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Digital Therapeutics 101: An Introduction and Overview

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eBook



Contents

Introduction	3
Market Definition and Segmentation	4
Product Design	9
Value of DTx	13
Business Models	15
Regulatory Oversight	17
Evidence Generation	19
Reimbursement	21
Distribution, Prescribing Authority, and Channels	23
Ex-U.S. Markets	26
Parting Remarks: Where we are now	27

Introduction

Welcome to the interesting world of digital health and more specifically, digital therapeutics! Before diving into this guide, it would be helpful to consider why digital therapeutics is such a compelling topic these days. There are several key factors that have made digital therapeutics “top of mind” for a diverse range of people and organizations, including biopharmaceutical companies, technology companies, healthcare providers, and patients. Consider that digital therapeutics:

1. **Challenge the norm** - At its most fundamental level, digital health and digital therapeutics are challenging existing models of care. In so many places around the world, healthcare systems face great challenges, including exorbitant costs, poor access, inefficiencies and more. As digital technologies have transformed industry after industry, healthcare has been somewhat resistant but it, too, will progress. With that, the hope is to create new care models and supporting operations that realign the values and incentives by which healthcare operates to be more balanced between care and the “business” of care.
2. **Offer the thrill of ambiguity** - Digital Health is literally being built right in front of us. There are few certainties in its application and potential despite what you may read in various news outlets. It is not clear which products really possess 10x value or which stakeholders are the best to shepherd them to success, nor is it clear how to integrate these tools with existing systems and offerings. This leaves room for a lot of creativity.
3. **Are “patient-centric”** - Despite being a common term thrown around these days, “patient centricity” is at best, an uneven reality. However, the software side of digital

health requires incorporation of user experience, engagement and usability. In other words, it demands a “patient centric” experience, which will actually stretch healthcare and life sciences into new domains and capabilities centered on the patient.

4. **Represent a new class of interventions** - We are in the early stages of understanding how our interaction with technology can change us for the better (or worse). Part of the interest in digital therapeutics is driven by a responsibility to be good stewards by working at the cutting edge of these novel interactions to maximize the good and limit the bad, and along the way protecting us all from taking too many wrong steps (i.e., Big Tech’s “break things” mindset won’t work in healthcare). Furthermore, these interventions work in unique “mechanisms of action” that can often complement existing therapeutics and open up avenues to address unmet needs in numerous disease conditions that were previously unreachable.
5. **Are for the mind** - A lot of digital therapeutics will be about interventions that affect the mind and how through focusing on thoughts and sensory information, we can change how we feel, think, believe, behave, and ultimately experience our lives. This is an area of unmet need in the United States if not everywhere. The mental experience of health and disease is poorly managed and served, and it is applicable across all therapeutic areas. If taken seriously, it could be a real “game changer.”

Now that you have insight into why so many innovators are passionate about digital therapeutics, let’s get into what you need to know!

Market Definition and Segmentation

Definitions in Digital Health broadly—and within Digital Therapeutics—are often ambiguous and contradictory. Below, we briefly review some of the more common approaches as well as the working approach for this guide.

Digital Health

Digital Health is a very broad and amorphous term that's often used to differentiate from traditional medical devices and capture the thrill of modern technology disrupting the healthcare market. One such definition which will suit our needs is from HIMSS, a major player in the industry¹. It's

useful, but perhaps a bit “buzz-wordy”:

Digital health connects and empowers people and populations to manage health and wellness, augmented by accessible and supportive provider teams working within flexible, integrated, interoperable, and digitally-enabled care environments that strategically leverage digital tools, technologies and services to transform care delivery.

Segmentation of Digital Health is in some ways a fool's-errand, as the products and values they provide overlap and evolve. For an illustration of this, you can see how various major publications (often investment reports) attempt to do this:

By Value Proposition - Rock Health ²	By “Function” - Startup Health ³	By “Categories” - Mercom ⁴
<ul style="list-style-type: none"> • On-demand healthcare services • Monitoring of disease • Treatment of disease • Fitness & wellness • Nonclinical workflow • Consumer health information • Research and development catalyst • Diagnosis of disease 	<ul style="list-style-type: none"> • Patient empowerment • Wellness • Biometric data acquisition • Admin workflow • Insurance • Research • Population health • ...maybe more? 	<ul style="list-style-type: none"> • Telemedicine • Analytics • mHealth apps • Wearable sensors • Clinical decision support • Healthcare service booking • Practice management solutions • Wellness

Our Approach to Digital Health Segmentation

Despite segmentation being a messy and time-draining exercise, we still need some ways to organize the landscape to make sense of the world. Some approaches have been used that categorize by patient journey, by technology and by data type. But for our purposes, we take a life sciences approach that identifies the main value / role in business for these technologies:

- **Digital Interventions** – new products to treat or care for patients
 - Digital Therapeutics (e.g. Pear Therapeutics® and Silvercloud®)
 - Wellness Apps (e.g. Calm App® and MySugr®)
 - Digital Medicine (e.g. Abilify MyCite® and Propeller Health®)
 - Neuromodulation (e.g. Cala Health®)
- **Precision Medicine** – new data and analytics to identify patients or inform clinical decisions

¹ “HIMSS Defines Digital Health for the Global Healthcare Industry ...” 2 Mar. 2020, <https://www.himss.org/news/himss-defines-digital-health-global-healthcare-industry>. Accessed 12 Mar. 2021.

² “2020 Midyear Digital Health Market Update: Unprecedented funding ...” <https://rockhealth.com/reports/2020-midyear-digital-health-market-update-unprecedented-funding-in-an-unprecedented-time/>. Accessed 12 Mar. 2021.

³ “StartUp Health.” <https://www.startuphealth.com/>. Accessed 12 Mar. 2021.

⁴ “9M and Q3 2020 Digital Health (Healthcare IT) Funding and M&A ...” <https://mercomcapital.com/product/9m-and-q3-2020-digital-health-healthcare-it-funding-and-mar-report/>. Accessed 12 Mar. 2021.

Digital Therapeutics 101: An Introduction and Overview

- Digital Biomarkers & Diagnostics (e.g. AliveCor® and Cognoa®)
- ePRO (electronic patient reported outcomes) / eCOA (electronic clinical outcomes assessment) platforms (e.g. Noona®)
- Clinical Decision Support (e.g. NAVIFY®)
- Digital Imaging / Pathology (e.g. Heartflow®)
- **Virtual Care** – new channels leveraging digital, often new customers
 - Telehealth (e.g. Amwell®)
 - Digital Care (e.g. Omada Health®)
 - Digital Clinics (e.g. Hims & Hers®)
 - Digital Pharmacies (e.g. Capsule®)
- **Clinical Trial Optimization** – new tools for research and development
 - Patient recruitment (e.g. Deep6 AI®)
 - Virtual / site-less trials (e.g. Science37®)
 - and more...
- **Health IT and Analytics** – new platforms to access healthcare systems
 - Electronic Health Record Technologies (e.g. Cerner®)
 - Tech-enabled care platforms (e.g. Tridium®)
 - Workflow solutions (e.g. Xealth®)

We utilize this approach as it generally aligns with the needs of commercial organizations to find new revenue-generating products (digital interventions), new ways to identify patients for products (precision medicine), and new ways to sell products (virtual care). Whereas the R&D organization often focuses on cost reduction or data-driven approaches to clinical trials (clinical trial optimization), which to be clear, often incorporates precision medicine and other digital health tools. Health IT and Analytics is a “catch all” for companies that are sometimes relevant based on specific business needs.

Digital Therapeutics

The Digital Therapeutics Alliance (DTA) remains the de facto industry group for defining digital therapeutics. It states⁵:

*Digital therapeutics (DTx) deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders.*⁶

The key attributes to understand about the DTA's definition are:

- **Medical interventions** – These are clinical-grade treatments, not simply related to wellness claims.
- **Directly to patients** - Patients should be self-administering or using as self-care. A physician is not active in the intervention, though they may be informed by the software about the patient's status, experience, and symptoms for purposes of administration, oversight, or incorporation into a broader treatment plan.
- **Evidence-based, clinically evaluated** - Often the mechanism of action (MOA) of a DTx needs to begin based on techniques that are considered evidence-based, though it is hard to truly understand how far this goes. For instance, APA's Div-12 has a database of evidence-based psychological treatments that appears fairly robust and useful, though in previous market research we conducted, few clinicians were aware of or leveraged the source.⁸ Rather, they used their own judgement of peer-reviewed academic publications from respected journals to determine for themselves that something was evidence-based. “Clinically evaluated” is about conducting double-blinded randomized controlled trials (RCTs) or other structured evaluations to demonstrate in a controlled manner that the intervention is clinically efficacious (not just “snake oil” as some label these products because of the flood of unregulated health apps).
- **Software** - Note the lack of hardware, which is likely purposeful as to directly integrate with the regulatory category of Software as a Medical Device (SaMD). But, as we look further it becomes harder to understand the rationale for some digital therapeutics, such as biofeedback, that have a hardware component to not be considered a digital therapeutic. But here is the first example of where definitions, segments and regulatory policies start to fray, a topic you will repeatedly see across this document.
- **Treat, manage and prevent** - This is closely aligned with the FDA's definition for medical devices and helps position DTx for regulatory oversight.⁸
- **Diseases and disorders** - This is also to differentiate from wellness products that often deal with symptoms or states and to aim for medical claims with FDA regulation.

⁵ “Core Principles - Digital Therapeutics Alliance.” https://dtxalliance.org/wp-content/uploads/2019/11/DTA_DTxDefinition-and-Core-Principles.pdf. Accessed 12 Mar. 2021.

⁶ “Digital Therapeutics Alliance.” <https://dtxalliance.org/>. Accessed 7 Mar. 2021.

⁷ “Research-Supported Psychological ...” <https://div12.org/psychological-treatments/>. Accessed 12 Mar. 2021.

⁸ “Medical Device Overview | FDA.” 14 Sep. 2018, <https://www.fda.gov/industry/regulated-products/medical-device-overview>. Accessed 12 Mar. 2021.



Ultimately, the DTA appears to be positioning their definition to differentiate DTx products from the immense number of “wellness” or “health” apps and establish DTx’s status as similar to pharmaceutical products: regulated, efficacious, and higher-priced.

The DTA attempts segmentation of the DTx landscape⁹ but it gets confusing quickly. Its segmentation framework includes:

- *Treat* a Disease
- *Manage* a Disease
- *Improve* a Health Function

“Treat” and “Manage” a disease are both fairly self-explanatory for a regulated product. However, “Improve a Health Function***” is less so. This was a notable iteration on their approach in articulating the segment description. The two asterisks point to a footer stating “**Includes

digital therapeutics that prevent a disease.” Apparently, the DTA needed to have a segment that wasn’t restricted to a medical claim like “disease” so “health function” was used, allowing access to companies that may work in pre-diabetes or other popular spaces which are unregulated and therefore may be slightly better described as “health functions.” We also interpret this last category to appease products that are very much digital therapeutics but may not quite be aiming or intending for regulation simply because of the uncertainty around oversight at this time. So, the DTA is likely straddling between the world of prescription and non-prescription digital therapeutics and somehow needs to cater to both for the time being. We bring this discussion up simply to illustrate how even with the industry-leading and excellent work that the DTA is doing to support digital therapeutics, it is still iterating on the approach. So, individuals coming into this area will still run into some confusion.

