and agree on a protocol, available sensors may have changed from what was originally envisioned in terms of the application programming interface, data standards, and algorithms for managing data, he explained. Moreover, the ability to take measurements remotely in large populations may result in data- and evidence-generation studies that look very different from classic clinical trials that have been done in the past. As a result, iterative designs and more agile methodologies are needed, as well as new regulatory pathways that enable rigorous evaluation of digital solutions and that are responsive to the different time scales at which these solutions evolve, he said.

Although digital technologies may help increase the efficiency of clinical trials in terms of recruiting and consenting participants as well as in maximizing adherence and retention, they also introduce several potential regulatory challenges, said Narayan. For example, given the variety of devices available, he advocated a device-agnostic paradigm where many different devices can be used to generate similar types of data. However, this approach introduces other challenges in terms of maintaining data quality, standardization, and interpretation, he said.

REGULATORY PATHWAYS FOR MEDICAL DEVICES

From a regulatory perspective, digital health technologies may be defined as medical devices if they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or if they impact the structure or function of the human body through a non-chemical action,[1] according to Carlos Peña, director of the Division of Neurological and Physical Medicine Devices at the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health. This includes devices that take measurements to provide users with information about their conditions, he said. Medical devices can be classified into one of three categories with different levels of regulatory control based, in part, on the individual risk/benefit profile of the device, said Peña. Clinical data are typically required only for the highest risk (Class III) devices such as deep brain stimulators, he said. Class II devices may follow the 510(k) submission pathway where clinical data is typically not needed, although there are cases where clinical data was submitted. For devices that are not comparable to anything on the marketplace and that present low to moderate risk, a de novo pathway is also available.

Peña strongly urged device developers to take advantage of FDA's free presubmission process, which allows them to obtain input from FDA on data that will be needed for regulatory approval. Presubmission allows regulators and developers together to map out important issues before a study is conducted so that everything is transparent moving forward. He said these front-end discussions are particularly important for digital health technologies because there may be an incomplete understanding about what the technology actually does. The presubmission process takes about 75 days to complete, said Peña. That process, as well as other efforts to increase interactions with sponsors and provide more transparent guidance on the regulators' expectations for different types of products, has helped support and in part expedited the review of investigational device exemption studies from an average of more than 400 days in 2011 to about 30 days in 2017, he said.

Even if the product is not subject to regulatory approval, if it speaks to people about their condition Peña suggested it may be helpful for developers to consult with the agency to ensure that the right information

[1]Definition of a medical device is specified in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

about the device is conveyed to users. Narayan added that literally thousands of apps are available that make claims related to behavioral health with no supporting data, including some of which give egregiously bad advice. The abundance of these apps makes it challenging for developers to create and promote rigorously designed products in the behavioral health field. Peña responded that a digital health software precertification pilot program, designed to expedite the approval of these technologies and reduce the burden for both sponsors and FDA, may represent part of the solution to the challenge of the pace of digital health, because it may encourage sponsors to come to FDA to help get their product to market. This program is in its formative stages, he said, but should soon be moving to more defined criteria.

Peña noted that the 21st Century Cures Act, signed into law in 2016 to accelerate medical product development and encourage innovation, established a "Breakthrough Devices" program and codified several FDA policies related to digital health. For example, it amended the definition of a "device" to exclude certain software functions, including those intended to provide recommendations to health care professionals for clinical decisions in which the user can independently review the basis of the recommendation. FDA has increased its focus on patient use and preferences in other ways as well, said Peña, in part by partnering with patients and advocacy organizations. For example, they recently held a meeting on the use of real-world data and have published guidance on using real-world evidence in premarket submissions (FDA, 2017b) to ensure that these data are of sufficient quality.

Peña added that federal agencies, including the National Institutes of Health (NIH) and FDA, have also been coordinating efforts to advance device development by including in their funding announcements a requirement for presubmissions.

REGULATORY USE OF DIGITAL DATA IN CLINICAL TRIALS

Digital technologies offer potential benefits for patient-centric drug development through electronic data transmission from patients at home or remote locations and from the ability to capture clinically meaningful measurements continuously in real-life situations, said Jacqueline Corrigan-Curay, director of the Office of Medical Policy at FDA's Center for Drug Evaluation and Research (CDER). Other clinical

trial efficiencies facilitated by digital technologies include enhanced recruitment and retention through the use of electronic informed consent, audiovisual presentations, and virtual visits; improved tracking of adherence to protocols; and increased use of patient-reported outcomes.

For example, CDER has developed a mobile app called FDA My Studies to gather real-time contextual data from research study participants about medication use and other health issues. The app has been tested in a small pilot study as a tool for recruitment and consent in a cohort preselected from electronic health records. Other apps have been developed to track adherence to medication protocols, said Corrigan-Curay. The simplest of these apps employs an electronic diary, but there are also apps that pair with an ingestible marker or approved drug delivery device such as an autoinjector or inhaler. Designed primarily for clinical practice, Corrigan-Curay said these devices may also be incorporated into clinical trials.

Corrigan-Curay classified these technologies into two groups: interactive technologies that rely on active submission of data, and electronic monitoring technologies that gather data automatically from sensors. In either case, devices would need to be evaluated in terms of reliability, reproducibility, sensitivity, specificity, and whether they provide clinically meaningful data, she said. The devices must also be suitable for the intended population, she added. Studies suggest that age and socioeconomic status are not necessarily barriers to the use of mobile devices and online health portals (Irizarry et al., 2017; Ramirez et al., 2016; Rothenhaus, 2015), but certain physical limitations or sensory impairments may be relevant. Whether passive data are fed back to participants remains an open question because of the possibility that they could influence trial results by introducing bias, said Corrigan-Curay. She said FDA has published a draft guidance on the use of electronic records and electronic signatures in clinical research, which addresses issues related to data security, privacy, and traceability (FDA, 2017a). While data security is key to prevent malicious or inappropriate access to data, she noted that clinical investigators and regulators need to have access.

Corrigan-Curay co-chairs the Clinical Trials Transformation Initiative (CTTI), which has developed a roadmap for using mobile technologies in clinical trials. These recommendations were unveiled at an event with the FDA on July 16, 2018.[2] Another organization working to advance the use

[2]To learn more about the CTTI recommendations, see https://www.ctti-clinicaltrials.org/projects/mobile-technologies (accessed August 8, 2018).

of digital tools in clinical trials is the Critical Path for Alzheimer's Disease. Originally named the Coalition Against Major Diseases (CAMD), the organization has worked over the past 10 years to establish data standards and clinical trial simulation tools to support AD clinical trials, said Stephen Arnerić. They established the first integrated database of anonymized information from AD trials and worked with the Clinical Data Interchange Standards Consortium (CDISC) to develop data standards for clinical outcome measures, genetic, and biomarker data (Neville et al., 2017). CDISC standards are now required for clinical trial data submitted to FDA (FDA, 2014). CAMD also developed the first clinical trial simulation tool to be endorsed by regulatory agencies as a tool to model disease progression, placebo and treatment effects, and patient dropouts in clinical trials (Romero et al., 2014, 2015).

The next frontier, according to Arnerić, is for these tools to incorporate biometric and other digital assessments and to use these measures to better model what happens in the presymptomatic stages of disease by understanding real-time changes in function. For example, Arnerić suggested that it may be possible to detect subtle changes in cognition by tracking medication adherence. Computer use and walking speed also predict changes in cognitive function, said Arnerić, and could lead to a dramatic reduction in the sample sizes needed for prevention trials in cognitively intact individuals, resulting in substantial cost savings and a reduction in exposure to potentially unsafe drugs (Dodge et al., 2015). Real-world data can be collected with many different devices across multiple domains (mental and physical function, social engagement, etc.), ideally with data-agnostic platforms. But to transform these data into meaningful real-world evidence will require careful data standardization to bring information into a consistent format, aggregation with other types of contextual information or metadata, and quantitative modeling, said Arnerić (Piwek et al., 2016). Eventually it would also be valuable to link these data to other types of observational data and health records, although these data would introduce additional noise. Data sharing through an integrated research platform such as the Global Alzheimer's Association Interactive Network (GAAIN)[3] is key to making this big data vision a reality, said Arnerić.

