

FEB 2021

healthxl | Exits & Outcomes

Prescription Digital Therapeutics (PDT)

THE FUTURE OF DIGITAL THERAPEUTICS



ABOUT HEALTHXL

Connecting
leaders to solve
health challenges
with technology.

OUR MARKET READY TOOLS...

We use **3 categories**
to showcase our
broad range of
market ready tools



Strategy & Market
Assessment

Scouting &
Competitive Intel

Innovation Programmes
& Seminars

..AND MEMBERS



PHILIPS

Johnson & Johnson



Baxter



Humana

MERCK



Bristol Myers
Squibb™

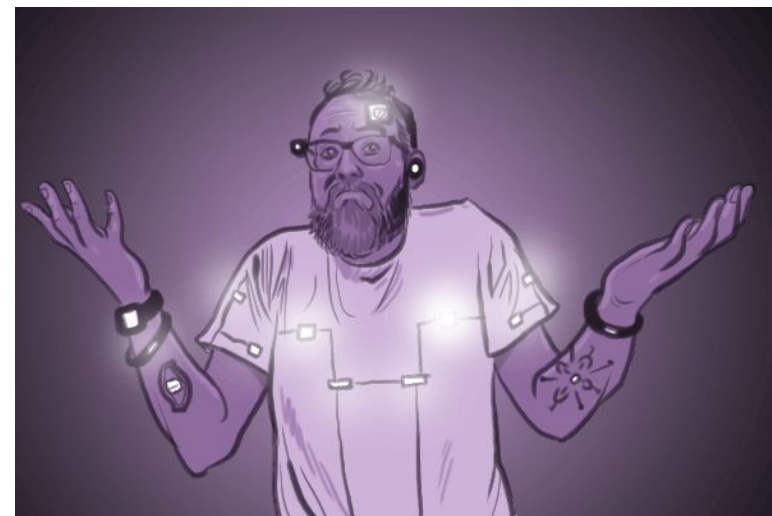
ABOUT EXITS & OUTCOMES

E&O is a digital health research and media company led by Brian Dolan, who also founded MobiHealthNews back in 2008.

E&O offers 3 newsletters focused on funding, pharma, and employers; long-form research reports; and a growing library of mini-databases.

E&O's LONG-FORM RESEARCH REPORTS HAVE DUG INTO:

- **UNITEDHEALTH GROUP** (8,000 words)
- **LIVONGO HEALTH** (3,600 words)
- **PEAR THERAPEUTICS** (4,400 words)
- **OMADA HEALTH** (5,300 words)
- **VIRGIN PULSE** (3,500 words)
- **EVIDATION HEALTH** (3,500 words)
- **HINGE HEALTH** (4,500 words)
- **PROTEUS DIGITAL HEALTH** (4,500 words)
- **GOOGLE HEALTH** (4,400 words)
- **ALIVECOR** (4,400 words)
- *and more...*



“Unsolicited plug. I can’t believe how good the digital health content on Exits & Outcomes is. So much more sophisticated than most other content out there on digital health and digital therapeutics. The subscription price is a total steal (don’t tell Brian I said that).”

- Digital health strategy consultant

“I must say, Exits & Outcomes is right now the only newsletter that I read from top to bottom. It feels personal, witty, and really well-curated.”

- Pharma VC

Then and Now

The objective of this HealthXL- E&O Report is to deep dive into one subsegment of DTx that has enormous potential: prescription products. We shine a light on clinical validation, adoption, investments, reimbursement and regulation.

This report contains key examples of PDT applications, industry implications and a critical viewpoint of the current reality of the DTx environment and those which must be addressed in order to deliver on the DTx promise in terms of optimized health outcomes.

Why prescription-only digital therapeutics for this report?

In the past two years a wide variety of companies have co-opted the term “digital therapeutics” to describe their digital health offerings. This report seeks to cut through some of that noise by focusing on a smaller subset of this group: prescription digital therapeutics (PDTs).

A Recap of DTx...

