Digital Health: A New-Age Spectrum of Therapeutics

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INTRODUCTION

Digital health and a wide spectrum of digital therapeutic products have begun arriving in the U.S. marketplace for use by consumers or patients and for prescribing by health care professionals (HCPs). This is relevant for P&T committees as

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the landscape for medical devices undergoes rapid and expansive change, both in the number and type of devices and their therapeutic uses. Similar to the experience seen with biologic and specialty drugs over the past 10 years, digital health applications represent another growth engine affecting care outcomes, costs of care, and sources of revenue.

The 21st Century Cures Act, which became law in December 2016, was designed to accelerate drug development and drive innovation to reach patients more efficiently.[1] It also strengthened mental and substance use disorder care, established new thinking on clinical trial designs, and modernized review processes along with FDA resources—all of which would speed the development and review of novel medical products. In

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addition, the act established that certain kinds of medical software are no longer considered to constitute a medical device and is not regulated as such a device.

INVESTMENTS ARE DRIVING INNOVATION

Digital health has attracted a great degree of attention in the past five years, in part because of rapid investment by pharmaceutical companies, technology companies, and startups. More than $8 billion was invested in the digital health space in 2018, and by mid-2019, the year's spending had passed the $4.2 billion mark.[2] Each year has seen substantial growth, leading to a number of initial public offerings (IPOs) among companies in 2019 (e.g., Peloton and Livongo). Nonetheless, digital health did not come out of nowhere; it is built on the groundwork of the past, such as the e-Health movement of the late 1990s and early 2000s and the mHealth initiative of the early 2010s.[3,4] Digital health gained currency as a term as mobile devices swept through society and became an integral part of so many people's lives.

In essence, digital health is the intersection of technology and health care services.[4] The Food and Drug Administration (FDA) has highlighted digital health as a means to reduce inefficiencies in care, improve access and scalability of services, and make health care more personalized for patients.[5] It is an umbrella term for many areas of technology in health care, and the FDA has shown interest in several of them **(Table 1)**. Many have been adopted and discussed for decades. However, several facets have led to concerns and discussions about integration into patient care and the nature of financial coverage by payers.

Foremost are the topics of digital medicines and digital therapeutics. Digital medicines are gaining attention as a novel means of tracking medication adherence. Several companies are manufacturing sensors that can be attached directly to a medication delivery device (e.g., an inhaler or insulin pen) to track utilization.

Table 1 Areas of Digital Health
• Wireless medical devices
• Mobile medical applications
• Telemedicine
• Health information technology
• Medical device data systems
• Medical device interoperability
• Software as a medical device
• General wellness
• Digital medicines
• Digital therapeutics
• Cybersecurity

However, pharmaceutical companies are now looking to create medications with the sensors built directly into the delivery hardware or the medicine itself, creating this digital medicine category. Some pharmaceutical companies **(Table 2)** are working to create their own devices internally or partnering with other health technology companies as needed. These ventures include the work by Otsuka Pharmaceuticals, in conjunction with Proteus Digital Health, to bring the first medication (Abilify MYCITE) to market in 2017 with a bioingestible sensor built in to track patient adherence.[6] Inhalers, insulin pens, and other injectables are also being adapted to use sensors with Bluetooth or related technology to track medication administration. The purported value of these advances is that adherence can be tracked clinically, reducing medication waste and negative outcomes—especially when their use focuses on diseases with high morbidity and costs.

Moving beyond digital medicines, the field of digital therapeutics is being heralded for potentially providing novel means of patient care, based on society's rapid adoption of mobile devices, that were previously unforeseen. Digital therapeutics, as defined by the Digital Therapeutics Alliance, "deliver evidence-based therapeutic interventions to patients

that are driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes."[7] Digital therapeutics can exist alone, in conjunction with wearables (e.g., smart watches), or with a medication. This concept has proven highly attractive to pharmaceutical companies, which are quickly partnering with digital therapeutics companies to align their products with these novel services. Examples have included Sandoz's partnership with Pear Therapeutics, Otsuka Pharmaceuticals and Click Therapeutics,[8] and Novartis and Biofourmis[9] **(Table 2)**. These partnerships are noteworthy in that the pipelines mostly reflect the pharmaceutical companies' therapeutic interests at this time, although there is a high likelihood that digital therapeutics companies, as they mature, will branch off from such partnerships. For example, Pear Therapeutics and Sandoz are ending their partnership after gaining FDA clearance for their products Reset and Reset-O (using cognitive behavior therapy to treat substance-use disorder); Pear is looking to expand its therapeutic areas of development outside of Sandoz's pipeline.[10]