A challenge that regulators will have to deal with is how to interpret findings when the objective data obtained through passive monitoring differs from how a person feels or what the physician thinks is happening,

[3]For more information about GAAIN, see http://gaain.org (accessed July 13, 2018).

said Corrigan-Curay. She said this points to the importance of transparency and dialogue with user communities to make sure users trust the technology and do not believe it is replacing their own experience. This can be a particular problem with technologies that purport to objectively measure symptoms such as fatigue and pain, said Narayan. He said contextual information incorporated into the algorithms can sometimes provide answers that align more closely with patient perception. Peña added that these issues are important topics that can be discussed in a presubmission.

NAVIGATING THE REGULATORY WEB

Structuring clinical trials and other clinical research to comply with an evolving web of laws and regulations presents a substantial challenge for research, especially for conducting collaborative research, according to Kristen Rosati. The challenge is particularly acute because these regulations are not harmonized across countries, states, or even across agencies within a country and are constantly in flux, she said. For example, drug and device developers in the United States must comply with the Health Insurance Portability and Accountability Act (HIPAA), the Common Rule (rules governing human subjects research across all federal agencies), FDA regulations, NIH policies, reimbursement policies from Medicare and various state Medicaid programs, and various state health information confidentiality laws. Developers of products for international markets must also comply with the European Union General Data Protection Regulation (GDPR), which became effective in May 2018.

Meanwhile, Rosati said potentially competing policies have emerged across the globe aimed at increasing the ease and utility of research and the ability of individuals to control their own data and biospecimens in both clinical care and research. This includes more individual control over deidentified data because of the potential for reidentification.

Another area of regulatory confusion arises because of the scope of various regulations, said Rosati. For example, in the United States, although HIPAA applies to the health care industry, which is the source of electronic clinical data, mobile medical device companies may fall outside the scope of HIPAA. In 2013, HIPAA was amended to give individuals the right to access their own data and also direct their health care providers to share their electronic data with a third party. This has allowed for the flow of data from mobile medical devices to third parties using the data for clinical care or clinical research, said Rosati. The GDPR, however,

has a much broader scope and thus places more restrictions on confidentiality and the flow of information among different entities, said Rosati, although she added that many aspects of the GDPR remain poorly defined and understood.

The Common Rule has also been subject to change in recent years. A new rule was supposed to take effect in January 2018, but was delayed until July 2018 and then delayed again until January 2019, said Rosati. The status quo at this time is that researchers must comply with the pre-2018 Common Rule, she said, but to future-proof their activities may want to follow the new rule, including one part of the rule that mandates use of a single Institutional Review Board for collaborative multisite research studies. This part was not supposed to take effect until January 2019. Another reason for following the new, but not yet implemented, Common Rule is that other elements related to the information included in informed consent documents and informational confidentiality may be more closely aligned with the GDPR and possibly other state health informational confidentiality laws, said Rosati.

The new Common Rule also has a new HIPAA exemption for secondary research using data or information derived from biospecimens (although not the biospecimens themselves) collected for clinical care or research repositories if the research is otherwise regulated by HIPAA, said Rosati. The new Common Rule also embraces the concept of broad consent, which although poorly defined has raised concerns in the research community as to how it will be implemented and whether it is more onerous than regular informed consent.

Rosati suggested that it might be beneficial for the United States to preempt all the different laws and regulations and replace them with a GDPR, as long it does not end up exactly like the GDPR, which she said poses real barriers to research. But as the laws exist now, anyone contemplating a collaborative research project will have to think carefully about whether their partners will be able to share data and implement appropriate governance activities in a manner that complies with the laws that oversee them. One measure that could help, she said, would be to build in consent to use data for future research, making the description of that research as broad as needed to cover anticipated studies, and also to build in consent to contact individuals about future research activities or future consent.

5

Integrating Mobile Technology into Clinical Practice

Highlights

- Mobile technologies may enable early identification of psychiatric and behavioral disorders and may enable people to optimize care in later stages (Ben-Zeev, Mangravite).
- Clinicians may be reluctant to incorporate mobile technologies into their practice for many reasons, including busy schedules, concerns about being sued, lack of experience with statistical data, and questions about whether the technologies will benefit patients (Ben-Zeev).
- Mobile technologies could reduce face-to-face interactions between clinicians and patients (Hyman), or alternatively could improve interactions if implemented correctly (Manji).
- Addressing clinicians' and individuals' concerns about incorporating mobile technologies into clinical practice will require integrating clinicians, patients, and family members into the device development process (Ben-Zeev, Brunner, Mangravite).
- Gaining the acceptance of digital technologies by health care organizations will require addressing their concerns about costs, privacy, and integration with existing systems (Ben-Zeev, Mangravite).
- Mobile technologies may facilitate a shift from outcome-based to fee-for-service–based payment models (Ben-Zeev).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Mobile technologies offer potential uses across the lifespan, even in the absence of symptoms in at-risk individuals, said Dror Ben-Zeev, professor of psychiatry and behavioral sciences at the University of Washington (See figure 5-1). For example, parents with severe mental illnesses or substance use disorders are vulnerable themselves, and thus they may contribute to a biological and environmental context that places their children at risk for mental health challenges. Deploying mobile health interventions that focus on mental health promotion, education, or parenting skills can have utility in this situation, said Ben-Zeev. Then, as a child with mental illness gradually starts showing signs of illness, mobile technologies may also play a beneficial role through the use of targeted online forums, analysis of social media content, and clinically relevant or diagnostic gaming, he said. Since the penetration rate of social media and gaming is very high in adolescents, these technologies may enable identification of biobehavioral markers at an early stage, he said.

The first episode of a mental illness can be an overwhelming and confusing time for those affected and their families as they struggle with symptoms, the complexity of the health care system, stigma, etc. As a result, clinical research using mobile health interventions has been relatively limited during this illness stage, but that can change, said Ben-Zeev. However, once symptoms are under control, mobile health technologies can be useful in helping people focus on their illness as well as their strengths to optimize symptom management and to think about vocational and psychosocial rehabilitation.

Lara Mangravite, president of Sage Bionetworks, commented that 5 or 10 years may pass before these digital technologies achieve the goal of transforming clinical care by not only monitoring and managing disease, but also understanding what it takes to be healthy in real-world settings through a combination of pharmaceutical interventions, lifestyle and environmental changes, and an overall focus on wellness.

Mangravite described one example of the kind of technology currently being studied at Sage—a smartphone-based application called mPower[1]—which she said has the potential to transition a traditional clinic visit from a place where acute testing is done to a place where the clinician and patient together review longitudinal data that have been collected over time. Alternatively, the data could be evaluated remotely and form the basis for

[1]To find out more about mPower, see https://parkinsonmpower.org (accessed July 29, 2018).