⁹ “DTx Product Categories* - Digital Therapeutics Alliance.” https://dtxalliance.org/wp-content/uploads/2021/01/DTA_FS_DTx-Product-Categories_010521.pdf. Accessed 12 Mar. 2021.

Our Approach to Digital Therapeutics Segmentation

Our working segmentation for digital therapeutics is primarily based on a biopharmaceutical / life science industry lens for identifying products that intend to commercialize via a regulated prescription model. Most important to us are Prescription Digital Therapeutics (PDTs), those DTx that are intended to “treat” (as opposed to “drive” or “inform”; which is an FDA classification where some DTx have clearance, such as insulin calculators) and which are seeking FDA clearance for medical claims.

PDTs are then followed in importance by Non-Prescription Digital Therapeutics (NDTs). These may very well “treat” but are not seeking FDA clearance for medical claims, though they possess significant evidence that could allow pursuit of regulatory pathways (well-designed real-world evidence or robust clinical trials with their actual products). Note that this last statement of “with their actual products” is purposeful and trying to separate from products that claim to be evidence-based in the sense that there is evidence for the underlying therapeutic techniques (e.g. evidence for cognitive behavioral therapy [CBT] or mindfulness) but not their product’s application of it. This distinction can get tricky and is open to debate on where to draw the line, though our assumption is that one can’t go to the FDA with non-product-based evidence.

As a last defensive move for our approach, most of what drives the distinction between regulated and non-regulated are the medical claims that are made about a given product. However, the FDA is not consistent here, neither within digital health nor in other areas sometimes. So, while a digital therapeutic may be currently available for purchase under some leniency of the FDA (e.g. COVID EUA), that could change. One of the few notable regulatory clamp downs in this space was in 2016 with Lumosity’s exaggerated claims that “its mind games could help users excel at work and school and reduce or delay ‘cognitive impairment associated with age and other serious health conditions.’” The situation cost them \$2 million in fines and some bad press.¹⁰

Furthermore, as the viability for a prescription model path to the market becomes clearer, it would be wise for NDT companies to be prepared to jump into the more lucrative prescription market. So our approach described below accounts for keeping an eye on both of these product types.

Our approach yields three main segments with hierarchi-

cal criteria starting from PDT, then NDT and then Wellness as a catch-all:

1. **Prescription Digital Therapeutics (PDT)**
 - a. FDA-cleared or FDA breakthrough designation
 - b. Self-proclaimed prescription DTx products
 - c. Product “pipeline” similar to pharma companies
2. **Non-Prescription Digital Therapeutics (NDT)**
 - a. FDA enforcement discretion
 - b. High quality evidence of their product (peer-reviewed publications, RCTs, etc.)
 - c. Ongoing clinicaltrials.gov listing of an RCT
3. **Wellness Apps (technically not a DTx at all to us)**
 - a. Default for those with none of the characteristics above

It’s not always clear how to separate a PDT from an NDT. We go into much discussion about this here, and will likely address it more in additional thought pieces. There are some interesting lessons to learn from these “edge cases.”

Our approach, though, is fairly-clean and easy to implement, and identifies PDTs that align well with life science company models (while those classified as NDTs are arguably less so). With some companies, it can be hard to discern the truth (especially from their corporate websites), so we may make a controversial distinction from time to time. We beg your pardon ahead of time, are open to feedback, and will update this publication periodically to “course correct.”

Lastly, we would like to reiterate that we often lean our discussion towards PDTs intended to “treat” rather than “drive” or “inform” clinical management. This is because the opportunity value of a novel intervention to life science companies is far higher with those that “treat” than either of the latter.

Other product types that often come up in conversation around digital therapeutics that could be described as “edge cases” include:

- **Digital Companions** – These are DTx-like products in support of—or in combination with—a pharmaceutical or medical device product. Technically, Pear Therapeutics’ reSET-O® (for opioid use disorder) could be considered a digital companion, as it is indicated for use as an adjunct to outpatient treatment that includes buprenorphine and a contingency management system.¹¹ However, we currently don’t leverage this terminology yet, but we do expect it will become more common in the future.
- **Digital Care Provider** - Sean Duffy of Omada Health®, an early advocate of the term “Digital Therapeutics”;

¹⁰ NBC News, Lumosity to Pay \$2M to Settle FTC Charges Over ‘Brain Training’ Ads, 5 Jan 2016, <https://www.nbcnews.com/business/consumer/lumosity-pay-2m-settle-ftc-charges-over-brain-training-ads-n490571>

¹¹ US FDA Letter, 23 May 2019 (with accompanying 510(k) information), https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173681.pdf

subsequently penned the term “Digital Care Provider” for his type of company, which typically refers to chronic care platforms that provide human-based care (physicians, coaches, therapists, etc.) enabled by a “constellation of hyper-personalized care pathways” leveraging digital health tools¹². Often there is an app involved and sometimes this app could be considered a digital therapeutic. However, as they are often not regulated and not available independent of the provider service, we have not included these in our DTx definition.

- **Virtual Reality / Augmented Reality** – Our approach currently includes these as DTx despite the hardware component.
- **Neuromodulation / Neurostimulation Devices** - Lately, there have been several companies in this space utilizing “digital therapeutics” to describe themselves (e.g. Neurolief¹³). Based on our interpretation, the majority of interventions here use electrical or magnetic stimulation which are then supported or informed by a software. Therefore, we do not include these in our approach and would consider them medical devices. However, some products we classify as digital therapeutics use neurostimulation via audio (MEDRhythms¹⁴) and/or visual (Cognito Therapeutics¹⁵ for Alzheimer’s¹⁵) as the intervention. These approaches seem a bit more in-line with the spirit of digital therapeutics as self-care devices. It’s hard to describe, but to us, there is a level of engagement or attention required for audio/visual stimulation that is not needed for the more passive electrical or magnetic stimulation. We consider that a relevant differentiation between those product types. It gets tricky because if one disagrees and prefers to argue that “all stimulation” devices are not digital therapeutics, then they would, in fact, be removing most of what is considered a digital therapeutic. For instance, AR/VR is similarly audio/visual stimulation. Even reading text in an app or chatting with a conversational agent is a form of visual stimulation. So, there is a point along the spectrum of stimulation that needs to meaningfully inform the approach. We use case-by-case judgements in this area while taking in the above considerations.
- **Digital Medicine** – This type is most clearly demonstrated by the adherence solution Abilify MyCite¹⁶ but also by the smart-inhaler Propeller Health¹⁷. These are true combination products of a pharmaceutically active substance with hardware and lastly, an app of some kind.

These often act via behavioral change interventions to inform care and/or impart new habits to taking medicine rather than as interventions in and of themselves.

- **Biofeedback via Hardware** - There are a handful of biofeedback systems that are designed to train patients to better perform a task and that have a significant software component. We treat these on a one-by-one basis to consider if the intervention is driven more by the hardware (some EEG neurostimulation feedback systems) as being medical devices or driven more by the software (e.g. Nightware¹⁷ for PTSD¹⁷) as being PDTs.

DTx Product Examples

Below is a sample list of some well-known products within each of the segments for reference and education. But don’t be fooled, there are numerous edge cases that blur these lines which are still open for debate. Incidentally, Blue Matter has constructed a PDT database for tracking the market and collecting information on a wide range of products in this space. Stay tuned for additional publications to share this work with the industry.

1. **Prescription Digital Therapeutics (PDT)**
 - a. Pear Therapeutics [reSET](#)[®] (substance abuse), [reSET-O](#)[®] (opioid use disorder), and [Somryst](#)[®] (chronic insomnia)
 - b. [Nightware Apple Kit](#)[®] (PTSD)
 - c. Palo Alto Health Sciences [Freespira](#)[®] (Panic Attacks and PTSD)
 - d. Click Therapeutics + Otsuka’s CT-152, clinical code-name: [Mirai](#) (Depression)
 - e. AppliedVR [SootheVR](#)[®] (pain)
 - f. Northshore Therapeutics [NSD-SSD](#) (schizophrenia)
 - g. [Headspace Health](#) (mental health) *note Headspace without the “Health” is an NDT below - see how they can be tricky!
 - h. Woebot Health [WB001](#) (mental health)
2. **Non-prescription Digital Therapeutics (NDT)**
 - a. Big Health [Sleepio](#) (sleep) and [Daylight](#) (worry and anxiety)
 - b. Silvercloud’s [Digital Mental Health Platform](#)
 - c. Pacifica / [Sanvello](#) (stress, anxiety, depression)
 - d. [Youper](#) (mental health)
3. **Wellness Apps**
 - a. [Headspace](#) (meditation and mindfulness)
 - b. [Calm](#) (meditation and mindfulness)

¹² “Digital therapeutics vs. digital care: defining the landscape - STAT.” 20 Feb. 2020, <https://www.statnews.com/2020/02/20/digital-therapeutics-vs-digital-care/>. Accessed 12 Mar. 2021.

¹³ “Relivion[®] - Digital Therapeutics Ecosystem for Brain Neuromodulation.” 28 Dec. 2020, <https://www.neurolief.com/relivion/>. Accessed 12 Mar. 2021.

¹⁴ “MedRhythms.” <https://www.medrhythms.com/>. Accessed 12 Mar. 2021.

¹⁵ “Cognito Therapeutics.” <https://www.cognitotx.com/>. Accessed 12 Mar. 2021.

¹⁶ “Stay on Top of Your Treatment - ABILIFY MYCITE[®] System.” <https://www.abilifymycite.com/>. Accessed 12 Mar. 2021.

¹⁷ “NightWare | We won’t rest until those with PTSD can.” <https://nightware.com/>. Accessed 12 Mar. 2021.



Product Design

Most digital therapeutics center on a software application, with many of the more modern ones being smartphone apps. The benefit of smartphone apps is the “always on” access to digital therapeutics that can be something to lean on when in trouble as well as a convenient method to access clinical care. Plus, the digital connectivity to other systems and people is a great strength. Alternatively, or in parallel, some products are on a PC desktop / web-version with the advantages being easier traditional keyboard interaction for long periods of typing, ability to see important visualizations on a larger screen, and gentler reading that can occur with program sessions of 20 minutes or more. After all, not everyone is built to tap away on a mobile phone for hours on end.

Some of the key components to be aware of when discussing digital therapeutic products are:

- **Therapeutic Basis** – This is nearly equivalent to the MOA of a pharmaceutical. Therapeutic basis describes the evidence-based techniques that are driving the intervention. Often, it will be a mix of various techniques that have been developed for other use cases (covered in detail in the next section).
- **Intervention Type** - This may not be an official term, but it’s commonly used to describe the technology and method of interacting with the software, such as through chat, video, images, VR/AR, etc. (also covered in more detail below)

- **Stand-Alone vs. Adjunct vs. Bridge** - Digital therapeutics can be used alone or in combination with other interventions, including pharmaceuticals, medical devices, psychotherapy, etc. There are implications for the degree of oversight and the study design. It is often the case that a given therapeutic could be used in any and all situations and that this comes more to the product strategy than the nature of the intervention itself. As an example, the “bridge” concept is to provide patients a digital therapeutic to support care while bridging from one treater to another, such as after a psychiatrist recommends seeing a therapist where the DTx would bridge the time until a first appointment. There are additional use cases for DTx beyond these mentioned which align well to the pharmaceutical concept of lifecycle management opportunities with potential label additions. For instance, a DTx could launch as a bridge, and then add stand-alone uses later.

