THE CONVERGENCE OF MEDICINE AND TECHNOLOGY

By Denise Myshko

Digital therapeutics are a hot commodity. The idea: software can improve a person's health as much as a drug can, but without the same cost or side effects.

Imagine instead of a pill, a doctor prescribes a game for a child with attention deficit disorder. Or imagine patients dealing with substance abuse being prescribed assessments they can do via a mobile device to track progress.

These software programs are part of a new class of therapeutics — digital medicines — that can lead to changes in behavior and provide clinical benefit. But digital therapeutics go beyond games or behavior modification programs; they are digital tools that have been tested in clinical trials to assess safety and efficacy. Digital therapeutics represent a new generation of healthcare that use innovative, clinically validated disease management, and treatment technologies to enhance, and in some cases replace, current medical practices and treatments.

And a new group of companies is pursuing regulatory approval of these new therapeutics.

"We see prescription digital therapeutics in the same vein as the emergence of the biotechnology industry 40 years ago," says Zack Lynch, general partner, JAZZ Venture Partners. "Digital therapeutics is in its beginning stages. There will be an emergence of multiple major corporations that will generate significant revenue in the years to come. Over the next decade, we will see the evolution of this trend as these companies tackle different indications."

Mr. Lynch adds that there will be multiple approvals across a wide variety of indications, which will generate significant revenue. "Then we'll see the emergence of even more start-ups tackling many of these indications where patients, hundreds of millions of individuals who are suffering from disorders and illnesses, will benefit from the emergence of these new applications to treat their symptoms as well as the fundamentals of disease."

Akili's product for ADHD uses mechanics and techniques from games that can engage and track a patient's progress over time.

The digital therapeutics market is expected to be valued at $457.9 million by 2021, according to MarketandMarkets. And, according to Rock Health's Mid-Year funding report, the amount of venture capital money invested into digital health companies in the first half of 2017 was monumental. The first quarter of 2017 broke multiple funding records, including total funding ($3.5 billion), number of deals (188), and the average deal size ($18.7 million).

Digital therapeutics includes a field of healthcare that is addressing behavior change, condition monitoring, compliance, and establishing a baseline of healthcare data through devices and connected services.

Industry leaders are excited about the possibility of digital medicines.

"There's a tremendous possibility, particularly as we move toward outcome-based versus service-based medicine," says Andrew Wright, VP of digital medicines, Otsuka America Pharmaceutical Inc. "There is a high level of interest to find use cases that are meaningful and can potentially deliver value back to the healthcare system."

Eddie Martucci, Ph.D., president and CEO, Akili Interactive, believes that five years from now we will see digital medicine being used in mainstream medical care, meaning alongside or even in combination with standard pharmacological treatment.

"There's a lot of receptivity from different communities to digital therapeutics," he says.

More than ever before, this field includes making patient data relevant and portable to a growing population of healthcare professionals, who are aligning patient behavior with their care needs, says Chris Cullmann, head of digital at Ogilvy CommonHealth Worldwide, a WPP Health & Wellness company.

"Digital therapeutics are a huge opportunity for pharma, an opportunity that needs to be addressed with nuance, but still a chance to move forward into the personalized health arena," he says. "For pharma companies, cre-

FAST FACT

THE DIGITAL THERAPEUTICS MARKET IS EXPECTED TO BE VALUED AT $457.9 MILLION IN 2021.

Source: MarketandMarkets

ating the architecture to safely share data with context to their provided therapies is going to be key. In exchange, manufacturers will have more specific response and outcome data and a greater field of view into interactions and behavior."

There is no existing marketplace model for digital medicines but companies such as Pear Therapeutics and Akili Interactive — along with a new organization formed in October, the Digital Therapeutics Alliance — are working with regulatory authorities, physicians, payers, and other stakeholders to create pathways for these therapeutics.

These companies are also working to overcome some of the skepticism about calling these therapeutics "medicines."

Alex Waldron, chief commercial officer at Pear Therapeutics, says the legitimacy of wellness apps or diagnostics apps in the minds of physicians and payers is marginal and their use has been limited due to lack of clarity on outcomes.