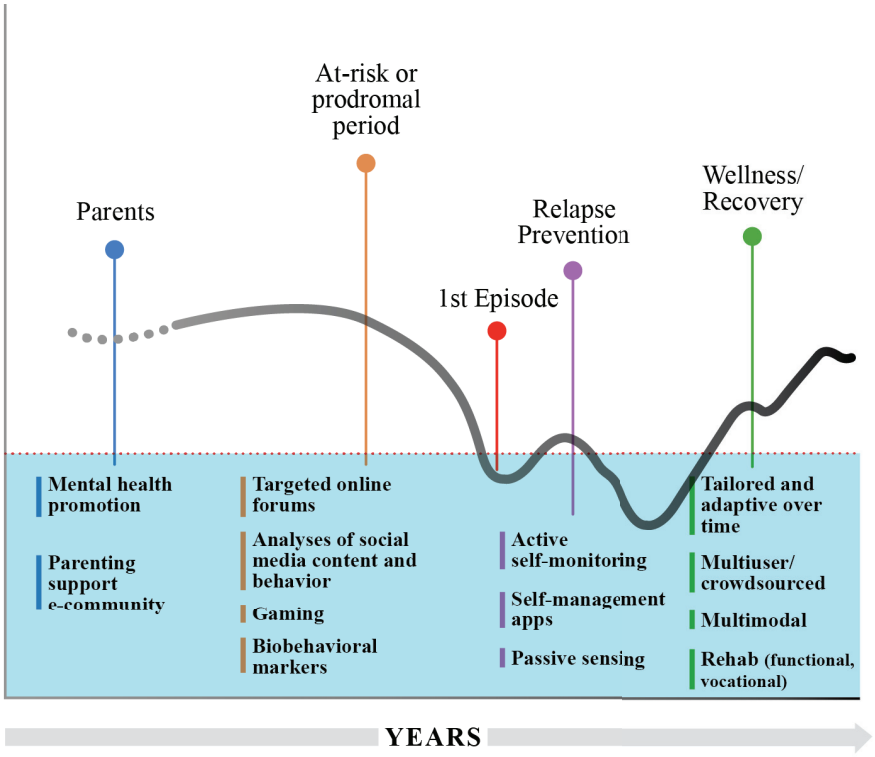

FIGURE 5-1 Detection, intervention, and prevention opportunities across the life span. Mobile technology encompasses a range of uses across the life span, from texting with SMS technology to self-management, to sensing, and finally to predictive modeling.
SOURCE: Adapted from materials presented by Ben-Zeev, June 6, 2018.

determining whether a clinic visit is necessary or even enable the clinician to remotely administer treatments or promote self-management.

Ben-Zeev and colleagues have conducted a randomized controlled trial of FOCUS, a smartphone-based intervention application for self-management of schizophrenia, versus a patient (peer) group intervention called the Wellness Recovery Plan. Both interventions improved clinical outcomes like psychiatric symptoms and recovery, in a comparable manner. Both interventions produced high patient satisfaction ratings. But, a significantly greater percent of patients who were randomized to the mHealth intervention actually commenced treatment (90 percent) compared to those assigned to the clinic intervention (58 percent) (Ben-Zeev

et al., 2018). These data suggest that remote management of health care can bring together the patient, caregiver, community, and clinicians over the course of a treatment plan, according to Mangravite.

Vaibhav Narayan suggested that there might be lower barriers to conducting this type of research in other parts of the world. Husseini Manji said Janssen has considered conducting work in parts of Germany and the United Kingdom that have more closed health care systems. Implementing and debugging these types of technologies may be possible before bringing them to the United States, he said. However, Ben-Zeev noted that different regulatory standards, clinical practices, and technological infrastructure may pose difficulties in terms of how much can be learned and applied to the U.S. context.

CLINICIAN USE OF MOBILE HEALTH TECHNOLOGIES

Clinicians vary in their acceptance, comfort, and willingness to use mobile health interventions in practice. The ideal but clearly non-existent hypothetical clinician, conjured up by Ben-Zeev for demonstration purposes, is a digital native who is already familiar with mobile technology; has formal mobile health training; keeps up with the latest interventional research; and is highly motivated, incentivized by his or her organization to deploy mobile health technologies, excited about multidisciplinary teamwork, a critical thinker, and an avid user of data. Such clinicians also have the time, patience, and capacity to learn, grow, and expand their clinical expertise to improve patient outcomes in a deep, meaningful, and sustainable manner.

In the real world, however, Ben-Zeev and colleagues have found that clinicians are often too busy to explore the use of mobile technologies. They want to know if digital data can be found in the electronic health records they are already required to integrate into their practices. They may resent having to incorporate the new technologies into their care plans because of the increased requirements and documentation. They have concerns about being sued, new training and certification requirements, and lack of experience with statistical data, said Ben-Zeev. Furthermore, they want to know if the technology will improve patient outcomes.

Steven Hyman raised the additional concern that reliance on computationally derived phenotyping could reduce face-to-face interactions between physicians and patients. Husseini Manji, however, suggested that if these technologies are implemented correctly, they could improve the

quality of patient interaction with the clinical team because people could come to their appointments armed with data on how they have been doing, thus enabling the conversation to move more quickly to more substantive issues. Moreover, said William Marks, in the future if physicians are able to monitor their patients remotely, they could focus their attention on those patients who are most in need, eliminating the trip to the clinic.

On top of clinician and clinical staff resistance to using mobile technologies, there is a gap between what researchers think is good for a subject and what the subjects may actually want, noted Daniela Brunner. One way to overcome this, she said, is to focus on educating people about what is available and then having them request it from their clinicians. Mangravite agreed that in the short term, people asking their physicians for these devices and apps is the main way they will penetrate the market. Indeed, said Ben-Zeev, there has been a pendulum swing in psychiatry toward more patient-focused care and shared decision making. In the digital health world, this has led to products specifically designed to inform patients on how to interact with their clinicians to ensure that their voices are heard. In the development of tools, this means integrating people with lived experience and their family members right from the beginning of the process, he said. For example, he recalled that in developing a mobile health intervention for people with schizophrenia, a topic that came up in focus groups with patients and family members was content focusing on sleep. Ben-Zeev said if patients and family members had not called this topic to their attention, he would never have thought of integrating it into a mobile health intervention for schizophrenia because it is not a core symptom.

HEALTH CARE SYSTEMS' INTEGRATION OF MOBILE TECHNOLOGY

User-centered design means more than just the patient and clinician, said Ben-Zeev; it also includes the health care system and the deployment context. Thus, even if there are compelling clinical data to support the use of mobile health interventions, they may not make sense if providers, health care systems, and payers do not embrace their use.

Health organizations' concerns include, according to Ben-Zeev: How much will it cost to integrate these technologies and who will pay for it? Will it generate new revenue or savings? Does our organization have suf-

ficient information technology capacity to use these tools, service and upgrade software, and provide adequate privacy and data security? Can our culture absorb this new technology successfully? How will this technology integrate into our existing services and workflow without being disruptive?

The much faster pace of technology development in comparison with health care delivery presents a major challenge to the integration of these technologies into clinical care, said Mangravite. She suggested that change is likely to come from outside of the traditional system. As an example, she cited Propeller Health,[2] a stand-alone company that provides services using Bluetooth-enabled inhalers to monitor patients with asthma. Propeller integrates data from the inhalers with patient reports on the context in which they are experiencing episodes as a means of helping patients to understand what is triggering these events and how they might avoid them. It even goes so far as to alerting people when particulate matter is above their threshold, suggesting they may want to exercise inside, said Mangravite.

Propeller provides universal benefits across stakeholder groups, said Mangravite. Clinicians can prescribe Propeller, but do not have to manage it. It reduces caregiver burden. For insurers, it reduces costs associated with emergency room visits. Mangravite suggested that these tools may also strengthen the relationships among clinicians, caregivers, and patients, allowing them to interact in a more holistic way. She added that although continuous monitoring may have benefits for people with chronic diseases, there is a different value proposition for healthy individuals, who first need to understand what they are getting into, what the value is, and what the potential consequences are.

The use of mobile technologies may also support a gradual shift among payers to outcome-based rather than fee-for-service–based reimbursement models, said Ben-Zeev. He suggested that payers may be willing to accept objective indicators of functional outcomes as pragmatic indicators of success, for example, if measures show that someone with a psychiatric disability is more socially engaged or is spending more time in the workplace. The promise is there, he said, although these technologies are in a very early stage of development and may not have been integrated into regular practice yet. This points to the necessity of engaging representatives of health care systems, providers, and caregivers and these early focus groups and usability testing projects, said Ben-Zeev. Lisa Holt of Intelligent Automation added that researchers should also be included in

[2]For more information about Propeller Health, see https://www.propellerhealth.com (accessed July 16, 2018).

these focus groups to ensure that clinicians and patients are willing to give them the quality data they need in their studies to advance the science.