Frequently augmenting the central software app are the often-controversial dashboards. These can be for clinicians to monitor and/or engage in the digital therapeutic use by patients and/or for payers, manufacturers and other stakeholders to understand the use and impact of these interventions. While at first glance these appear like clear wins, on the flipside, dashboards can open a Pandora’s box of physician liability and additional burden for the already digitally exhausted. Because the physician was—or should have been—monitoring the patient, they could potentially be held accountable if a patient has a serious issue or highly negative outcome. Plus, what payers will pay a physician to stare at these screens? The answer is, not many (RPM codes exist for monitoring some digital tools, but not DTx yet)! So just note that dashboards may not always be a good idea. When brought up, it’s advisable to do some market research on what physicians want or need to see. Also, see the section on Telehealth as a channel. Many DTx companies are commercializing with wrap-around telehealth for prescribing and are likely monitoring users (as opposed to the users’ physicians performing the monitoring).

Therapeutic Basis

The vast majority of digital therapeutics are leveraging, in part or in full, aspects of psychosocial interventions. So, it’s useful to know of this term. The American Psychologi-

cal Association (APA) defines psychosocial as “describing the intersection and interaction of social, cultural, and environmental influences on the mind and behavior.”¹⁸ It is commonly used to be a bit broader than psychological interventions which focus on mental disease or disorders.¹⁹ Wikipedia²⁰ has a thoughtful commentary on psychological interventions that touches both on the breath of approaches and its goals:

In applied psychology, interventions are actions performed to bring about change in people. A wide range of intervention strategies exist and they are directed towards various types of issues. Most generally, it means any activities used to modify behavior, emotional state, or feelings. Psychological interventions have many different applications and the most common use is for the treatment of mental disorders, most commonly using psychotherapy. The ultimate goal behind these interventions is not only to alleviate symptoms but also to target the root cause of mental disorders.

A few psychosocial interventions that are commonly incorporated in digital therapeutics are cognitive behavioral therapy (CBT), mindfulness and meditation, acceptance and commitment therapy (ACT), interpersonal psychotherapy, and social skills training (there are many more, and the [APA Div-12](#) is a good first reference). Note in the description above and generally that these techniques are for symptom management as well as getting to the “root cause” in some but not all cases.

After psychosocial interventions, neurocognitive training, neurocognitive remediation and biofeedback in their many forms are utilized in digital therapeutics. According to one source, neurocognitive training is “a method of brain training that uses cognitive exercises to stimulate and raise brain-wave activity. In so doing, this form of training works on two levels of the brain: neurological and cognitive.”²¹ While we’d love a better source, the basic gist seems accurate. Neurocognitive remediation therapy (aka. Cognitive remediation training, CRT) “is a set of techniques designed to teach ‘thinking skills’ and can be thought of as a form of cognitive rehabilitation. It involves training in a set of tasks designed to improve cognitive abilities and social functioning. The domains targeted depend upon client need, but might include attention, working memory, planning, and executive function.”²² Finally, according to the Mayo Clinic,²³ biofeedback is a technique in which a person can learn to

¹⁸ APA Dictionary of Psychology, <https://dictionary.apa.org/psychosocial>, accessed 11 June 2021

¹⁹ APA Dictionary of Psychology, <https://dictionary.apa.org/intervention>, accessed 11 June 2021

²⁰ “Psychological intervention - Wikipedia.” https://en.wikipedia.org/wiki/Psychological_intervention. Accessed 14 Mar. 2021.

²¹ “What is Neuro-Cognitive Training ... - AttenGo.” <http://www.attengo.com/how-it-works/what-is-neuro-cognitive-training-2/>. Accessed 14 Mar. 2021.

²² <https://www.psychologytools.com/professional/techniques/cognitive-remediation/>, accessed 11 June 2021

²³ “Biofeedback - Mayo Clinic.” 6 Feb. 2019, <https://www.mayoclinic.org/tests-procedures/biofeedback/about/pac-20384664>. Accessed 14 Mar. 2021.

control aspects of his or her body's functioning, such as heart rate. Biofeedback encompasses a few techniques with the most notable for us being neurofeedback, *"a kind of biofeedback, which teaches self-control of brain functions to subjects by measuring brain waves and providing a feedback signal. Neurofeedback usually provides the audio and or video feedback. Positive or negative feedback is produced for desirable or undesirable brain activities, respectively."*²⁴ Within each of these there are different therapeutic techniques that we will not go into here.

The notable observation for neurocognitive vs. psychotherapeutic approaches is that neurocognitive techniques may be uniquely possible with digital therapeutics because often there is no counterpart in normal clinical care (rapid presentation of images, video games, etc.). The software often "learns" or is truly "responsive" to the user and can adjust the training regimen, intervention type, or experience to tailor itself to be a truly precision care option. Granted, we may be years from having a slam-dunk example of this but Akili Interactive's [EndeavorRx](#) video game for improving attention function in pediatric ADHD is a nice example. Furthermore, Akili describes its therapeutic basis as "Selective Stimulus Management Engine (SSME™)" "Body Brain Trainer (BBT™)" and "Spatial Navigation Engine (SNAV™)"; all trademarked and likely with hard-to-copy algorithms for those interested in protection for intellectual property.²⁵

Another therapeutic basis mixing pot occurs within virtual reality and augmented reality. A few examples of how these products describe themselves are by affecting reward circuitry ([Northshore Therapeutics](#)), sensory and emotional brain processing ([AppliedVR](#)), and then the more easily understood CBT ([Limbix Spark](#)).

Ultimately, there are a wide variety of MOAs and therapeutic basis that can be combined in traditional or novel ways in digital therapeutics. This section is not meant to be exhaustive, but rather a snapshot of some common approaches.

Intervention Types

To answer the common question of "what really are DTx?" or "How do you get the therapeutic benefit?" we would like to outline some of the common methods of

engaging and/or interacting with digital therapeutics. As we do this, keep in mind that you may come to believe, and rightly so, that a big part of digital therapeutics is not simply the intervention, but the design of the product so that it is engaging to use. What is sometimes called "engagement science," are the skills and techniques used to maintain a user's presence and focus with a given task or program. Often, the "magic" is in the combined recipe of the intervention and the engagement ingredients.

Think of engagement ingredients as antidotes to "patient drop out" or "no shows" that through (perhaps) a virtual reality environment one may be more engaged in an experience that provides psychosocial interventions that one could also receive in-person. However, the in-person version would require a 30-minute drive each way, a \$5 toll, and needing to borrow your sister's car without telling her it's for seeing a "shrink." All of those can be barriers to engagement with the in-person version. Furthermore, there have even been mounting reports that patients may be more willing to be open about their thoughts and experiences with robots than with people. According to a 2020 Oracle survey of 12,000 respondents:

83 percent of the global workforce would like their company to provide technology to support their mental health, including self-service access to health resources (36 percent), on-demand counseling services (35 percent), proactive health monitoring tools (35 percent), access to wellness or meditation apps (35 percent), and chatbots to answer health-related questions (28 percent).^{26 27}

Forbes describes the same study by summarizing that, "In fact, only 18% of people surveyed preferred to talk to a human about their problems, meaning that 82% would prefer to talk to a robot."²⁸

With that in mind, below are some intervention types (some overlap with therapeutic basis):

- **Chatbot / Conversational Agent** – This is a fascinating technology that, if thought through, has some profound implications on philosophy including areas of consciousness, what it means to be human, and more.²⁹ One very interesting review of this space is a [99% invisible podcast](#)

²⁴ Marzbani, Hezgameh, et al, Neurofeedback: A Comprehensive Review on System Design, Methodology and Clinical Applications, NIH, April 2016, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892319/>

²⁵ "Science & Technology — Akili Interactive." <https://www.akiliinteractive.com/science-and-technology>. Accessed 14 Mar. 2021.

²⁶ "Your Robot Therapist Will See You Now: Ethical Implications of ..." <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6532335/>. Accessed 14 Mar. 2021.

²⁷ "Global Study: 82% of People Believe Robots Can ... - PR Newswire." 7 Oct. 2020, <https://www.prnewswire.com/news-releases/global-study-82-of-people-believe-robots-can-support-their-mental-health-better-than-humans-301147083.html>. Accessed 14 Mar. 2021.

²⁸ Asar, Adnan, Opening Up To A Robot? How Mental Health Tech Can Help Patients, Forbes, 2 April 2021, <https://www.forbes.com/sites/forbestechcouncil/2021/04/02/opening-up-to-a-robot-how-mental-health-tech-can-help-patients/>

²⁹ "The Most Human Human | Brian Christian." <https://brianchristian.org/the-most-human-human/>. Accessed 15 Mar. 2021.

that traces the roots of therapeutic chatbots to Joseph Weizenbaum's program, ELIZA. He eventually fought against their development as being inhumane and dangerous. We only note this because there is potential risk in digital therapeutics that can justify regulatory oversight. Moving beyond this, chatbots often feature "locked" or "canned" answers where users have a choose-your-own-adventure style prompt. In other cases, they can incorporate open-ended discussions that can tailor the chatbots' behaviors ([Woebot](#) is an example). Furthermore, emerging research from Woebot indicates that the therapeutic alliance or patient "bond" with an "admitted" chatbot is quite high for users, which may be an advantage vs in-person in some cases.³⁰

- **Rich Media (Video, Audio, etc.)** – Often, there are pre-made visual or auditory media to teach lessons (CBT, for example). This veers into the area of education, which payers sniff out for not being something they really want to cover.
- **Biofeedback** - During biofeedback, patients are connected to electrical sensors that help them receive information about their body to inform them on how to make subtle changes, such as relaxing certain muscles, to achieve results, such as reducing pain. In essence, biofeedback gives patients the ability to practice new ways to control their bodies, often to improve a health condition or physical performance. A good example is [Nightware](#), which monitors a person's sleep via a smart-watch to disrupt undesired nightmares. Another example is [Freespira](#), which monitors breathing to teach relaxation skills for panic attacks. This intervention type often requires a hardware component in addition to software.
- **Neurocognitive Training** - These approaches can feel like video games, which is an emerging and controversial area of misunderstood influences on our minds. The hope is that users are having so much fun playing that they don't even realize there is a positive therapeutic impact. It's supposed to be a win-win. However, due to the familiarity of most consumers with video games, we have heard in market research that the concept is attractive but meeting expectations can be challenging, as the therapeutic games can appear underwhelming when compared with traditional video games. This is an area where more work and education is needed to manage expectations and gain consumer buy-in for those with evidence for therapeutic impact.

- **Augmented / Virtual Reality** – To learn more about the difference between augmented and virtual reality, go [here](#). This is a fascinating technology that can change our perception of the world we inhabit. It's a long-time "coming soon" technology that has failed to gain market traction but is so compelling that most big players (Apple, Facebook, Google, etc.) continue to invest in research and development. The major use in clinical care to date is for pain management (Example [AppliedVR](#)).