"Wellness apps can confuse physicians and patients more than help them," Mr. Waldron explains. "Clinicians have been taught in medical schools to look at clinical data and make an unbiased judgment based on the data at hand. If there is a lack of data, the legitimacy can be diminished. These digital products have not been run through the regulatory agency for approval to show efficacy nor do they have a label in place."

Mr. Waldron says the company is working with payers to develop reimbursement codes and pathway for reimbursement for reSET, a 12-week interval prescription therapeutic for substance use disorder, which was approved to be used in conjunction.

In October 2017, Pear Therapeutics received an Expedited Access Pathway-O (EAP) designation from the FDA for its reSET Prescription Digital Therapeutic, the first of its kind designed for treating opioid use disorder. reSET, is the first FDA-cleared prescription digital therapeutic to treat any disease. In randomized clinical studies, reSET demonstrated improvement in the outcomes of abstinence and treatment retention in patients with substance use disorder.

Mr. Waldron says Pear Therapeutics realized that to create a therapeutic that patients and physicians would use, the company would need to show that reSET, as well as other therapies in its pipeline, would legitimately help people.

"The degree of legitimacy we wanted was only going to come if the medicine was reviewed by the highest healthcare authority in this country and that's the FDA," Mr. Waldron says. "We also wanted to provide clarity for payers. Payers will not pay for apps because frankly, the data isn't compelling if the product hadn't been reviewed by the FDA."

Dr. Martucci says market research shows prescribers want to see data supporting the use of games and other digital solutions as being therapeutic, and the mental health arena is ripe for a new type of therapeutic. Akili's product uses mechanics and techniques from games that can engage and track a patient's progress over time.

"The healthcare system, especially in neuroscience and neuropsychiatry, does not have new modalities of treatment for a number of really important diseases," Dr. Martucci says. "If we could converge medicine for disorders related to the brain with tools deployed entirely digitally, we could target neurological function at the basic level and we could do this through phones and tablets using exciting and engaging experiences."

Dr. Martucci from Akili says the trials

Defining Digital Therapeutics

Digital therapeutics are clinically validated solutions that may be used as standalone interventions or in association with other treatments to engage patients and improve the overall quality, cohesion, outcomes, and value of healthcare delivery. These products demonstrate safety and efficacy in randomized clinical trials, receive regulatory clearance when used as a medical device, integrate into clinical practice, and tailor to patients' clinical needs, goals, and lifestyles. These solutions consist of patient-facing treatments, clinical assessment and outcomes tracking tools, clinician monitoring dashboards, and HIPAA-compliant data storage.

Prescription digital therapeutics are designed to enhance clinical outcomes, and, where clinically relevant, may be combined with current treatment regimens, including approved drug or device therapies. Prescription digital therapeutics usually include: patient-facing applications, clinical assessment and outcomes tracking, clinician monitoring dashboards and HIPAA-compliant data storage.

Source: Digital Therapeutics Alliance

were necessary to bring validation for families and for physicians.

"There are a lot of products on the market that report or claim to have a benefit or allude to having a benefit," he says. "It's very hard for families — rightfully so — to have confidence in what's out on the market. We want to go through the FDA to receive a direct treatment claim. We want to show the product has legitimacy as a medicine that a doctor could use and prescribe and have in their tool set."

Software as a Therapeutic

Akili and Pear Therapeutics are among a handful of companies developing software programs that are being tested in clinical trials to assess their efficacy.

Pear Therapeutics' reSET is a 12-week prescription therapeutic approved to be used as an adjunct to standard, outpatient treatment for substance use disorder related to stimulants, cannabis, cocaine, and alcohol. The product combines patient-facing interventions and assessments via a mobile device, with clinician-facing dashboards and data analytics on the back-end.

"Our platform and the thesis for the company is that in many diseases, particularly diseases of the brain, there are two primary mechanisms by which the disease can be treated," says Yuri Maricich, M.D., chief medical officer, Pear Therapeutics. "One is by modulating brain chemistry through drugs and the second is using what we call neurobehavioral interventions or behavioral interventions to transform and impact the neurobiology and neuropathophysiology of neurocircuits involved with the disease."