The Health Information Technology for Economic and Clinical Health (HITECH) Act, signed into law in 2009, aims to promote the broad adoption and meaningful use of health information technology to improve health care.[3] Ben-Zeev and colleagues have proposed inventing a new breed of health care professionals called "clinical technology specialists" as one mechanism to integrate these technologies in existing health care systems (Ben-Zeev et al., 2015). Not necessarily physicians or other licensed practitioners, these professionals would be embedded within a health care system, have both patient- and provider-facing functions, and be familiar with the range of digital health options available. They could assess and educate patients, provide technical troubleshooting, and support engagement over time, all while relieving busy clinicians of these responsibilities. They could also educate and train clinicians on the functions and resources relevant to their work, said Ben-Zeev.

[3]For more information about the HITECH Act, see https://www.hhs.gov/hipaa/for professionals/special-topics/hitech-act-enforcement-interim-final-rule/index.html (accessed July 16, 2018).

6

Designing Mobile Technologies for Research and Clinical Practice That Reflect Patient Attitudes and Preferences

Highlights

- Realizing the potential of mobile technologies in health care will require widespread adoption by consumers and acceptance by clinicians (Haas).
- To maximize the adoption and usage of smartphone apps and other digital devices, technology developers need to understand the attitudes, beliefs, and experiences of the targeted population and test the technologies in real-world settings (Kaye).
- A survey by the Accelerated Cure Project suggests that people with multiple sclerosis strongly support having access to their own data; however, ensuring that those data are meaningful and understandable is critical (Loud).
- Digital biomarkers are currently being incorporated into clinical trials primarily as exploratory measures, but eventually may supplant rating scales and other more subjective measures of function (Simpson).
- Moving from sensing to intervening may be the next frontier for digital technologies (De Choudhury).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Mobile technologies have the potential to impact health care through monitoring, therapeutic intervention, participant recruitment for clinical trials, and more, but only if there is widespread adoption and use by consumers, and only if the information collected is useful for physicians, said

Magali Haas, CEO and president of Cohen Veterans Bioscience. Consumer attitudes vary with regard to data ownership, access, and privacy; the usability of different types of devices; and the utility of their data, said Haas. Whether they have a disease or are well but worried about the future may impact their decisions about monitoring as well as their propensity to use certain technologies and adhere to protocols, she said.

For example, Haas cited the case of an app called PTSD Coach,[1] which was developed by the Department of Veterans Affairs to help people learn about and manage symptoms resulting from trauma. Despite being one of the most successful apps available in terms of demonstrated validity and number of downloads, an analysis by the developers revealed that actual adoption and usage rates were low, said Haas. This raises questions about the design of the devices, how the devices are implemented in research studies or marketed to consumers, how easy the devices are to set up and use, and the cost of using these devices, she said. In addition, if the devices are intended to be used for self-management, the quality of the data comes into question, as well as the appropriateness of providing direct feedback to people without any physician review of the data or regulatory approval of the device.

A recent review of initial experience with Apple's open-source smartphone platform, ResearchKit, demonstrated a similarly dramatic dropoff in use after initial enthusiasm for five smartphone apps developed in 2015 (Dorsey et al., 2017), said Jeffrey Kaye, Layton Professor of Neurology and Biomedical Engineering and director of the Oregon Center for Aging and Technology (ORCATECH) at the Oregon Health & Science University (OHSU). Kaye suggested that one reason for low adoption rates may be the introduction of a novel technology without first developing a full understanding of why and how the data collected will provide value and why a person would want to become involved in the study. Theories of adoption, including the Unified Theory of Acceptance and Use of Technology (Venkatesh et al., 2003) and the Technology Acceptance Model (Holden and Karsh, 2010), have been around for many years, said Kaye. Essentially, he said, they propose that acceptance of a technology requires developers to "know their customers"; that is, to understand the attitudes, beliefs, and experiences of the people who will be using it.

[1]To learn more about PTSD Coach, see https://www.ptsd.va.gov/public/materials/apps/ptsdcoach.asp (accessed July 18, 2018).

Age is a particularly important factor for technology developers to consider, said Kaye, noting that advanced age is a crucial factor in neurological disorders, with most of the people affected by dementia over the age of 80. A recent Pew Research Center survey found that while use of digital technologies is high even among adults over the age of 65, only about 17 percent of those over age 80 own a smartphone, said Kaye (Pew Research Center, 2017). Thus, technologies developed for the "oldest old" may achieve limited adoption if they rely on use of a smartphone. Moreover, he said, as people age, even the digitally mature will become naïve to the next new technology. Older people with cognitive decline may also have trouble making sense of technology, added Deborah Estrin.

SURVEYING CONSUMER ATTITUDES ABOUT MOBILE TECHNOLOGY

Focus groups and surveys such as those conducted by the Pew Research Center are critical to understanding peoples' preferences and attitudes about a range of issues related to the use of digital technologies, said Kaye. For example, to learn about what multiple sclerosis (MS) patients think about the collection and sharing of health-related data through mobile technology, the Accelerated Cure Project for Multiple Sclerosis surveyed their community of more than 4,600 members, according to Sara Loud, COO of the Accelerated Cure Project. They were able to push this survey to members through iConquerMS.org, an online portal designed to help patients drive MS research by providing personal health information as well as their experiences and opinions, she said.[2] About 650 members responded to the survey. Most respondents (91 percent) own a smartphone or tablet and 28 percent own a wearable. Only about one quarter of them use their smartphone to track their own health, but 71 percent of those with wearables use them to track their health. These numbers are similar to those seen in the general population, said Loud.

About half of those with wearables share their data, mostly with family and friends through social media, but also with health care providers, device manufacturers, and researchers, said Loud. The survey did not assess how receptive health care providers were to the shared data, and Loud noted that health care systems may not have the means to accept these data

[2]To learn more about iConquerMS, see https://www.iconquerms.org (accessed July 29, 2018).

in a format that fits within the constructs of the providers' jobs. Only a few respondents reported sharing data with employers or insurance companies. The primary reason people are not sharing data, according to the survey, is the belief that others are not interested. Other reasons included a lack of knowledge about how to share data and fear of being judged or otherwise negatively impacted.

Loud said the survey also asked participants to imagine how they would feel about using an implantable device designed to help with symptom management if it was offered in a clinical trial setting. The device, they were told, would collect not only symptom-specific data, but also other biological and health activity information, location, etc. Eighty-five percent of respondents said they would consider participating in such a trial, and 39 percent said they would be willing to share any data collected. Some said they would be willing to share only certain information, and 17 percent said they wanted to be able to select what they would share. Respondents were most willing to share data with MS and device researchers, as well as with their health care providers, demonstrating their interest in driving research and improving their health, said Loud. "They want to see that their data can have a manageable and tangible effect on what happens in the understanding of the disease," she said.

Not surprisingly, respondents also expressed concerns about data sharing. These concerns mostly related to fear of losing insurance or health care coverage and loss of privacy, said Loud. She said a few also raised concerns about the reliability of the data.

Respondents also expressed strong feelings about having access to their own information, although Loud acknowledged some reluctance in the research community to provide participants with large amounts of data that may not be actionable. The issue of data return to participants should be addressed in the consent process, with provisos that those returned data are understandable, meaningful, actionable, and accessible, said Loud. She advocated a co-design paradigm where study participants and patient communities are involved both in the design of the study and the crafting of the informed consent.