While we are talking engagement, a note on Gamification... this is not really an intervention type to us, but it's a common ancillary ingredient for improving engagement. Gamification is "the application of typical elements of game playing (e.g. point scoring, competition with others, rules of play) to other areas of activity, typically as an online marketing technique to encourage engagement with a product or service."³¹ Numerous DTx try to incorporate gamification but reasons exist to be careful. It was a potential cause of one of the largest DTx flops to date, Posit Science's heart-breaking e-Caeser trial in schizophrenia (26 weeks and 150 patients and a lot of work). They note in the conclusion:

In particular, in the current study, an unforeseen consequence of the gamification approach was that users would receive the same virtual cash earnings regardless of their performance levels in the cognitive training tasks, because each cognitive training task adapted in difficulty to track the user to ~80% correct trials. This may have resulted in a lack of incentive for users to attend to the cognitive exercises and improve in-exercise performance.³²

Competitive Protection

What's of interest with the intervention type is often how "protected" the product is from competitors. It can be easy to duplicate software regardless of the actual word-by-word coding, so simply digitizing CBT is something hundreds of people have done. Protection is elevated when there is something in the digital therapeutic that can respond to the user to either tailor their specific clinical experience and efficacy or that can be sent back to improve the product's overall engagement and efficacy. These feedback loops to improve the product could be what really pro-

³⁰ Hackett, Mallory, Mental health chatbot does best when acknowledging it's not human, MobiHealthNews, 17 May 2021, <https://www.mobihealthnews.com/news/mental-health-chatbot-does-best-when-acknowledging-its-not-human>

³¹ Lexico, <https://www.lexico.com/en/definition/gamification>, accessed 9 June 2021

³² "Evaluation of a plasticity-based cognitive training ... - PubMed - NIH." 28 Mar. 2019, <https://pubmed.ncbi.nlm.nih.gov/30930034/>. Accessed 14 Mar. 2021.

tect from competition. They would function in a way that's similar to Google's search algorithms, which are continually improved through network effects.³³

Early DTx entrants will not easily maintain a first-mover advantage without ongoing improvement. Whereas pharmaceuticals get years of marketing protection with FDA approvals, the reality is different with software as a medical

device approvals. In addition, inconsistent FDA oversight and the nature of these early-stage DTx often being based on well-known psychotherapeutic techniques make it likely they won't necessarily be protected. For an informative read on a controversial 510(k) clearance for a second-to-market digital therapeutic, review Vox's article on [Natural Cycles vs. Clue in FDA regulated birth control apps](#).³⁴

Value of DTx

In this section we discuss the common value propositions that DTx as products offer the market. Then, we shift to a discussion of DTx as a business opportunity for providing value to life science companies.

Value Propositions

As a starting point, the DTA summarizes that DTx products, using evidence-based, clinically evaluated technologies, have the ability to:³⁵

- Optimize clinical and health economic outcomes
- Deliver high quality therapies to underserved populations
- Easily scale and be accessible through patient-owned devices
- Offer at-home convenience and privacy
- Transform how patients understand, manage, and engage in their healthcare
- Extend clinicians' ability to care for patients
- Support healthcare teams in settings with varying degrees of health care infrastructure
- Lower overall costs of care

While the above is perfectly accurate, our research shows that most of the discussion with HCPs and Payers really revolves around:

- **Improved access to known effective therapies** - This is common for psychotherapy-based DTx interventions which typically have robust evidence for clinical efficacy. The drawback, however, is that patients don't access them³⁶ as much because of mental health professional shortages,³⁷ lack of specialized therapists (most treat the common anxiety and/or depression, pediatrics is lacking, etc.), cost (due to poor reimbursement a lot of therapists are private and charge OOP), and convenience (weekly one-hour sessions for 12-weeks with travel). DTx will allow patients to engage with these interventions in a new way that may be cheaper and more effective than getting nothing. Do note that this value proposition could spark the controversial charge of "replacing" therapists, which is of course not the intention of DTx developers. Nevertheless, it is a potential outcome of digitizing a historically human-driven process.
- **Higher quality via standardization and efficacy via on-demand** - There was a movement in psychology into evidence-based care³⁸ that pushed for standardized, manualized approaches to ensure some reliable level of quality and efficacy. However, our research suggests it can still be quite variable based on therapist training and practice. So, one potential value of DTx is to truly deliver a standardized model of psychotherapy. This could in

³³ "The Network Effects Manual: 13 Different Network Effects ... - Medium." <https://medium.com/@nfx/the-network-effects-manual-13-different-network-effects-and-counting-a3e07b23017d>. Accessed 14 Mar. 2021.

³⁴ "Birth control apps show the contradictions in FDA device oversight" 17 Mar. 2021, <https://www.theverge.com/22335858/birth-control-app-clue-natural-cycles-fda>. Accessed 10 May, 2021.

³⁵ "Value of DTx - Digital Therapeutics Alliance." <https://dtxalliance.org/value-of-dtx/>. Accessed 14 Mar. 2021.

³⁶ "The mounting behavioral health crisis is our next pandemic" 14 Mar. 2021, <https://medcitynews.com/2021/03/the-mounting-behavioral-health-crisis-is-our-next-pandemic/>. Accessed 15 Mar. 2021.

³⁷ "New Federal Analysis of Behavioral Health Care Workforce Released." 13 Dec. 2018, <https://www.thenationalcouncil.org/capitol-connector/2018/12/new-federal-analysis-of-behavioral-health-care-workforce-released/>. Accessed 14 Mar. 2021.

³⁸ "Evidence-Based Psychotherapy: Advantages and ... - NCBI - NIH." 26 Jun. 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5509639/>. Accessed 14 Mar. 2021.

fact be more reliably effective than face-to-face therapy. Lastly, there is the concept of “in-between” sessions being a big gap with traditional psychotherapy practice. DTx may be able to increase the “dose” of these approaches by providing more therapeutic touch-points in between sessions. This may result in higher efficacy, but this is still speculative.

- **New therapeutic approaches** - The last major bucket of value is that DTx provides previously unforeseen approaches to interventions and new clinical areas of effectiveness. Top of the list is the expectation for lower risk when combined with other interventions such as drugs. Without the risk of drug-drug interactions, DTx may provide a good option for sub-optimal responders before adding more pharmacotherapies or switching. The challenge here is determining how much of any improvement or change can be attributed to DTx. There are also individuals who simply don't want to use drugs if possible (in ADHD, for example). Perhaps DTx can “replace” drug therapy in these cases. Admittedly, that's a tall order, but there are some cases for this (depression, anxiety, neurology). Lastly, there are truly novel interventions that cannot exist without digital software interventions. These include neurocognitive training approaches that change the stimulus based on user performance to continually adapt a training task for achieving a specific outcome (again [EndeavorRx](#) for ADHD and attention).

With the above in mind, the first value, access, is fairly-easy to grasp. The middle, higher quality, is a nice idea but would require head-to-head comparisons. The third, new approaches, are fascinating, but the bar is quite high here and sometimes veer into establishing novel endpoints (Akili with TOVA).

Lastly, it may come to be more appreciated that DTx has a role to play in empowering patients in their care while ultimately improving the therapeutic alliance between clinician and patient. There is a lot of time “in-between” sessions and the accuracy and usefulness of patient recall during face-to-face meetings is mixed. So while DTx as an intervention may provide the most near-term value, the role as a tool to bring the patient's experience closer to the clinician's view may help accelerate treatment decision making and overall clinical effectiveness. Typically, this increased view is accomplished via electronic patient reported outcome platforms (ePROs) that can be provided without the DTx at a far lower cost and are currently being adopted in many clinical situations under terms like Measurement-Based Care. However, we believe the combination of DTx and ePRO through data-driven feedback could lead to par-

ticularly notable therapeutic improvements in the future.

Value to Life Sciences

For life sciences, various monetization strategies have been proposed which can incorporate the value of the product, the data, and the platform. As a starting point, there are three key areas of value that we discuss with life science clients:

1. **New Revenue:** DTx products proven clinically effective should produce new revenue. How much revenue is difficult to predict. To date, the most successful DTx are of the NDT or Wellness varieties where companies like Silvercloud, Big Health, Headspace and Calm monetize directly from consumers and/or employers. For PDTs, most public expectations fall in the \$100 million to \$300 million (US) peak. That pales in comparison to pharmaceutical blockbusters. Pioneering life sciences companies will need to set reasonable expectations for revenue and profitability in the near-term. In addition, DTx companion apps could boost revenue from existing pharmaceutical products through higher prescribing, initiation, adherence, and efficacy, though this approach lacks any commercial analog at this time.
2. **New Data:** The patient's digital exhaust from using DTx (via ePRO or utilization patterns) could provide real customer insights that can help improve the product itself, as well as inform new avenues for targeted marketing, label expansion, and product design and development. This value could theoretically be monetized directly while keeping to all necessary privacy rules and regulations. Indirect value could also come from the intelligence alone.
3. **New/Improved Competencies:** DTx can also provide indirect value to a life sciences organization through its use of cutting-edge technology and techniques. Learnings from AI/ML to data analytics to patient-centricity—which are central techniques in DTx—could disseminate across the organization as valuable skills and best practices for use in R&D, digital marketing, customer support, and more. These products may even provide compelling recruitment for highly coveted data and tech talent that have been sluggish to choose pharma over other industries.

Simon-Kucher Partners has an [article](#) discussing an approach to value for the broader digital solutions landscape which boils down to (1) efficiency, (2) outcomes, and (3)

educational/experience. most useful for our discussion is the monetization strategies that complement our value framework above:³⁹

- **DTx Explicit Monetization** - Revenue Benefits
 - Traditional pharmaceutical or medical device reimbursement
 - Offer multiple versions of a customized solution for the digital solution
 - License the digital platform to other manufacturers
 - Sell data to other manufacturers
- **DTx Implicit Monetization** - Non-Revenue Benefits
 - Strategic advantage from developing AI
 - Innovative contracting
 - Improved value story and pricing / market access negotiations
 - Increased product engagement through updates and upgrades

Overall, both of these approaches demonstrate that any discussion of the opportunity for digital therapeutics will entail both direct revenue and indirect non-revenue benefits. However, the overall value of the indirect benefit is speculative and really comes down to the subjective determination and inspiration of the key stakeholders involved.

It's easy to acknowledge indirect benefits but hard to build a compelling case around them.

Often with DTx, the financial value can be mixed or uncertain as stated above, so discussion sometimes drifts to indirect value more and more as opportunities are assessed. What is sometimes lost is a balance of how to make strategic decisions based on both. Patient data is notoriously challenging to value and to gather at scale via high-priced prescriptions (Fitbit's valuation vs. user base is one analog). Drug combinations require evidence generation that is overly risky for pipeline assets (don't want the DTx to confound the drug's potential) and the hopeful bump in share or value for in-line assets is uncertain and maybe not profitable in the end. Furthermore, differentiation of a bland me-too drug via a DTx sounds nice but is likely a strategy to take after establishing the DTx alone as having value.

Ultimately, strategic approaches that properly balance risk / reward investments in DTx are critical to prevent an organization from over-extending and getting "burned" by a bad bet in the early stages of market development. Furthermore, as pharma companies often have revolving leadership, it is important to clearly articulate the intended value of a DTx investment to maintain alignment and prevent a loss of vision.

Business Models

One of the most intriguing parts of digital therapeutics (in contrast with pharmaceuticals and medical devices) is the variability in business models and ultimately, the uncertainty in how the market will develop. The key points to consider regarding business models are product development agility, regulation, pricing, and speed to adoption. Below are the most common models.