He says this integrates the same approach of evidence-based modalities such as neuropsychotherapy, cognitive behavioral therapy, and desensitization therapy.

Dr. Maricich says there is a corpus of data and literature that shows for many diseases of the brain, for example depression, when a drug therapy is augmented by a form of neurobehavioral therapy such as cognitive behavioral

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therapy that the clinical outcome is better when used in combination rather than either approach alone.

Pear's reSET has been shown in randomized clinical trials to increase both abstinence from a patient's substance abuse during treatment and retention in the outpatient treatment program. The product also provides access to self-reported substance use, triggers, cravings, and outcomes to the patient's medical provider to support both the clinician and the patient.

The company worked closely with the FDA, submitting the prescription digital therapeutic via a De Novo pathway regulatory filing to create a new classification code and label claims. The FDA cleared reSET as a therapeutic to improve the outcomes of patients with SUD.

To support the FDA submission of reSET, a National Institute on Drug Abuse (NIDA) sponsored clinical trial evaluated the digital therapeutic in 399 patients with substance abuse disorder across 10 treatment centers in NIDA's Clinical Trial Network nationwide over 12 weeks. Patients were randomized to either a standard treatment as usual, which consisted of standard face-to-face counseling, or to a reduced amount of face-to-face counseling plus the digital therapeutic.

The clinical study demonstrated that the digital therapeutic more than doubled the rate of abstinence compared with standard, face-to-face counseling.

In a sub-group analysis of non-abstinent patients at study start, a poor prognostic indicator, patients randomized to the digital therapeutic demonstrated an almost five-fold improvement in abstinence.

"We are bridging the intersection between healthcare and technology," Mr. Waldron says. "We took proven clinical outcomes that have been seen in the world of behavioral therapies and used our technology platform to create a digital therapeutic that helps people modify their behavior.

"We are using an iterative learning program that helps the brain readjust from the malady that it's facing, in this case addiction," Mr. Waldron adds. "Our product also progresses the patient along a path to make sure that he or she understands the benefits of this behavioral modification and provides an outcome base that's superior to just counseling itself."

Dr. Maricich says diseases of the brain are an area where there are high rates of failure for existing therapeutics.

"Patients and physicians need additional options," he says. "These digital products are not intended to replace traditional medications. They're intended to be used in combination to help make patients better, which is ultimately the goal."

About 11.8 million people 12 or older misused opioids in 2016, and the number of opioid-related overdose deaths has quadrupled since 1999 with 91 Americans dying every day from an opioid overdose.

Pear's product development pipeline includes reSET-O for opioid use disorder and additional prescription digital therapeutics for schizophrenia (Thrive), combat post-traumatic stress disorder (reCALL), general anxiety disorder (reVIVE), and pain, major depressive disorder, and insomnia.

Akili is another company in the digital medicine space. The company is developing a therapy for pediatric attention-deficit/hyperactivity disorder (ADHD). In December, Akili announced top-line results from the company's STARS-ADHD pivotal study of its lead investigational digital medicine, AKL-T01, in pediatric ADHD.

In the 20-site multi-center, randomized controlled trial, the 348 children and adolescents with ADHD and objective attention deficits were evaluated before and after four

weeks of at-home treatment with either AKL-T01 or an active control, which was designed and tested to have a similar level of expectation of benefits and engagement.

Children and adolescents who used AKL-T01 showed a statistically significant improvement in attentional functioning on the Attention Performance Index (API), a composite, objective measurement of attention and the pre-defined primary endpoint of the study, compared with no improvement in the active control group. AKL-T01 was safe and well-tolerated with only 11 treatment-related adverse events reported, primarily headache and frustration. No serious adverse events were reported and only one patient discontinued treatment.

Dr. Martucci says the control was a game with rewards and engagements but without the company's active algorithms.

"The strong effects in attention that we showed were related to only our product," he says. "This may be a video game as the delivery vehicle, but at its core we have a clinical benefit that will help patients in their lives. I think that's what medicine — the phrase — should be reserved for."

The company's core technology is based on patent-pending technology from the University of California, San Francisco, which allows Akili to render sensory stimulus.