	Digital Therapeutic to: TREAT A DISEASE	Digital Therapeutic to: MANAGE A DISEASE	Digital Therapeutic to: IMPROVE A HEALTH FUNCTION (Includes prevention)*
Medical claim types	Medium to high-risk claims	Medium to high-risk claims	Low to medium-risk claims
Clinical endpoints	Must use clinical endpoints to support product claims	Must use clinical endpoints to support product claims	Must use clinical endpoints to support product claims
Clinical evidence	Clinical trials and ongoing evidence generation required	Clinical trials and ongoing evidence generation required	Clinical trials and ongoing evidence generation required
Regulatory oversight	Third-party validation of efficacy and safety claims by regulatory or equivalent national body	Third-party validation of efficacy and safety claims by regulatory or equivalent national body	Degree of regulatory oversight depends on local regulatory body frameworks
Patient access	Prescription required	Prescription required OR Non-prescription product	Prescription required OR Non-prescription product

* Includes digital therapeutics that prevent a disease

Report Content

PDT Basics Pg. 8 - 10

- Definition and Checklist (9)
- Four Categories of PDT Companies (10)

Investments in PDT Pg. 11 - 16

- The Impact of Covid (12-14)
- Top Investors and Clinical Areas (15)
- Highest Funded PDT Companies in 2020 (16)

PDT Solutions Landscape Pg. 17 - 19

- Market Mapping of PDT (18)
- Akili: Example of a PDT Pipeline (19)

Commercialization & Business Models Pg. 20 - 24

- Current PDT Business Models (21)
- Pricing Strategies and Examples (22 - 23)
- PDT and Big Pharma Partnerships (24)

Clinical and Economic Outcomes Pg. 25 - 32

- Clinical Validation: Rigor of Evidence (26 - 28)
- Validation: Current Frameworks (29 - 31)
- Case Study of Economic Validation: Pear Therapeutics (32)

Report Content

Regulatory Environment Pg. 33 - 36

- The FDA (34 - 35)
- The EU (36)

Reimbursement and Cost Coverage Pg. 37 - 41

- Highlights of the Previous Two Years (38 - 39)
- Reimbursement in the US (40)
- Reimbursement Outside of the US (41)

Enablement and Adoption Pg. 42 - 47

- Prescription Pathways (43)
- Digital Health Formularies, Registries and Health App Libraries (44 - 45)
- Prescription Capabilities (46)
- EU Landscape (47)

Final Thoughts and Next Steps Pg. 48

Contributors to This Report Pg. 49 - 50



SECTION 1

PDT Basics

Definition and Checklist | Four Categories of PDT Companies



PDT Basics: Definition and Checklist

Typical characteristics of a Prescription Digital Therapeutic

DEFINITION:

A prescription digital therapeutic is a **prescription-only software** that delivers **evidence-based therapeutic intervention(s)** to prevent, manage or treat a medical disorder or disease.

In other words, software driven behaviour change is the active ingredient in this formulation.

Checklist

- ✓ Should treat or manage a medical condition
- ✓ Should have a patient facing therapeutic intervention
- ✓ Should have a core software element as the active ingredient
- ✓ Should demonstrate robust measurable clinical outcomes
- ✓ Should have regulatory approval or clearance
- ✓ Should be prescribed by a physician only
- ✓ Should prove cost effectiveness relative to a drug
- ✓ Should be covered by insurance

Four Categories of PDT Companies

01	PDT companies with Rx products that are regulated by the FDA as Rx-only	  
02	PDT companies that are regulated by the FDA as Rx-only, but not due to the digital therapeutic component of their product.	
03	PDT companies with over-the-counter solutions (not FDA-regulated as Rx-only products) but who are using a prescription distribution channel.	
04	PDT companies that only have over-the-counter products today but are planning an FDA-regulated Rx-only product	  