WITH INNOVATION COMES QUESTIONS

The concept of digital therapeutics raises several questions. While digital therapeutic products are receiving FDA clearance and becoming available for providers to use in patient care, coverage by payers is an issue. Concerns from payers likely stem from the novel process of regulation governing how digital therapeutics enter the market, and the level of evidence to support their clinical utility over current medical practices. The FDA is working to clarify what digital therapeutic products must have demonstrated to allow their use with patients; one of the challenges has been the availability of expert personnel at the FDA.[11] The FDA has created a Digital Health Innovation Action Plan[12] and launched a Digital Health Software Precertification (Pre-Cert) Program in which it is working with pharmaceutical companies and start-ups to test how to bring digital therapeutics and other products to market with regulation.[13] One of the highlights of this program, aside from traditional review of a product and the organization behind the product, is reliance on real-world performance. Traditional randomized clinical trials (RCTs) are often held to be the best

form of evidence, but digital therapeutics companies face significant limitations with this model even as they engage in such trials.[14,15] This includes factoring in users' experience and

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the product's user interface, which may change with multiple updates, adjustments to the hardware they operate on and design issues that may or may not affect products' clinical impact. As a result, traditional RCT design may not be the way to gauge the effectiveness of digital therapeutics. Besides, the time required to test each new iteration of a product would be excessive. Using real-world evidence may be the way to take into account these issues, which traditional medications with a single active ingredient do not pose.[16]

DISCUSSION

Health plan sponsors and other third-party payers will have to determine how best to select the digital therapeutic products and digital medicines they cover and allow providers to use in clinical practice. The process of selecting a digital therapeutic will expand beyond traditional review of a medication in a class to encompass other considerations, such as perceived benefit and uptake among patients. In addition, utilization of digital therapeutics will have to take into account factors such as patients' use of technology, which can vary. Digital literacy may pose a barrier for some patients, along with a potential digital health divide because some digital therapeutic products may not be available to some patients depending on the type of smartphone they own.[4] The business models of some digital therapeutics companies also will need to be addressed. Some (such as Kaia, which created a digital therapeutic for managing low back pain) are in the U.S. looking to engage directly with employers,[17] while other digital therapeutic products must be prescribed by a provider, throwing open the question of who to bill for such services.

Similarly, P&T committees will have to address the appropriate use of digital therapeutic products within their organi-

Table 2 Sample Digital Medicine and Digital Therapeutic Companies and Their Pipelines	
Proteus Digital Health	Bioingestible capsule sensors or sensors embedded in tablets for medication adherence[21]
EtectRx	Bioingestible capsule sensors for medication adherence tracking, currently undergoing clinical trials[22]
Otsuka Pharmaceuticals	Abilify MYCITE (in partnership with Proteus Digital Health) for schizophrenia, bipolar I disorder, and major depressive disease[23]
Teva Pharmaceuticals	ProAir Digihaler for bronchospasm[24] AirDuo Digihaler for asthma
Eli Lilly	Smart insulin pens[25]
Novo Nordisk	Smart insulin pens (NovoPen 6 and NovoPen Echo Plus)[26]
Bayer	BetaConnect for multiple sclerosis[27]
Pear Therapeutics	RESET (with Sandoz) for substance use disorder—FDA cleared RESET-O (with Sadoz) for opioid use disorder—FDA cleared Somryst for insomnia/depression—submitted to FDA[28]
Voluntis	Oleena, a mobile application for oncology patients—FDA cleared[29]
Kaia Health	Kaia Back Pain for back pain management—in process[30]
Biofourmis	Biovitals analytics engine—FDA cleared[31]
Click Therapeutics	Clickotine for smoking cessation—in clinical trials[32]
Akili Interactive	Products in clinical trials for cognitive impairment[33]

zations or in health-plan administration. Potential options may include utilizing third-party formularies or central databases that are being built. For example, Express Scripts has announced a digital health formulary,[18] and organizations such as Rx.Health[19] and IQVIA Appscript[20] are reviewing the clinical utility of medical apps (without saying whether they will focus on digital therapeutics). Given the spectrum of digital therapeutic products in development or reaching the U.S. market, guidance and guidelines around digital therapeutics uses, appropriate patient selection, measures of success, and extent of reimbursement must be addressed. FDA-approved digital therapeutic products will be the easiest to address but represent the tip of the iceberg, akin to what we've seen with natural or nutritional products that don't require FDA approval or prescription.

CONCLUSION

Digital health is here and expanding rapidly. Investment is increasing. Consumers and patients are becoming more accepting. Since most digital therapeutics will not require FDA approval or a prescription, HCPs can play an important role in education along with promoting appropriate use. As a result of this rapid growth in digital therapeutics, P&T committees should begin assessing, addressing, and approving products for appropriate use in their organizations or allowing for reimbursement in accordance with their plan benefits.

Digital health products, including digital therapeutics, represent the latest task for P&T committees and HCPs to manage as part of their professional responsibilities. The number of different health care innovations speeding onto the market represent: 1) a significant challenge to those parties that already operate under real-time pressures to deal with care innovation, and 2) reimbursement questions associated with the adoption of innovations that may have questionable economic value for their organization.

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