ASSESSING FUNCTION IN REAL-LIFE SETTINGS

Kaye also uses surveys and focus groups as a first step in an iterative research process for studies aimed at developing technologies to assess real-world functional changes associated with aging (Kaye et al.,

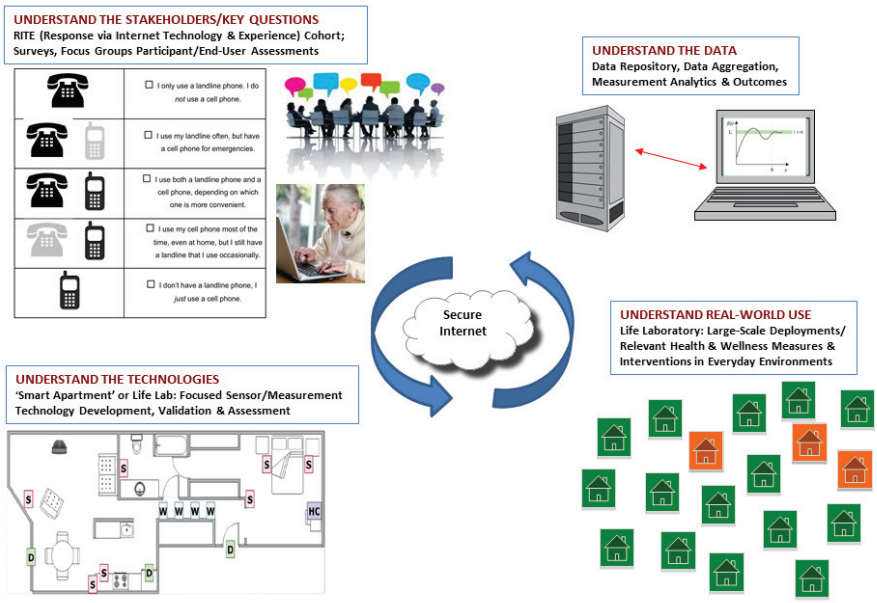

FIGURE 6-1 The Iterative Research Process is a model for developing, executing, and assessing mobile technology trials that are conducted within a real-world setting.
SOURCE: Presented by Kaye, June 6, 2018.

2011) (See figure 6-1). Taking the time to understand the views of all stakeholders involved in the research enterprise is yeoman's work, but necessary to ensure that the research is carried out properly, he said.

To understand how technologies can work in real-world settings, Kaye and his ORCATECH colleagues created the Life Laboratory, where multiple sensors and devices are deployed in people's homes to assess a multitude of functions—activity, mobility, sleep, cognition, social engagement, medication adherence, etc. (Kaye et al., 2011; Lyons et al., 2015). These rich data are stored in a secured data repository and made available for sharing with other researchers, said Kaye. His lab's focus is not about any specific technology, he said. Rather, it is about being able to plug in different technologies to test these functions in a real-life context and compare the data over time.

For example, Kaye's team has used the Life Laboratory to test people's attitudes about using a remote-controlled robot in an older person's homes to facilitate communication between the senior and a "remote collateral individual" (e.g., an adult child or other family member). Both the

older adult participants and the remote collaterals gave the robot high marks in terms of both usability and acceptability, commenting that the robot improved communication, provided a sense of safety, and gave family members peace of mind, said Kaye (Seelye et al., 2012). Only one participant with some cognitive impairment rated the robot unfavorably, he said. Another study conducted by Kaye and colleagues used video chats to boost social engagement in people with normal cognition and mild cognitive impairment (Dodge, 2015). Very high acceptance and adherence to this protocol suggested that isolation among participants made them highly motivated, said Kaye. "They had a reason to want to use the technology, and the technology didn't get in the way," he said.

Developing user-focused technologies also requires consideration of cultural factors, said Kaye. For example, his team collaborated with OHSU's Raina Croff on the Sharing History through Active Reminiscence and Photo-imagery study, which aimed to motivate aging African Americans to walk more by using technology to enhance the culturally relevant experience of walking around historically Black neighborhoods that have been gentrified. As groups of participants walk along a prescribed path, memory markers relevant to their lives are delivered over their smartphones to stimulate discussion (Croff et al., 2018). Kaye said the program has been very popular.

Kaye noted that some of research studies have been less successful despite employing user-centered design principles. For example, he had hoped to show that continuous functional data could be used by decision makers to delay the transition to higher levels of care in retirement communities. However, despite initial enthusiasm, adoption of the technology was poor, and exit interviews suggested that decision makers were not sure how to use the trend data they were provided, said Kaye. Additionally, the technology was not integrated well enough into the systems that already existed at the facility. Nonetheless, Kaye noted that the technology itself worked well and provided a great deal of natural history data from the cohort.

INTEGRATING DIGITAL TECHNOLOGIES INTO CLINICAL TRIALS: BENEFITS TO PATIENTS

Digital technologies can speed up trials, reduce the number of participants required and thus their exposure to potentially harmful treatments, and potentially allow assessments to be conducted remotely, thus reducing

participant burden, said William Marks. As a result, future trials that employ digital technologies may be much more decentralized and diverse in terms of the characteristics of participants, said Vaibhav Narayan. Moreover, said Iain Simpson, they have the potential to provide more precise measures of real-world function. Indeed, Stephen Arnerić predicted that digital technologies will transform the way clinical trials are done.

If designed well, digital technology platforms enable trialists to communicate very clearly with research participants what they are signing up for in the trial and what data they do or do not want to contribute, said Marks. Kaye and Loud agreed, noting that people participate in clinical studies for different reasons. For example, some people participate out of a sense of altruism, while others believe they are going to get information that is meaningful or useful to them, including information that will allow them to self-manage their disease, said Kaye. Various incentives can be used to encourage participation by a broad population.

INFORMED CONSENT

Obtaining informed consent for studies conducted online and using digital devices requires special considerations to ensure that people are truly informed, said Loud. In addition to clear language, she suggested that infographics and other visualizations, as well as quizzes at the end of the consent process, may be needed to be certain that participants fully understand their agreements. The iConquerMS cohort wants a tiered approval process, she said, where they can select who gets the data and be provided full disclosure of the ramifications of their choice to share their data.

Kristen Rosati added that building platforms that enable leveraging data collected for one purpose to be used for other clinical research activities would require structuring the consent to allow this. This should be addressed at the beginning of a study, she said.

DIGITAL TECHNOLOGIES AS INTERVENTIONS

Interventions are the next frontier for digital technologies, said Munmun De Choudhury; however, there are many unresolved research questions about how to move from sensing and predicting to intervening. For example, if an algorithm suggests someone may be at high risk of a health event, what should the intervention look like and how should it be communicated

to the individual? Should the messages point to available resources? De Choudhury emphasized that humans—both clinicians and patients—should be involved in the intervention delivery process loop to ensure that incorrect assessments are circumvented and inappropriate interventions reduced.

Tanzeem Choudhury added that developers of these technologies should think about measurement and intervention simultaneously, including consideration of individuals' acceptance, willingness, and motivation to act on their data and change behaviors. To marry sensing and intervention, she suggested that it will be important to make behavioral interventions fit into the person's routine and lifestyle with low effort. In her experience, individuals with behavioral health problems have been overwhelmingly accepting of digital sensing technologies, which she hypothesized is because they know how debilitating these conditions can be and readily accept anything that keeps them functioning at a healthy level.

7

Moving Forward by Building Partnerships

Highlights

- Different types of partnerships with a broad range of stakeholders have been established to advance the use of digital technologies in health care and treatment development (Kopil, Manji, Peumans, Simpson).
- Bringing companies together across the entire product development spectrum has enabled innovation in the digital technology space, including devices to stimulate behavioral change and assess brain activity for early diagnosis and disease progression monitoring (Peumans).
- People with neuropsychiatric disorders have been willing and valuable partners in research studies demonstrating novel ways to assess depression, suicidal ideation, and impending relapse of schizophrenia (Torous).
- To address physicians' concerns that digital devices may interfere with the patient–clinician relationship, clinicians, patients, and device developers need to work together as partners (Torous).
- Digital platforms have been developed that enable individuals to share their data with their physicians as well as with researchers (Arianpour).
- Data sharing enables partners to work together and to correct and avoid mistakes (Onnela, Simpson).
- To enable data aggregation from multiple types of sensors and devices, raw data need to be shared as well as information about the sensor itself and the context in which data were collected, but this sharing can run counter to device

manufacturers' business models and practices (Narayan, Onnela, Peumans).
- Consortia could enable pooling data across many neurological diseases that may share common constructs and domains to maximize learnings, but many issues need to be resolved to move these types of projects forward (Haas, Kopil, Potter).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Having a large and diverse group of stakeholders together at the table from the very beginning of the process of developing digital technologies is essential as society addresses ethical and privacy issues related to their use, said Husseini Manji. Magali Haas noted that the workshop itself brought together precisely those stakeholders who could play a part in building precompetitive partnerships with patients at the center providing the data.