"What pops up on the screen or the motor tasks that can be rendered in a very specific way activate the midline prefrontal cortex of the brain," Dr. Martucci explains. "This is the strong differentiating factor. These patent-pending algorithms adapt the game interface with specific targets for the patient, these targets are nonexistent in the control game we tested against and any other games that we know of."

Based on the results of the study, Akili plans to file AKL-T01 with the FDA for clearance as a novel treatment for children and adolescents with ADHD. Dr. Martucci believes AKL-T01 will have an impact on patient groups that are currently underserved by the medication alone: those that try medication but do not have either a good response or experience an adverse event or risk profile, such as weight loss or sleeplessness; and families that do not want to put their child on medication.

Digital Pills

Another area of digital medicine involves the convergence of pharmaceutical products with digital and smart technologies. For example, in November, Otsuka and Proteus Digital Health received approval from the FDA for the digital medicine system Abilify Mycite, a drug-device combination product comprised of Otsuka's oral aripiprazole tablets embedded with an ingestible sensor the size of a grain of sand.

The system includes: Abilify Mycite; the Mycite Patch — a wearable sensor, developed by Proteus; the Mycite app, a smartphone application, used with a compatible smartphone to display information for the patient; and web-based portals for healthcare providers and caregivers that display a summary of aripiprazole ingestion over time.

The sensor, when swallowed, emits a signal, similar to an EKG. That signal is then detected by a patch worn on the body and then, via Bluetooth signal, is transferred to the Otsuka cloud, where it can be accessed by physicians and patients.

"The data are transferred to the cloud and then passed back down to both the person's app on the phone as well as the HCP, and if consented to other caregivers that the person selects," Mr. Wright says.

The system records medication ingestion and communicates this to the patient and healthcare provider. In addition, the product can collect data on activity level, as well as self-reported rest and mood, which, with patient consent, can be shared with the healthcare provider and selected members of the family and care team.

The system provides an objective summary of drug ingestion over time to help enhance collaboration with healthcare providers, who treat patients with certain serious mental illnesses.

"Patient adherence in chronic conditions is a major challenge," Mr. Wright says. "From a serious mental illness standpoint, there is a much higher rate of nonadherence in chronic disease; the rates of nonadherence ran about 50% to about 70% in serious mental illness."

The consequences are significant because nonadherence may lead to relapse, which can cause uncontrolled health conditions, excess hospitalizations, emergency room visits and office visits, resulting in additional costs to the U.S. healthcare system of $290 billion annually, according to the Network for Excellence in Health Innovation, a nonprofit, nonpartisan national health policy institute. In fact, of the about 187 million Americans who take one or more prescription drugs, up to one-half do not take their medications as prescribed.

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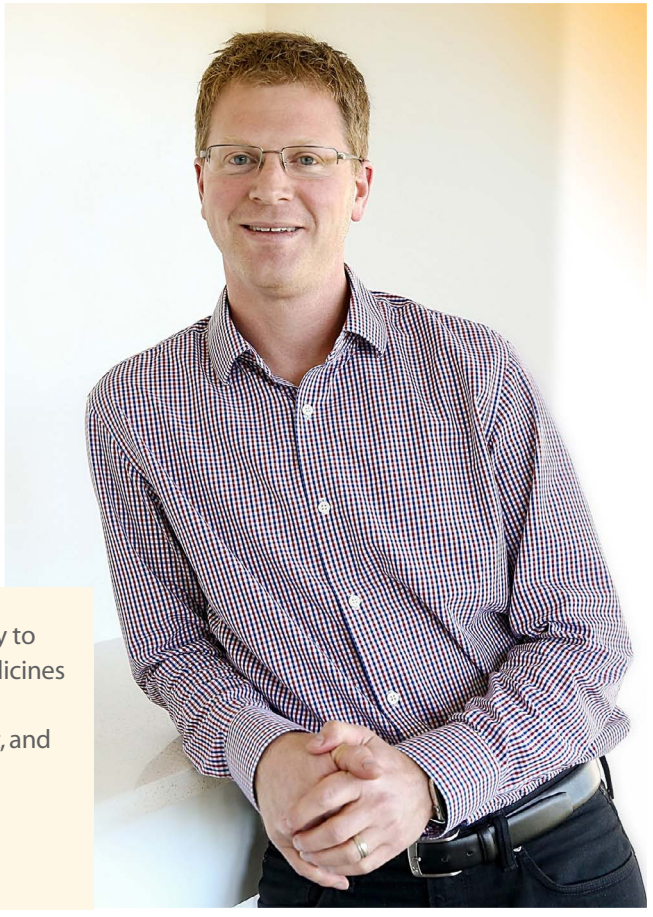
ALEX WALDRON
Pear Therapeutics



We have an opportunity to provide innovative medicines as well as best-in-class programs, engagement, and services.