- **Direct-to-Consumer (DTC)** - Users can download the app and pay for it directly. Some notable DTC products include Woebot® (free) and on the wellness side, good analogs are Headspace (\$69/yr) and Calm (\$69/yr). Benefits are agility and speed of adoption. The key challeng-

es are limited medical claims and low pricing potential. Furthermore, eventually these companies are challenged by customer acquisition costs and the need for DTC marketing campaigns that are too expensive. Most companies that gain significant traction pivot or augment using different models.

- **Employee Assistance Programs (B2B)** - Organizations/ companies contract for access to the DTx at low to no cost for their employees via a "perk" or employee benefit program, often referred to as Employee Assistance Programs (EAP). This approach is similar to DTC in benefits, but it sacrifices a bit of pricing power for scale in order to contract for large volumes of us-

³⁹ "Monetizing Digital Therapeutics - Simon-Kucher." 16 Jul. 2018, <https://www.simon-kucher.com/en/blog/monetizing-digital-therapeutics>. Accessed 14 Mar. 2021.

Digital Therapeutics 101: An Introduction and Overview

ers. For instance, Big Health's Sleepio® is believed to start contracts at a minimum of single-digit thousands of employees. Payment is a combination of approaches such as per-user per-month or -year basis, or per active user, or per activation, the latter of which accounts for engagement in use of the app. Most DTC companies pivot into this space as the selling dynamics are more favorable, meaning the cost of each win is high but the volume of users is significantly better when won, plus they get to further build evidence for the product to drive subsequent sales. Some estimates have been suggested for popular meditation apps achieving >\$100M in annual revenue with estimates of a 50/50 split from DTC and EAP channels.

- **Payer Wellness Benefits (B2B)** – This is similar to the EAP, but this is a perk and added benefit via users' insurance coverage. Payers are perfectly willing to add these in and often do but are also known to develop their own competitive solutions in-house. An example is United Healthcare's purchase of Sanvello as a digital mental health platform, as well as its in-house built Level2⁴⁰ for diabetes (competes with Livongo, etc.).
- **Pharmacy/Medical Reimbursement (B2B2C)** - With regulatory clearance, prescription level business models are hoping to establish high pricing power by bolstering their clinical evidence package and ability to differentiate with claims. However, the downside is more uncertain or sluggish product development as there is a relative "freeze" for trials and for FDA approval. The FDA is still working out how to regulate on-market product updates but inherently the ability to create a top-notch customer

experience is more challenging. The market is also nascent for whether payers see the value of DTx and if they are willing to pay drug-level prices when a digital product does not carry the same distribution and development costs as pharmaceuticals.

Ultimately, emerging cases exist where there are very similar DTx products competing for similar users but under different business models. An example is in the chronic insomnia market. In this space, the prescription DTx, Somryst® is offered via payers while Big Health's non-prescription DTx is offered via employee benefits. Added to the mix is the VA's CBTi-Coach, which is DTC... and also free (there are more free or low-cost DTC options, too). All three of these products are leveraging the same fundamental therapeutic intervention in cognitive behavioral therapy for insomnia (CBTi), a standardized course of psychotherapy with some perks around sleep restriction and sleep hygiene. What is unclear is how the market will reach equilibrium between these products.

As of this publication, Big Health seems to be doing just fine overcoming the free and less user friendly CBTi-Coach, but Somryst launched in 2019 and is charging nearly \$1K for a course of treatment. By comparison, let's estimate that Big Health is \$100 max. This dynamic is still playing out but raises questions around whether the FDA will choose to regulate Sleepio or allow them to operate without making strong medical claims. Will Somryst be able to convince payers and possibly employers that their product is better than lower-priced unregulated options because of the evidence?



⁴⁰ "UnitedHealth creates its own digital health program for type 2" 13 Jul. 2020, <https://medcitynews.com/2020/07/unitedhealth-creates-its-own-digital-health-program-for-type-2-diabetes/>. Accessed 15 Mar. 2021.

Regulatory Oversight

FDA regulatory oversight of digital therapeutics is inconsistent and evolving. Currently, digital therapeutics are reviewed by CDRH and considered Software as a Medical Device (SaMD, [FDA SaMD Guidance](#)), defined as:

“Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.”⁴¹

The visual below provides a helpful snapshot of SaMD regulatory classification which determines the regulatory pathways that will be available. Notice that it is the familiar balance of intended medical purpose and the targeted healthcare situation. So, while a certain medical purpose like CBT may be considered benign, depending on the population one targets (think anxiety vs. suicide) it may have more oversight (and potentially a more protected competitive landscape).

SaMD Definition Statement			
<ul style="list-style-type: none"> Intended Medical Purpose of a SaMD <ul style="list-style-type: none"> Treat or Diagnose Drive Clinical Management Inform Clinical Management Targeted Healthcare Situation or Condition of a SaMD <ul style="list-style-type: none"> Critical Serious Non-Serious 			
SaMD Categories			
	Treat or Diagnose	Drive Clinical Mgmt	Inform Clinical Mgmt
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I

SaMD N12 Risk Categorization Framework

To date, DTx products have generally been classified as Class II Medical devices (though the expectation is that Class III are possible). [The official SaMD risk classification documents](#) provide more information on what these defini-

tions really mean. There was a brief scare during COVID, as the outgoing Trump administration put forth a federal notice to deregulate a large swath of medical devices including digital therapeutics. However, with the administration change and some industry lobbying, the notice was removed and thus preserves the potential regulated market.⁴²

One additional element of regulatory oversight to point out is the Quality Management System (QMS). It is turning out to be a significant part of the IP and capability differentiation for valuing a DTx company.

A quality management system (QMS) is defined as a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS helps coordinate and direct an organization's activities to meet customer and regulatory requirements and improve its effectiveness and efficiency on a continuous basis.⁴³

What has happened in the industry is that some DTx companies with their own pipelines are also offering their services as developers, thus supporting anyone's desire to create a DTx and leveraging their own "proven" QMS as a differentiating value-add. The value proposition for life science is this: There is no need to build, maintain, and struggle with a QMS when you can just use ours, and the FDA likes it already! [AmalgamRx](#) provides a good example. Others that appear to be going this way are Happify and Pear Therapeutics.

A quick disclaimer here, we are not regulatory specialists, but we would like to outline the broad strokes of regulatory pathways for DTx, as well as some insights that may be of use:

- **510(k)** – One must demonstrate that the product to be marketed is at least as safe and effective (substantially equivalent) to a legally marketed device that is not subject to a Premarket Approval (PMA). Overall, this is the most straightforward and easy path, but it requires a predicate

⁴¹ "fda.gov – Software as a Medical Device (SaMD)." 4 Dec. 2018, <https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd>. Accessed 12 Mar. 2021.

⁴² "Here - Federal Register/Vol. 86, No. 72/Friday, April 16, 2021/Notices." 16 Apr. 2021, <https://www.govinfo.gov/content/pkg/FR-2021-04-16/pdf/2021-07760.pdf>. Accessed 10 May. 2021.

⁴³ "What is a Quality Management System (QMS)? | ASQ." <https://asq.org/quality-resources/quality-management-system>. Accessed 15 Mar. 2021.

against which to build evidence to support equivalence. This path is not seen as a measure of effectiveness but rather of safety, as clinical data are not closely scrutinized, and payers know it. This includes the slim majority of DTx approvals to date. But as mentioned earlier, don't forget to review this controversial situation of a follow-on 510(k) approval that may challenge one's belief in the protective power of this path ([Natural Cycles vs. Clue in FDA regulated birth control apps](#))

- **De Novo** – This pathway addresses novel devices of low to moderate risk that do not have a valid predicate device. It takes a bit more effort but also grants the product as first of a new class. Clinical evidence is more closely considered for the De Novo path. A few DTx have been down this path including Pear's reSET® for substance abuse and Akili Interactive's Endeavor® for ADHD. Timelines via this path may vary, as Akili took a long time to get theirs approved.
- **PMA** – This is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. It's the most stringent of the device marketing applications. To date, DTx have not been burdened with this path but some indications from the COVID emergency use authorization of DTx may indicate that conditions like suicide may be of higher concern.

Also of note is "discretionary" or even "exempt." While not a true path, it can be a result because on occasion, the FDA judges that the product does not pose a significant enough risk to require oversight. How companies' marketing departments speak when this happens can be confusing, as they may use terms like "authorized" or "fulfills FDA..." or others. Some products have received this including Voluntis' [Oleena](#)® which helps manage cancer

treatment symptoms.

Numerous DTx have also been granted FDA breakthrough designations such as Cognoa for Autism, Attune for Cancer related distress, and Woebot for postpartum depression. Furthermore, there is a proposed rule being considered to guarantee CMS reimbursement through Medicare for FDA breakthrough-designated devices (though there are also known barriers to accessing a benefits category for DTx which is currently expected to prevent this from coming to fruition).⁴⁴

Lastly, FDA is exploring novel ways to keep up with SaMD and the broader Digital Health and AI-driven product markets. Originally there was the Digital Health Software Pre-Certification Program⁴⁵ which aimed to certify companies to be good stewards of high-quality clinical software products and allow more "hands-off" freedom to update products while on the market. Unfortunately, it has been around a while and wasn't showing much sign of life until recently, when Pear Therapeutics' Somryst passed through the pre-cert program in parallel with their 510(k) process.⁴⁶ More recently, CDRH launched the Digital Health Center of Excellence⁴⁷ with one objective being to:

"Innovate regulatory approaches to provide efficient and least burdensome oversight while meeting the FDA standards for safe and effective products."

Overall, the FDA has some ground to cover to continue clarifying its role, as the market and its overall value may be defined by their presence or lack thereof ([see this article for more on FDA regulation gaps](#)⁴⁸). If the FDA is stricter with oversight, then prescription products may grow in use and dominance. With weak or inconsistent oversight, non-prescribed products may spread faster at lower prices and "eat" the PDT market opportunity.