AN ECOSYSTEM OF PARTNERSHIPS

One of the goals of the workshop, said Manji, was to brainstorm about how to bring diverse stakeholders together in what he called an "ecosystem of partnerships" to advance the use of digital technologies in health care and treatment development. These partnerships may take many forms, including public–private partnerships and through work with foundations.

Building Partnerships with a Disease and Patient Focus

The MJFF has been an exemplar of a foundation that has moved the field forward through partnerships, said Manji. Their scope extends across the research and development continuum and all the way through health care delivery, according to Catherine Kopil. Thus, they engage a wide array of partners—individuals with PD and their families, health care providers, pharmaceutical and biotechnology companies, medical device and app developers, regulators, and payers—to maximize the chance of success over both the long and short terms. They do so, she said, in service to

people who are living with this chronic neurodegenerative disease and who are willing to take risks to expedite discovery of a cure.

MJFF takes a portfolio approach to investing both in therapeutic development directly and in projects that tackle field-wide challenges, such as the development of biomarkers and novel endpoints that could be used for clinical trials and to improve clinical care, said Kopil. These endpoints include data from biosensors that could help detect the cardinal symptoms of PD: tremor, rigidity, and bradykinesia. Indeed, she said that in 2014, MJFF decided to take a proactive role in developing mobile tech endpoints by establishing a partnership with Intel to develop a tool that could provide an objective measure of function as well as patient-reported outcomes. One lesson from this early effort was the need to integrate the patient community's perspective in an iterative fashion throughout every step of the development process, said Kopil. They also encountered challenges that are still ongoing around data standards and privacy, and the challenge of transforming data into usable information.

An unintended consequence of the Intel partnership, said Kopil, was that by aligning themselves with an exclusive partner, they positioned themselves as competitors to other device developers rather than as a facilitator and sharer of information. This led them to convene the Mobile Tech Advisory Council, which gathered 10 industry partners and the Critical Path for Parkinson's Consortium to work together in a collaborative manner. They have also partnered with Sage Bionetworks to contribute data from the Intel project to a shared data challenge.

To facilitate the collection of real-world data from people with PD, Kopil said MJFF also invested in a digital platform they call Fox Insight, which uses online questionnaires to collect data on the experiences of persons living with PD. In addition to using Fox Insight for this longitudinal observational study, MJFF is also partnering with two NIH-funded clinical trial teams to conduct long-term follow-up of trial participants with PROs, biosensors, mHealth apps, and telemedicine visits.

Building a Partnership to Advance Digital Biomarkers

Developing digital biomarkers is an iterative process, requiring collaboration from a broad range of stakeholders, said Iain Simpson of IXICO. At every step of the way, from biomarker discovery to clinical trials to clinical practice, IXICO brings together clinicians, academic researchers, technology companies, and pharma partners. They evaluate and

validate biosensor measures as markers of disease state; translate algorithms for use in clinical research; deploy them in clinical trials in a way that minimizes site and patient burden; collect the data alongside existing clinical endpoints; and interpret the data to improve clinical outcomes and inform decision making. IXICO is independent and technology agnostic, said Simpson, which allows them to focus on what is important to measure rather than trying to advance a particular technology. "We are sort of a broker between the technology providers and the pharmaceutical companies," he said.

Building Partnerships That Look to the Future of Technology

Peter Peumans, senior vice president for life science technologies at imec, calls his company an "ecosystem enabler." By bringing together companies across the entire product development spectrum—from material suppliers to chip designers and manufacturers to application companies that integrate chips into their products—they are figuring out how to build the next generation of nanoelectronic and digital technology and leverage those technologies to provide useful products in the life sciences and health care.

For example, Peumans described a silicon probe that records neural activity from multiple brain structures in freely moving animals. The probe was developed by imec and academic partners, with funding from the Allen Brain Institute, Gatsby Charitable Foundation, the Howard Hughes Medical Institute, and the Wellcome Trust. The system is capable of reading signals from hundreds to thousands of neurons at the single-neuron level simultaneously, thus allowing assessment of neural circuitry at a much lower cost than could be done with other technologies, said Peumans. One of imec's requirements for this project was that after the technology was developed and validated, it would be made available to the community at large as a standardized tool, he said.

imec is also looking to advance wearables that produce high-quality medical data and has begun to build an ecosystem around using these devices to stimulate behavioral change, said Peumans. Other projects focus on developing better ways to measure the brain directly to enable earlier diagnosis and disease progression monitoring, and developing preclinical tools that will improve understanding of disease and translational success.

imec and its partners at the Universitaire Ziekenhuizen Leuven, the Katholieke Universiteit of Leuven, and the life sciences research institute

VIB have also launched Mission Lucidity to "decode" dementia by creating technologies that enable high-resolution measurement of brain activity,[1] said Peumans.

Clinicians and Patients as Partners

People with various neurologic and neuropsychiatric disorders have demonstrated a willingness to use digital tools both as partners with their clinicians in managing their health and as participants in research studies. In many cases, these studies have shown that smartphone apps and other digital tools may more accurately capture intraindividual variations in symptomatology over time, said John Torous, director of the division of digital psychiatry at Beth Israel Deaconess Medical Center in Boston. For example, in a partnership with JP Onnela and colleagues, Torous used a personal smartphone custom app to assess depressive symptoms, including suicidality, in participants with major depressive disorder. The study compared daily scores on questions from the Patient Health Questionnaire-9 (PHQ-9) with scores obtained using the traditional paper form of the PHQ-9. Torous said the scores were closely correlated, although the app scores were higher and with more reports of suicidality than the paper scores, suggesting that people may report more severe symptoms when providing data over a smartphone (Torous et al., 2015). In another study using the Beiwe digital phenotyping platform discussed in Chapter 3, Torous and colleagues showed that passive data collected on a smartphone can signal an oncoming relapse in individuals with schizophrenia (Barnett et al., 2018).

Torous noted that some psychiatrists may be resistant to these technologies, seeing them as coming between them and their patients. He suggested that new clinical models developed in partnerships among clinicians, patients, and device developers may be needed to move these technologies forward. Indeed, he cited a case where a man taking antipsychotic medication conducted his own smartphone-based study to track the relationship between auditory hallucinations and medication dose (Torous and Roux, 2017). The system he created helped the man understand how his medication was working in a way that made sense to him, said Torous, illustrating the importance of listening to people's lived ex-

[1]To learn more about Mission Lucidity, see https://www.missionlucidity.com (accessed July 24, 2018).

periences and how they are using technology to manage their health problems. Indeed, he said, there are hundreds of apps available already that patients are using, and clinicians are being called on to provide guidance about the use of these apps. To address this topic, the American Psychiatric Association has developed a hierarchical framework to guide informed decision making around smartphone apps for use in clinical care (Torous et al., 2018).

Digital platforms can also be engineered to enable people to share their personal data with family members, clinicians, and researchers. For example, Ardy Arianpour, CEO of the consumer-driven health care technology platform, Seqster,[2] said his company has created two platforms—Health One for individuals and the multigenerational platform Health Trust for families—that enable people to aggregate their health data together from apps and wearables, genomic studies, electronic health records, and questionnaires, thus empowering them to take control of their health. The main challenge, said Arianpour, was interoperability. He said that Seqster has integrated cross-platform, multisourced data. They have also built a research portal as a way for participants to share anonymized data for research purposes. This has allowed them to partner with Boston University, the Boston University Ryan Center for Sports Medicine, and the National Football League on a concussion study, and with the Glenner Alzheimer's Family Centers on a reminiscence technology project. Seqster is built on the idea that individuals have a legal right to accessing their own health data and sharing those data with whomever they choose, said Arianpour. Developing the platform required extensive consultation with lawyers and data scientists to ensure there were no violations of HIPAA or GDPR regulations.