LARRY BROOKS
Boehringer Ingelheim

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>
> **DR. EDDIE MARTUCCI**
> Akili Interactive

The Proteus sensor helps physicians track the medication ingestion, which will over time enable them to see whether the patient is following his or her treatment plan.

"This is an opt-in process; it requires the consent of the individual and we see it as part of the therapeutic alliance," Mr. Wright says. "Part of this is having a nonjudgmental discussion between the treatment team and the individual to find ways to help."

Mr. Wright says the company's initial roll out of the product has been very purposeful.

"We're going to a very small number of select payers and physicians because we want to understand how the product integrates into the physician work flow and how it integrates into the consumers' lifestyle so we can enhance and optimize the experience moving forward," he says. "This way, we can listen more carefully to a limited number of patients, we can learn about uptake and how we can continuously improve the process."

He says the company will be gathering real-world evidence to determine if the sensor improves outcomes and will then determine if the sensor is a fit for other products.

Smart Therapies

Several large pharma companies have already made attempts to merge various "smart" devices with their products to improve data collection, provide physicians with information about patient adherence, and provide a better experience for the patients.

Boehringer Ingelheim is one such company, which has been working with Propeller Health for its respiratory products. In March 2015, the FDA granted clearance for Propeller's health technology platform in association with BI's Respimat. Propeller uses a combination of inhaler sensors, apps, analytics, personal feedback, and education. The platform passively tracks how and when patients use their inhaled medications and can send alerts to patients and their caregivers. In 2016, the companies formed a partnership to determine whether the tool impacts adherence rates and patient engagement.

Respimat is the platform inhaler for Boehringer Ingelheim's respiratory medications: Spiriva Respimat is approved to treat asthma for people 6 years and older and Stiolto Respimat is approved to treat chronic obstructive pulmonary disease.

Larry Brooks, director, business innovation, digital health at Boehringer Ingelheim, says a year ago the company began enrolling health systems and patients using the Respimat Soft Mist inhaler in a remote monitoring program with Propeller Health. Patients receive the Propeller sensor for Respimat, as well as a MDI rescue sensor and access to a mobile app to passively track and manage their condition. Physicians are able to monitor patients through a dashboard.

"Algorithms are built in to show if, for example, an exacerbation is imminent based on a patient using their rescue inhaler multiple times in a given time period," he says. "This data could be useful to physicians or a care team so that they can intervene appropriately. In addition, the Propeller system sends patients and caregivers medication reminders, as well as custom alerts. For example, a patient could receive notifications focused on humidity or other weather and environmental factors that may be useful in helping him or her manage the disease."

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>
> **ZACK LYNCH**
> JAZZ Venture partners

Mr. Brooks says the program is ongoing and the company is still collecting data.

"We will iterate the program accordingly," he says. "One of the promises behind digital health is the connections that can be made with patients beyond a particular time during an office visit. Physicians seem to appreciate this type of connectivity."

Boehringer Ingelheim also has a collaboration with Qualcomm to develop a connectivity solution for the Respimat inhaler. Qualcomm is developing the prototype for a small, wireless, low-power, disposable module for the inhaler. This fully-integrated inhaler will be able to track puffs from the Respimat inhaler, and the collected information can be shared with healthcare providers and patients.

"We believe strongly in complementing our core assets and capabilities through external digital health collaborations with entrepreneurs and innovators in established companies," Mr. Brooks says.

Smart technologies and connected sensors are being adopted across the industry, and leaders believe technology will continue to play a pivotal role in advancing the future of the pharma and healthcare industries. PV