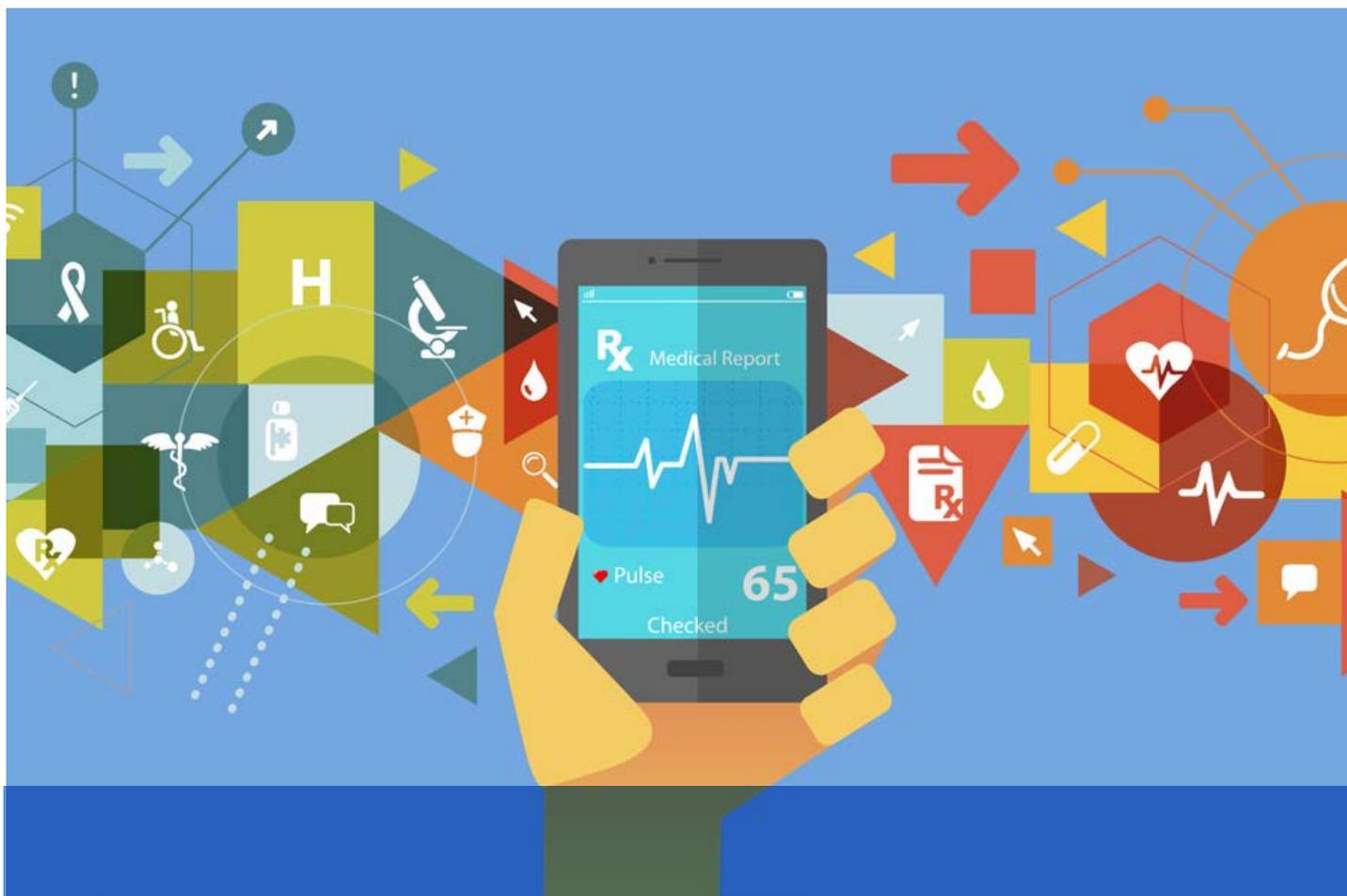
⁴⁴ "Proposed Medicare Coverage of Innovative Technology (CMS-3372" 31 Aug. 2020, <https://www.cms.gov/newsroom/fact-sheets/proposed-medicare-coverage-innovative-technology-cms-3372-p>. Accessed 15 Mar. 2021.

⁴⁵ "Digital Health Software Precertification (Pre-Cert) Program | FDA." 14 Sep. 2020, <https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program>. Accessed 12 Mar. 2021.

⁴⁶ "FDA clears Pear's digital insomnia therapeutic through 510(k), Pre" 26 Mar. 2020, <https://www.mobihealthnews.com/news/fda-clears-pears-digital-insomnia-therapeutic-through-510k-pre-cert-pilot-pathways>. Accessed 12 Mar. 2021.

⁴⁷ "Digital Health Center of Excellence - FDA.gov." 12 Jan. 2021, <https://www.fda.gov/medical-devices/digital-health-center-excellence>. Accessed 12 Mar. 2021.

⁴⁸ "FDA's enforcement discretion for digital health is more ambiguous" 25 Feb. 2021, <https://www.mobihealthnews.com/news/fdas-enforcement-discretion-digital-health-more-ambiguous-ever-2021>. Accessed 10 May. 2021.



Evidence Generation

Mechanisms for Generating Evidence

While the use of clinical trials and real-world evidence are common in life sciences and healthcare, the requirements for both have been variable. However, demand for both is now significant if not a requirement for prescription digital therapeutics.

- **Traditional Clinical Trials** - Prescription digital therapeutics will follow a similar clinical trial process as pharmaceuticals and medical devices (see below for details of

phasing). However, it is proposed that the speed to market is faster, as a software offering can leverage site-less trial approaches and could cost significantly less.⁴⁹ To date, these trials have proven sufficient for FDA approval but not payer coverage.

- **Real-World Evidence** - Thought to be DTx's missing ingredient for payer coverage, this requires sponsor-paid pilots or other arrangements to gather both clinical and economic data to support coverage and pricing. In some ways the time and budget savings from traditional trials may just be diverted to these RWE activities as, again, payers typically don't pay for them.

⁴⁹ "Mirai Depression Study | Project Baseline." <https://www.projectbaseline.com/studies/mirai/>. Accessed 14 Mar. 2021.

One approach that is of immense interest right now is to somehow accomplish both regulatory and real-world evidence needs in parallel. For an example, Better Therapeutics published their investor presentation for going public via a SPAC deal in 2020 on the SEC website, and slide 21 shows how they intend to run “pilots” and “pivots” simultaneously to achieve all their evidence needs.⁵⁰

When exploring evidence generation strategy with life science clients, this approach is also of interest, but some flags have been raised including

1. Depending on the timing of the pilot and FDA submissions, the FDA may want the RWE data as part of the evidence package, which may or may not help the product's case.
2. Product development can get trickier as priorities for the clinical trial needs vs the RWE needs may be different and additional resources or trade-offs may introduce new risk.
3. Recruitment and/or “blinding” of trial participants from those with access to the RWE pilot could complicate clinical trial execution or interpretation.

Lastly, many life science companies are intrigued by the thought of cheaper and faster DTx trials. However, this additional layer of RWE evidence may increase the spend for market entry, so it's important to consider the overall cost impact.

Required Types of Evidence

While not going into the weeds, the common evidence types needed for DTx evaluations are summarized via [Evernorth's Digital Formulary](#):

- **Clinical effectiveness (most relevant to regulators, providers, and patients)**
- **Security and privacy compliance (most relevant to patients directly, but important to all)**
- **Value and affordability (most relevant to payers)**
- **User friendly experience (most relevant to providers and patients)**

Clinical effectiveness should generally align with known drug-like endpoints. The challenge comes with the concept of “durability” as most DTx are courses of treatment for 6 to 12 weeks. Insurers want to see that the investment in

the treatment has a lasting and meaningful effect. These durability studies can go anywhere from 6 to 24 months beyond the course of treatment. A number of DTx are attempting to use novel endpoints, especially around cognition via neurocognitive training. These have historically been controversial at the FDA because some argue that subjects simply train to beat their own test. In addition, they are criticized for not having a connection to any tangible value in reality. For example, what is the value of children being more attentive on an attention test? Do they get better grades or a job or some other meaningful output?

Security and privacy compliance is always a hot button topic and a legitimately scary one to get wrong. For instance, review the story of [Vastaamo](#), an online mental health provider in Finland whose system of private therapy notes was hacked, then used for company and individual ransomware attacks. It was eventually released wholesale online to the dismay of more than 30,000 users. Also of consideration is how the manufacturer (especially if a biopharma company) accesses patient data and to what end. The data is useful for refining user experiences and possible machine learning algorithms. There are options to allow for this via third party data warehousing and de-identification, but it may raise some eyebrows and will blow with the greater winds of tech privacy conversations.

Value and affordability comprise the economic story. This is likely the piece that gets a DTx company farthest for coverage but is also the trickiest to deliver as costs can be hard to collect, analyze, and document clear improvements.

User friendly experience, or rather usability, is also critical for DTx. Reviewers want to know that the patients are using the tool. Where medication adherence to pharmaceuticals is a major topic (but with few solutions), insurers and clinicians expect that software should have much better access and evidence for impact since activity can be tracked directly. One analog that has been mentioned is how Medicare manages CPAP machine compliance for payment.⁵¹

Ultimately, some may argue that the true differentiator and competitive element to the emerging digital therapeutic landscape may be user friendliness / engagement, not the intervention itself. Most interventions to date could be replicated. For example, if we assume that anyone can make a 12-week CBT course for insomnia, then what will be the competitive elements to decide coverage and use? Well, engagement and design: how good is the experience

⁵⁰ Better Therapeutics Investor Presentation, March 2021, https://www.sec.gov/Archives/edgar/data/0001832415/000121390021020544/ea139081ex99-2_mountain2.htm

⁵¹ CMS, <https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/ProviderComplianceTipsForPositiveAirwayPressureDevicesAndAccessories-ICN909376Print-Friendly.pdf>, accessed 11 June 2021

for users in order to ensure the maximum efficacy and use? Refer back to the regulatory section about how prescription digital therapeutics may have their hands tied here as oversight of updates is unclear, so the ability to improve products on market is nebulous. Basically, how would a prescription digital therapeutic ever compete with a similar non-prescription DTx if it can't iterate as fast? For a deeper look at the complexities of engagement look [here](#).

Development Stages

While historically it was challenging to assess where a DTx was in development, most organizations are aligning around a pharmaceutical-like pipeline to communicate development status such as:

- [Phase 1 – Discovery, Design, Translation or Research](#)
- [Phase 2 – Proof of Concept, Usability and Human](#)

Factors

- [Phase 3 – Pivotal Trial](#)
- [Regulatory](#)
- [Launch](#)

Of note is that Phase 1 uses translation as a means to describe taking therapeutic interventions that are already known and “translating” them into digital experiences. Sometimes “discovery” is about looking into these cocktails and/or the not-so-hidden acknowledgement that they simply have an idea based on existing literature but not an actual product. Phase 2 has a proof of concept which is often heavily dominated by the need for usability testing (either simultaneously or separately) as discussed in evidence types above. The remaining pivotal, regulatory and launch are apparent and self-explanatory.

A broad overview of DTx clinical trials and more can be found via Evidera for those interested in a deeper view.

Reimbursement

Much of the DTx industry is currently focused on reimbursement. This is because numerous products have successfully navigated the regulatory requirements but lack the clarity on coverage, coding and pricing mechanisms needed to scale effectively.

Coverage and Coding

Coverage decisions are the real complication for DTx at the moment and it appears that the industry is waiting to see how CMS approaches a resolution. As Medicare is a defined benefit plan, by law it has defined categories for coverage. Unfortunately, DTx don't really fit into any.

The majority of discussions revolve around various options, e.g.

- [As a physician service within the medical benefit \(via CPT codes\)](#)
- [As an ancillary service under the medical benefit covered](#)

[and reimbursed under a fee for service “buy and bill” model, similar to drugs administered incident to physician services \(via HCPCS codes\)](#)

- [As Durable Medical Equipment \(DME via HCPCS codes\)](#)
- [Via pharmacy benefit coverage \(via NDC codes or equivalents\)](#)

Additional conversations may occur around Medicare Advantage mechanisms via supplemental benefits, or Medicaid coverage via more flexible home health services or “Any Other Medical Care”.

Lastly, commercial payers could feasibly do whatever they want. If real-world pilots or evidence is demonstrated in their populations, then they appear open to finding coverage solutions via multiple paths to reap the value. So there is no easy answer here, though some legislation has been proposed to help push a federal-level resolution that would feasibly trickle down to some degree.