Partnerships Across Disciplines

Munmun De Choudhury added that partnerships across disciplinary boundaries are critical for developing social media-based approaches to diagnose, treat, and prevent mental illnesses. For example, she collaborated with clinical partners to develop a human-centered machine learning approach applied to a linguistic analysis and of Twitter data to identify social media markers of schizophrenia (Birnbaum et al., 2017). This approach, she said, has the potential to reduce the duration of untreated psychosis. She and her collaborators are also studying Facebook and Google archives from a set of young adult psychosis patients to develop a model

[2]To learn more about Seqster, go to https://seqster.com (accessed July 24, 2018).

predictive of early relapse, based on language and behavior expressed through social media.

ENABLING PARTNERSHIPS THROUGH DATA SHARING

Data sharing is one of the biggest challenges that limits the ability for partners to work together effectively, said JP Onnela. Simpson agreed, adding that while there will always be mistakes made in the development of new technologies and drugs, by working together and sharing data, it may be possible to minimize those mistakes and avoid making them again.

As an example of how data sharing facilitates the correction of mistakes, Onnela cited the Hubble telescope. When it was first put into orbit in 1990, a major problem was discovered with the mirror, he said. However, a group of scientists working together and sharing their data were able to compensate for the problems by coming up with new image-processing techniques that turned very noisy data into meaningful information, essentially turning blurred images into clear pictures. Similarly, Onnela argued that the "golf cart problem" mentioned in Chapter 3, when a smartphone registered driving over terrain in a golf cart as steps, was not a failure of data but a failure of inference. If you have the underlying data, they can be reanalyzed, he said.

Onnela wondered if there might be a way to collect raw data across different devices, feed those data into openly available algorithms culled from different sources, and reanalyze the data to produce meaningful and harmonized output. The process begins with collecting the data, which requires a collection platform and a way to standardize the data to put it all on a level playing field, said Arianpour. Standardization enables both data sharing and data aggregation, he said.

One problem with data aggregation from digital devices such as wearables is that sensors and devices, especially in the consumer space, provide access only to reduced data such as step counts, which would not be informative for algorithms, said Vaibhav Narayan. Custom-designed devices provide differentiation in the marketplace, which has commercial value for developers. The challenge for researchers, he said, is to convince and/or incentivize consumer tech companies to collect and store high-resolution raw data so they can be compared with data from other devices and used for other purposes. For example, Onnela said that raw data extracted from the accelerometers and gyroscopes in both Android and iOS devices are typically packaged by those devices to provide information on the number of steps taken, but could also be used to estimate the frequency

and amplitude of tremors in people with AD or PD. Peumans said that in addition to sharing the raw data, device developers would also need to share information about the sensor itself to enable cross-calibration of the data. Sharing the context in which data were collected is also important to enable translation of data into meaningful information, said Simpson.

For medical device and app developers interested in having access to research cohorts, Kopil suggested that groups like MJFF can play a role in forming partnerships contingent on the partners' willingness to share raw data and algorithms. Although there is a long contracting process involved in these partnership agreements, Kopil said access to patient populations and other resources may incentivize developers to share data and algorithms. Simpson added that the bigger the pool of data is, the more valuable it becomes. However, he suggested that the raw data, not the algorithms, are the currency that is important to share because comparison of raw data can often resolve differences among devices and allow recalibration.

The other value of raw data is being able to reanalyze it as the devices and algorithms improve, said Simpson. However, he said some devices are not designed to provide raw data because they do the processing on the device itself and then discard the raw data. Deborah Estrin added that in some contexts, higher level processed data may be sufficient, and as Kopil noted, storing processed data is much more cost effective. Simpson advocated retaining as much raw data as possible, recognizing that there are tradeoffs to be made between the cost of storage now and the cost of lost information in the future.

Arianpour commented that these raw data exist in various forms that may or may not be understandable to researchers depending on the type of data (e.g., genotyping data, geolocation data, etc.). On the one hand, he said there may be platforms that have automated the process of transforming these raw data into a form that is more easily understandable and thus potentially more useful to researchers and other individuals. On the other hand, Narayan said that for researchers searching for a signal, such as might be the case for an investigator working with potential digital biomarker data, getting access to the raw data is very helpful. He suggested that research-grade devices such as those developed by imec may be able to facilitate the collection, storage, and deployment of raw data. Peumans agreed, noting that imec does exactly that: developing such devices with input from clinicians and then sharing those devices with the community. He added that they are very open to further discussions and collaborations in this area.

The desire to make data sharable, while still maintaining usefulness and fidelity, aligns with the patient-centered work of disease-focused foundations such as MJFF and Accelerated Cures for MS, said Magali Haas. Moreover, she suggested that this model could be used to create public–private consortia around the use of digital medical devices in neurosciences research and health care. Across many neurologic diseases, there are many common constructs and domains, she said, as well as a range of approaches to measure them systematically using next-generation wearable devices. Consortia could facilitate putting all these data in a common pot for multiple researchers to analyze, confirm, and validate. Another benefit of such consortia that take a person-centered approach, said Kopil, is the potential emergence of collective shared responsibility to understand health holistically rather than individually tackling each specific interest group.

One project already operating in this space is Verily's Project Baseline. This is an effort to map human health, initially by studying 10,000 adults, many of whom have or are at risk for various medical conditions, said William Marks. Another potential opportunity on the table was mentioned by William Potter, senior advisor at the National Institute of Mental Health. The All of Us research program has already begun enrolling what is anticipated to include 1 million participants in this longitudinal, data-driven observational study, although final decisions about how to collect, store, analyze, and interpret the data are still being formulated, according to Potter (see Box 7-1). He said NIH is bringing together not only its various institutes, but also advocacy groups and other stakeholders to ensure alignment of goals and operational aspects of the project.

BOX 7-1
All of Us

The All of Us Research Program, launched by the National Institutes of Health in 2015 as part of the Precision Medicine Initiative, has set its sights on capturing genetic and personal health information from 1 million Americans. The goal: to gain a better understanding of the biological, environmental, and behavioral factors that contribute to the diseases that impact public health as a prelude to developing better treatments, cures, and preventive strategies.

Digital health data from mobile devices and electronic health records, combined with genomic data, biospecimens, and participant-provided information, will be collected over a 10-year period. A participant portal will provide participants with access to their own data. Academic and industry researchers as well as citizen scientists will also have access to deidentified data.

Enrollment for All of Us began in May 2018, although many components of the research program are still in development, including selection of mobile devices, apps, and other sensors.

FINAL REMARKS

William Marks concluded his remarks by saying that the convergence of these technologies and opportunities offers the prospect of developing better measures of brain disease. Initially complementary, digital measures may at some point replace more traditional measures, he said. To improve beyond what he called "the crude methodology" currently available, he asserted that the thoughtful collection, organization, and activation of data are critical. Beyond that, he said, there is an immense opportunity to expand research, accelerate therapy development, and ultimately improve outcomes for our patients.

A

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B

Workshop Agenda

Harnessing Mobile Technology to Predict, Diagnose, Monitor, and Develop Treatments for Nervous System Disorders—A Workshop

June 5-6, 2018
Keck Center of the National Academies
500 Fifth Street, NW, Washington, DC

Background:

Despite the prevalence of central nervous system (CNS) disorders worldwide, there is limited understanding of natural disease course, patients' own experiences of the illness, the manifestation of its symptoms, and responses to treatment. Assessment of function for many disorders—including Parkinson's disease, Alzheimer's disease, mood disorders, and schizophrenia—typically is based on subjective or self-report tests during clinical visits. These provide only snapshots in time, and patients may use extra effort in a doctor's office, which obscures usual function. The miniaturization and proliferation of devices and mobile technology has led to an explosion of interest in developing tools that provide reliable, high-quality, continuous data collection from large patient populations in their natural settings and activities.