For more information on coverage, Nisarg Patel has writ-

ten a [nice article](#) in Health Affairs (paywall, sorry to some).⁵² The coding issue can be a complicated and technical one, beyond the scope of this document though a [June 2020 article](#) on Exits and Outcomes is quite informative.⁵³ Ultimately, there are very real and stubborn barriers in the way of obtaining coverage, coding and reimbursement for DTx that are yet to be resolved.

On the commercial benefit front, there are similar challenges in that no payer knows exactly where to put a DTx: into the pharmacy benefit, medical, behavioral health, or even the wellness benefit. It is truly a question of “fit” across the current benefit category norms, each one having some degree of complication. Furthermore, medical and pharmacy benefits are not integrated, so the ensuing back-and-forth game of “who owns it?” can take time to resolve as well as each payer having a different result. Below are some comments on each but, for the time being, it appears that reimbursement is a one-by-one situation that may result in a blend of various coverages when looking holistically at a DTx business.

- **Pharmacy Benefit** - DTx would love to be here as it has the highest pricing potential. The main issue is that there is no active pharmaceutical ingredient so most payers won't entertain it. A few have covered device products for things like insulin strips but it's not common. To date, WellDoc is the only DTx with a bona fide NDC code that we know of, while FDA has supposedly shut the door on any future NDCs for medical devices (including SaMD).⁵⁴ Furthermore, the pharmacy benefit is geared towards a physical “dispensing” system, where drug is held in inventory, claims are adjudicated at the point of sale / dispensing, etc. With DTx, there's no need for all the logistics that are in place for physical drugs and therefore there is a lack of perfect fit.
- **Medical Benefit** - If it isn't pharmacy, then it must be medical! Maybe. Most DTx being developed utilize psychotherapy-based techniques often deployed by psychotherapists, which are paid via medical benefits. So as the strongest analog to the intervention, the medical benefit is the current front-runner for DTx coverage. However, a CPT or HCPCS code is still needed for ease of coverage while the pain points of “buy and bill” persist.

- **Wellness Benefit** - The third rail of prescription DTx, this approach would downgrade pricing and market potential to that of the EAP market approach and by some estimates is a 100x reduction in overall value. Payers sometimes argue that psychotherapy-based DTx are a fancy version of “education” because anyone can go pick up a CBT book for themselves.

Ultimately, it may be calming to know that payers are often willing to find a way to cover a product that is demonstrated to deliver clinical and economic value to them. So while the above benefit category barriers exist for wide-scale adoption, the “one-on-one contracting battle” can be won. Nevertheless, that is an awfully slow way to access the fragmented U.S. market.

Pricing and Market Access

There are a few DTx products on the market with public pricing available at the time of this publication and they each seem to think of the market differently.

- **Pear Therapeutics' reSET and reSET-O for abuse disorders** are priced at around \$1,200⁵⁵ (12 weeks) and **Somryst for chronic insomnia** is priced at \$950 (6 lessons, 9 weeks). They are using a higher-tier drug-like pricing.
- **Orexo / Gaia's Deprexis for depression** is priced at \$400 (3 months) appears low-priced while **Vorvida for alcohol abuse** at \$599 (~3 months) is more moderate
- **Akili Interactive's Endeavor Rx for ADHD** is priced at \$450 (3 months) also has a somewhat middle of the road approach.

Overall, the pricing strategy for DTx appears to balance somewhere across the spectrum of the analogs below with a total course of therapy currently between (\$400 - 1,200):

- **Low price** = DTC, EAP and Wellness benefit pricing (\$10 - \$100/month)
- **Moderate price** = Weekly public psychotherapy (\$150 - 400/month)
- **High price** = Drug-like pricing, high unmet needs or

⁵² Patel, Nisarg, Modernizing Medicare Coverage Pathways For Prescription Digital Therapeutics, Health Affairs, 13 May 2021, <https://www.healthaffairs.org/doi/10.1377/hblog20210510.303135/full/>

⁵³ “Thanks to Apple, Alivacor goes more DTC. Part II: Software as a drug..” <https://exitsandoutcomes.com/thanks-to-apple-alivacor-goes-more-dtc-part-ii-software-as-a-drug/>. Accessed 12 Mar. 2021.

⁵⁴ US FDA, Enforcement Policy Regarding Use of National Health Related Item Code and National Drug Code Numbers on Device Labels and Packages, 21 May 2021, <https://www.fda.gov/media/95794/download>

⁵⁵ “ICER says more data are needed on digital app treatments for ...” 6 Nov. 2020, <https://www.fiercebiotech.com/medtech/icer-says-more-data-needed-digital-app-treatments-for-opioid-use-disorder>. Accessed 12 Mar. 2021.

private psychotherapy (\$400 - \$600/month); the cap is based on specialty tier placement which is around \$600 and no DTx in existence right now should go there

Concerning access, beyond the coverage mechanisms discussed above, some pharmacy benefit managers (PBMs) have established access pathways for digital therapeutics including Evernorth's (ExpressScripts, Optum) Digital Formulary and CVS Point Solutions Management. Upon announcement, this seemed like a fantastic development for digital therapeutics but there is reason to be cynical in that neither currently offers an FDA-cleared digital therapeutic (PDT). Only non-prescription digital therapeutics can be accessed. So, in some ways, this approach may be damaging the prescription DTx market development. Furthermore, it's very easy for PBMs to offer this to their customers as it only extends their middleman status and doesn't commit them to any real risk. Customers have the option to leverage the

formulary or not and uptake is not clear as of yet.

One benefit of these digital formularies to the industry is that they are developing frameworks for evaluating DTx for "coverage," which can inform evidence packages for the future. Below is Evernorth's approach:

Each solution on the Evernorth Digital Health Formulary has been clinically reviewed and evaluated by a panel of pharmacists, physicians, user experience experts and health research PhDs. Solutions are only given the Digital Health Formulary's seal of approval if they meet our stringent requirements for: Clinical effectiveness, Security and privacy compliance, Value and affordability, and a user-friendly experience⁵⁶

Mark Bini of Express Scripts is the "face" of the digital health formulary and more can be learned from an interview with him [here](#).

Distribution, Prescribing Authority, and Channels

Distribution

Most DTx to date are distributed via the web in one form or another. Commonly, their products are listed on the Apple and Google app stores or via the product's own website, but are locked behind a code that permits access.⁵⁷ The patient, once prescribed the PDT, will obtain a code from the manufacturer via their patient support center. Most prescription DTx are offered in courses of treatment that eventually deny long-term access to the therapeutic components when the treatment course concludes. Refills are available and typically require a new payment event and some allow users to save workbooks, worksheets or other materials for reference later. To date, payers are very wary of refills as they demand evidence that these therapies can be of repeat benefit.

Prescribing Authority

Prescription business models are the strength of life science companies and the prescriber targeting, messaging and sales force execution are highly developed and refined. However, with DTx a few new issues come up that are important to note:

- **Value propositions around "access" lead to primary care physician (PCP) sales force needs** – Companies with DTx that are trying to improve access to a known therapeutic intervention (like CBT) will eventually require consideration of PCPs as a valuable point for prescribing. There are drop-offs at every step following PCP interactions and for conditions like depression, anxiety, ADHD, and some other front-line DTx therapeutic areas it

⁵⁶ ExpressScripts corporate website, <https://my.express-scripts.com/digital-health-formulary.html> accessed 10 June 2021

⁵⁷ "EndeavorRx - ADHD on the App Store - App Store - Apple." <https://apps.apple.com/us/app/endeavorrx-adhd/id1458156758>. Accessed 14 Mar. 2021.

Digital Therapeutics 101: An Introduction and Overview

seems obvious to develop PCPs. The issue is that building and paying for a PCP sales force is very expensive. So, a thorough business case is required to determine whether the cost would be justified. Novel distribution and commercial models are being explored to overcome this, mainly via telehealth.

- **Who exactly has the authority to prescribe?** - DTx are often psychotherapy-based and therefore the expert domain of therapists, but they can't commonly prescribe⁵⁸ (except in a few states⁵⁹ but they don't always do it because their clinical training and philosophy center around being a non-pharmaceutical option and many don't feel it's appropriate to engage in both). However, this could change, particularly for DTx, which are not pharmaceuticals. A word of caution: companies thinking of a traditional sales force model targeting therapists should exercise caution. There are a ton of them! Furthermore, the concentration of patients for any one therapist is astronomically low. They commonly see patients for an hour every week or every other week, so a bit of math would suggest that they see far fewer patients than the average PCP or other specialist. Thus, the potential "value" of any single therapist is likely to be low to a company.

Channels

With the above in mind—as well as the fundamental shifts in care models as a result of the broader digital health movement—there are numerous commercial models for distribution and channel management being explored. A top consideration, though, is the resistance to change when it comes to physician workflow.

- **DTx are not "plug and play," as physicians can't just write a prescription and say goodbye as the patient goes to the pharmacy to fill it. There is no "it" like medications. It's an app...so what happens?**
- **How do physicians even prescribe a DTx or put it into the EHR or e-prescribing platform (a challenge that some are trying to solve)?**
- **Often, DTx have clinician dashboards because they want that therapeutic alliance to boost the product claim. But**

how are physicians paid for reviewing this data and/or learning how to even understand the data? Lastly, if it's outside the EHR, most want nothing to do with it, adding integration costs for manufacturers.

Nevertheless, DTx seems to be changing the way healthcare is provided from within. Below, we review some innovative ideas that many are exploring for getting DTx to patients.

- **In-Person Consultations** – This is as discussed above. Just a reminder: A company following this path might be taking on a big battle that could take a long time. One slight innovation here is that Kaiser appears to have implemented some DTx access via "referrals" which is interesting.^{60 61}
- **Telehealth Partnerships** - As this area grows rapidly post-COVID, it seems like a nice match to have virtual providers and digital therapeutics. This bleeds into the options below, but it wouldn't be surprising to see traditional Amwells and Teladocs having an eye on digital therapeutics. Also, note that Pear Therapeutics launched Somryst with [access to UpScript telehealth provider](#) via its website (though customers still pay the \$45 consultation fee and are not guaranteed a Somryst prescription). Akili Care also exists, thought it seems to be more of a patient support option than for prescribing. Nevertheless, it's worth watching.
- **Digital Clinics (e.g. Hims & Hers, Ro, Cerebral)** - As this market of DTC medication access skyrockets, the companies are fighting for the ever coveted "front door of healthcare" with the fundamental organizational principle being the condition. With this in mind, they are all exploring additional services and offerings like Hims & Hers going into psychiatry and therapy,⁶² while Ro goes into home services.⁶³ So, like telehealth, they may also move into digital therapeutics.
- **Digital Care / Chronic Care Platforms** - These companies, as opposed to digital clinics, go beyond easy medication access and actually have robust digital care service offerings (coaching, physicians, community, apps, devices, etc.). In a lot of ways, these are the emerging future digital care models but are still only serving a

⁵⁸ "About Prescribing Psychologists - APA Services, Inc." <https://www.apaservices.org/practice/advocacy/authority/prescribing-psychologists>. Accessed 14 Mar. 2021.

⁵⁹ "Prescribing Psychology Gets a Boost | Psychology Today." 12 Aug. 2020, <https://www.psychologytoday.com/us/blog/alpha-blog-charlie/202008/prescribing-psychology-gets-boost>. Accessed 14 Mar. 2021.

⁶⁰ "KAISER Integrates DTx Into the Behavioral Health Treatment" <https://www.cbpartners.com/kaiser-integrates-dtx-into-the-behavioral-health-treatment-paradigm-at-no-extra-cost-after-a-clinician-referral/>. Accessed 14 Mar. 2021.

⁶¹ "How Kaiser Permanente Created a Mental Health and Wellness" <https://catalyst.nejm.org/doi/abs/10.1056/CAT.20.0295>. Accessed 14 Mar. 2021.

⁶² "Hims & Hers Takes On Mental Health | by Hims | hims & hers | Medium." 7 Apr. 2020, <https://medium.com/hims-hers/hims-hers-takes-on-mental-health-dc9e7cfe78b0>. Accessed 14 Mar. 2021.

⁶³ "Ro will start making house calls to vaccinate elders in New York for" 3 Mar. 2021, <https://www.mobihealthnews.com/news/ro-will-start-making-house-calls-vaccinate-elder-new-york-covid-19>. Accessed 14 Mar. 2021.

Digital Therapeutics 101: An Introduction and Overview

small percentage of the overall population. This segment is already active in digital therapeutics with Teladoc (telehealth) and Livongo (digital therapeutic elements), as well as mergers, partnerships or acquisitions like Omada Health (diabetes) acquiring MyStrength (CBT software)⁶⁴ and AbleTo (virtual therapy) acquiring Joyable (app-based therapy).⁶⁵ Augmenting these models via partnership or their own strategies may incorporate digital therapeutics.

- **Retail Pharmacies** – Some have suggested ways to get pharmacists more involved and to leverage them as a mechanism for DTx fulfillment and onboarding. This is an option, but it has not been a major push to date.
- **Over-the-Counter (OTC)** - For those that FDA deems as needing prescriptions, this option is years away. Though the FDA's discretion with similar products straddling prescription and non-prescription status may provide easier access options in the future for some.

As a bit of a side note on innovative care models: While above we discuss telehealth, digital clinics, and digital care—all innovative care models coming from the provider-first direction—Pear Therapeutics as a pure DTx has shown signals of moving into broader digital care offerings with

acquisition and licensing of multiple products in biomarkers and virtual reality⁶⁶ as well as medication adherence.⁶⁷ In addition, keep an eye on Happify Health, who in 2020 revealed a more expansive digital-care-like model that integrates their DTx origins and supports how point solutions may be united.⁶⁸ The question will become how these systems coordinate, if at all, with third party PDTs.

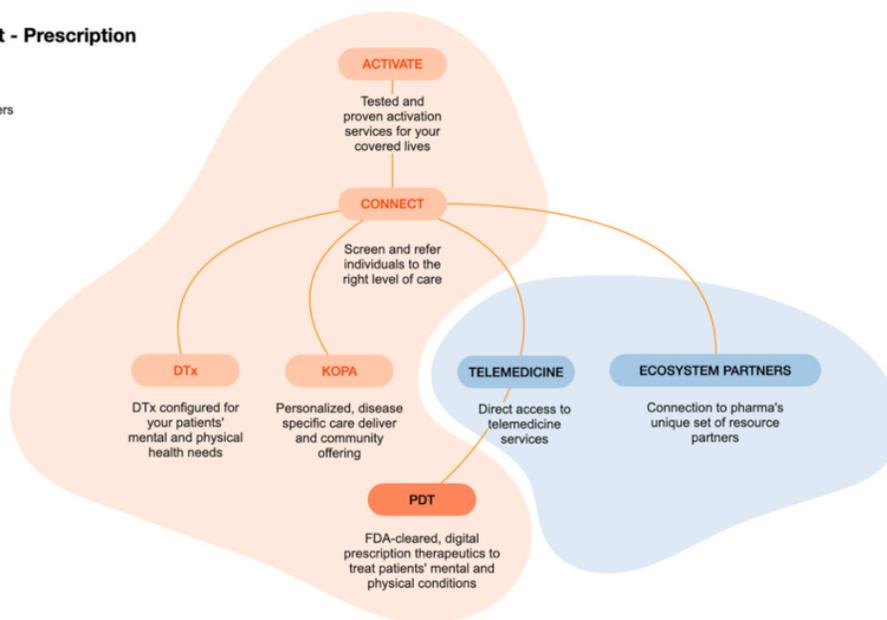
To end this section, via Exits and Outcomes, Akili's Eddie Martucci shared his thoughts in a podcast around exploring various commercial models which is quite revealing:⁶⁹

"I'll be honest when I was first planning this, and we were running trials... I was very much in the typical pharma mindset. Right? So I was thinking, okay, well, we'll have to have a few hundred sales reps, and we'll be flooding the market and whatever the product is, we're just going to push it Day One and try to get max and cover the globe. That has changed pretty dramatically for a few reasons.

One, on looking at it deeper, we felt like it was an extremely inefficient strategy from a resource and spend perspective – in the same way pharma many times sees that it's inefficient, especially given our technology reso-

For Pharma : Post - Prescription

- Happify
- External Happify Partners



⁶⁴ "Livongo moves into behavioral health with acquisition of Denver" 30 Jan. 2019, <https://medcitynews.com/2019/01/livongo-moves-into-behavioral-health-with-acquisition-of-denver-based-mystrength/>. Accessed 14 Mar. 2021.

⁶⁵ "AbleTo Acquires Joyable to Further Increase Access to High-Quality" <https://www.ableto.com/news/ableto-acquires-joyable-2019/>. Accessed 14 Mar. 2021.

⁶⁶ "Pear Therapeutics acquires new VR therapeutics, licenses CBT" 7 Jan. 2020, <https://www.mobihealthnews.com/news/pear-therapeutics-acquires-new-vr-therapeutics-licenses-cbt-vocal-biomarker-tech-flurry-new>. Accessed 14 Mar. 2021.

⁶⁷ "Pear Therapeutics inks deal with digital pill ... - MobiHealthNews." 15 Jan. 2021, <https://www.mobihealthnews.com/news/pear-therapeutics-inks-deal-digital-pill-company-etectrx>. Accessed 14 Mar. 2021.

⁶⁸ Happify Health Corporate Website, <https://www.happifyhealth.com/solutions>, accessed 10 June 2021

⁶⁹ "Digital Therapeutics Edition with Eugene Borukhovich - On Health" <https://healthpodcastnetwork.com/show/digital-health-today-digital-therapeutics-edition/>. Accessed 14 Mar. 2021.

notes in a way that it doesn't need a heavy sales push in the same way. The other important piece is, I think we fully have embraced now that our technology, like many other technologies, [and this] relates to the question you asked earlier about iteration, everything about our model can change related to feedback...

So we actually swung nearly 180 degrees in the other direction from a kind of big bang pharma launch, and have, instead, been pursuing these smaller, more targeted tests. We're seeing live patients come through, live prescriptions come through, full payment cycle, full use cycle. And we're adapting and iterating ... and so for us, that meant, start in a lean way and grow over time."

He goes on to say:

"We also have what our business calls, Akili Care, which is humans, support team that can help patients. So we're deploying in some ways a care model along with our digital

therapeutic as a support. I think we will see that a lot more. Now, every company won't be able to invest in that, right, because in some ways, it doubles your investment from just helping with the product. But I do think that whoever ends up distributing it, whether it's partnerships, or whether it's a company like ours alone, I do think you're going to see more of a convergence there where it's the duty and the obligation in my mind of digital to make use of the data and the connection and the experience you have with patients. And that lends itself so cleanly to some of these care type platforms. The difference is, I think there's a lot of value starting with the treatment product so that you understand the direct effect you're having with the patient and then build around it versus the opposite... 'We're going to build a holistic solution, and then somehow back into the treatment,' that's just not my general way of thinking. I like to start with the core issue for the patient."

If that isn't a call for creative thinking – I am not sure what is.

Ex-U.S. Markets

While the U.S. tends to be everyone's favorite healthcare market for its size and its high level of spend, in reality, several ex-U.S. markets are likely ahead of the game when it comes to digital health and digital therapeutics.

We don't have the space for a full overview in this publication, but below are a few notable events that are worth exploring more deeply.

- Germany's new Digital Healthcare Act (Digitale-Versorgung-Gesetz or DVG) entitles all individuals covered by statutory health insurance to reimbursement for certain digital health applications (i.e., insurers will pay for their use).^{70 71} Currently, they have more than 10 digital therapeutics that are covered and reimbursable.

- Belgium is also following Germany's lead with reimbursable DTx pathways.⁷²
- Japan has approved an offering for CureApp for smoking cessation (and cleared it for reimbursement).⁷³
- The UK has a clear digital health assessment framework in beta for informing coverage decisions.⁷⁴ [NICE has also released a recent evidence standards framework for digital health technologies](#) which is also worth reviewing for both clinical and economic effectiveness.⁷⁵
- Other countries exploring this space are Sweden, Singapore, Australia and South Korea.

⁷⁰ "Germany's digital health reforms in the COVID-19 era ... - Nature." 10 Jul. 2020, <https://www.nature.com/articles/s41746-020-0306-7>. Accessed 14 Mar. 2021.

⁷¹ "How Germany vows to become a top country for digital health" 17 Mar. 2020, <https://www.mobihealthnews.com/news/emea/how-germany-vows-become-top-country-digital-health-solution-providers>. Accessed 14 Mar. 2021.

⁷² "[Medical applications now reimbursed by ... - mHealth Belgium." <https://mhealthbelgium.be/news/medical-applications-now-reimbursed>. Accessed 14 Mar. 2021.

⁷³ "CureApp SC nicotine addiction treatment app & CO checker" 27 Aug. 2020, <https://www.mobihealthnews.com/news/apac/cureapp-sc-nicotine-addiction-treatment-app-co-checker-receives-regulatory-approval-japan>. Accessed 14 Mar. 2021.

⁷⁴ "NHSX launches assessment criteria for digital health tools." 26 Oct. 2020, <https://www.digitalhealth.net/2020/10/nhsx-launches-assessment-criteria-for-digital-health-tools/>. Accessed 14 Mar. 2021.

⁷⁵ "Evidence standards framework for digital health technologies | Our" <https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies>. Accessed 24 May. 2021.

Parting Remarks: Where we are now

In closing, we offer a “short and sweet” summary if not a blatant teaser for follow-on publications of what we think is happening and where all of this leads:

1. DTx are often resonating as innovative solutions for areas of high unmet medical need.
2. Clinical evidence is mounting steadily for DTx to have a role in new care models.
3. It is not yet clear which stakeholders are best to shepherd DTx into widespread existence (start-ups, payers, providers, life science companies, etc.).
4. The FDA still has a role to play in clarifying how the market will develop, and that role is still evolving.
5. Reimbursement is still nearly non-existent, as the market is not there yet. This could change relatively soon though, but don't expect it to then be easy: clinician and patient adoption may still be a significant obstacle.
6. The profitability of various business models and strategies is uncertain, so clear strategic planning is required and agility needs to be baked in.
7. It's been a rocky path so far, but investment and interest remains high.

Ultimately, these are opinions and there are many ways to look at this market. More importantly, there are many ways to be involved in making an impact on how healthcare is provided. We're confident that digital therapeutics have a significant place in the healthcare equation, and the market will continue to evolve in ways that incorporate them effectively.

So if you've made it this far, then I commend you and strongly invite you to reach out to us. We are excited to contribute to the emergence of digital therapeutics and are looking for like-minded folks to work alongside... and it appears that means you!

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