The use of devices to advance research and treatment for CNS disorders holds tremendous promise, including enabling major advances in identifying prodromal and subclinical states, but also raises important technological, methodological, ethical, privacy, security, and regulatory issues. For example, there are challenging questions regarding validation of data obtained using device and mobile health technologies. Other important methodological considerations arise with novel approaches for data collection and treatment delivery, such as

open source platforms for obtaining and distributing digital biomarker data, behavioral and digital phenotyping, data-driven learning engines, and the use of real-world evidence. There are also questions about who bears responsibility for supporting the cost and infrastructure for data storage and analysis, and how to integrate these data with clinical records. Additionally, while the use of mobile technology for treatment may increase access to care, it also raises ethical issues related to the "digital divide," informing people about prodromal and subclinical states, as well as data ownership and release.

To help advance the appropriate use of devices and mobile technology to predict, diagnose, monitor, assess adherence, and develop treatments for CNS disorders, the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders will host a public workshop.

Workshop Objectives:

The workshop will bring together experts and key stakeholders from academia, government research and regulatory agencies, the technology and pharmaceutical sectors, and non-profit organizations to explore current opportunities afforded by developments in device and mobile health technology to advance research and treatment of CNS disorders. Invited presentations and discussions will:

- Explore innovative approaches to using device and mobile health technology to predict, diagnose, monitor, assess adherence, and develop treatments for CNS disorders, including discussion of methodology, analytical techniques, and the evidence needed to validate the data for use in research and the clinic.
- Share approaches and lessons across efforts to apply device and mobile health technology in different CNS disorders, and identify opportunities for collaboration.
- Discuss regulatory, privacy, ethical, security, and practical issues that specifically arise when using devices for CNS disorders, such as collection, analysis, storage, and use of behavioral information and assuring parity in access to these technologies.

DAY ONE: June 5, 2018

1:30pm **Welcome**
HUSSEINI MANJI, Janssen Research & Development, LLC, *Co-Chair*
JP ONNELA, Harvard School of Public Health, *Co-Chair*

Session 1: Current Measurement Gaps and Opportunities Afforded by Mobile Technology

Session Objectives:

- Provide an overview of current measurement challenges and gaps in predicting, diagnosing, monitoring, and assessing treatment effects for central nervous system disorders.
- Discuss how mobile technology could address these gaps, illustrated with use cases from different domains, such as neurodegenerative, neuropsychiatric, and substance use disorders.
- Highlight which technologies are viable now and outline a vision for future digital technologies that could be useful in this domain.

1:40pm **Introductory Remarks**
STEVEN HYMAN, Stanley Center for Psychiatric Research, Broad Institute of Harvard and Massachusetts Institute of Technology, *Moderator*

1:50pm **Speakers**
WILLIAM MARKS, Verily
HUSSEINI MANJI, Janssen Research & Development, LLC
JP ONNELA, Harvard School of Public Health

2:25pm **Discussion**

2:50pm **Break**

Session 2: Making Sense of Mobile Technology Data, Data Standards, Validation, and Reproducibility

Session Objectives:

- Explore challenges in making sense of raw smartphone sensor and log data for the purposes of predicting, diagnosing, monitoring, and developing treatments for nervous system disorders.
- Examine how data standards and validation requirements differ according to intended purpose—such as basic research, use in therapeutic development, clinical decision making, and patient self-management—with a focus on challenges specific to CNS disorders.
- Discuss data analytic approaches that could help address these challenges and enhance interoperability, validity, and reproducibility.

3:20pm **Session Overview**
JP ONNELA, Harvard School of Public Health, *Moderator*

3:30pm **Speakers**
DANIELA BRUNNER, Early Signal Foundation
TANZEEM CHOUDHURY, Cornell University
MUNMUN DE CHOUDHURY, Georgia Institute of Technology
LUIS MATOS, Roche

4:30pm **Discussion**

5:30pm **Adjourn Session**

DAY TWO: June 6, 2018

8:30am **Overview of the Second Day**
HUSSEINI MANJI, Janssen Research & Development, LLC, *Co-Chair*
JP ONNELA, Harvard School of Public Health, *Co-Chair*

Session 3: Regulatory Considerations and Pathways

Session Objectives:

- Provide an overview of current regulatory pathways that involve digital technologies, including any specific policies or considerations for nervous system disorders.
- Explore challenges, such as the need to balance data required for regulatory purposes with the speed at which this field is moving.
- Discuss standards and metrics of quality and strength of evidence, beyond safety considerations, and how these standards and metrics can be developed.
- Examine how to "future proof" research through the evolving Common Rule, and consider key HIPAA compliance issues in research and development of wearables.

8:40am **Session Overview**
VAIBHAV NARAYAN, Janssen Research & Development, LLC, *Moderator*

8:50am **Speakers**
CARLOS PEÑA, Center for Devices and Radiological Health, FDA
JACQUELINE CORRIGAN-CURAY, Center for Drug Evaluation and Research, FDA
STEPHEN ARNERIĆ, Critical Path Institute
KRISTEN ROSATI, Coppersmith Brockelman; Past President, American Health Lawyers Association

9:50am **Discussion**

10:45am **Break**

Session 4: Designing with the Users
Part 1: Integrating Mobile Technology into Clinical Practice

Session Objectives:

- Discuss potential benefits of integrating mobile technology into clinical practice, for example, for use as decision-making tools and for forecasting.
- Explore how to better engage physicians as a key stakeholder and user of mobile technologies to predict, diagnose, and monitor nervous system disorders.
- Consider incidental findings related to brain disorders, especially with regard to predicting and diagnosing prodromal and subclinical states, and discuss how approaches in other fields (e.g., radiology) could inform policies in this domain.

11:00am **Session Overview**
LINDA BRADY, National Institute of Mental Health,
Moderator

11:10am **Speakers**
DROR BEN-ZEEV, University of Washington
LARA MANGRAVITE, Sage Bionetworks

11:40am **Discussion**

12:00pm **Lunch**

Session 4: Designing with the Users
Part 2: Patient Attitudes and Preferences

Session Objectives:

- Describe user/consumer attitudes and ideas related to mobile technologies—both universal themes across different populations of people with health conditions as well as preferences and considerations specific to patients with CNS disorders.
- Explore potential benefits to patients; innovative digital technologies that enable implementation of patient preferences on data ownership, access, and privacy; and use of digital technologies in patient self-management.

1:00pm **Session Overview**
MAGALI HAAS, Cohen Veterans Bioscience, *Moderator*

1:10pm **Speakers**
SARA LOUD, COO, Accelerated Cures Project for Multiple Sclerosis
JEFFREY KAYE, Oregon Health & Science University

1:40pm **Discussion**

2:15pm **Break**

Session 5: Moving Forward Through Building Partnerships

Session Objectives:

- Synthesize key highlights from the workshop presentations and discussions, including identifying next steps and promising areas for future action and research.
- Explore the "ecosystem of partnerships" needed to drive the field forward, and discuss mutually beneficial models that could help overcome differences in business models and incentives used by the various stakeholders in this space, including tech companies, app developers, therapeutics developers, foundations, and electronic health records companies.

2:30pm **Session Overview**
HUSSEINI MANJI, Janssen Research & Development, LLC, *Co-Chair*
JP ONNELA, Harvard School of Public Health, *Co-Chair*

2:45pm **Panel Discussion**
KATIE KOPIL, The Michael J. Fox Foundation for Parkinson's Research
IAIN SIMPSON, IXICO
PETER PEUMANS, imec
ARDY ARIANPOUR, Seqster
JOHN TOROUS, Beth Israel Deaconess Medical Center

3:45pm	**General Discussion**
4:50pm	**Closing Remarks from the Co-Chairs**
5:00pm	**Adjourn Workshop**

C

Registered Attendees

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Leigh Abts
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