*Representative, not-exhaustive



SECTION 2

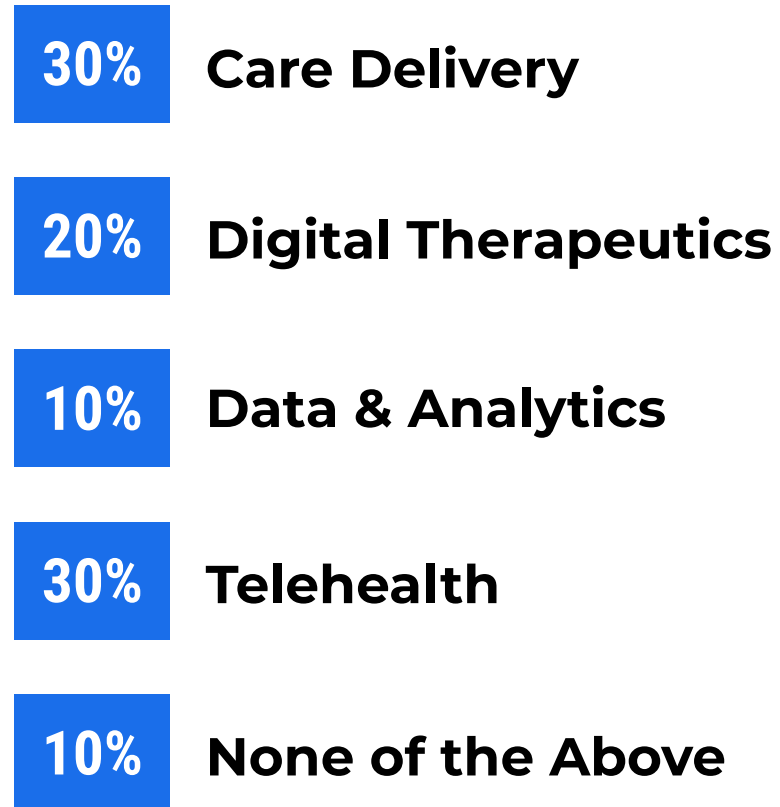


Investments in PDT

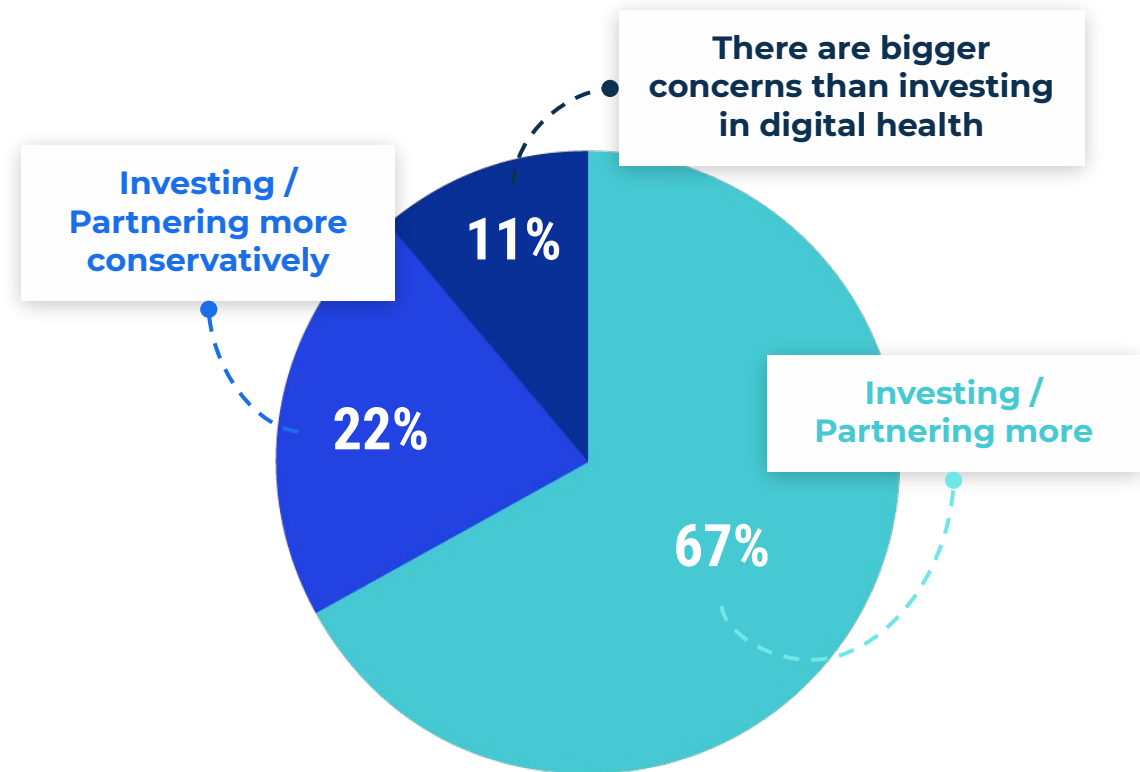
The Impact of Covid | Top Investors and Clinical Areas
| Highest Funded PDT Companies in 2020

COVID Investment Implications on DTx

Q1: Areas I see greatest promise for investment in?



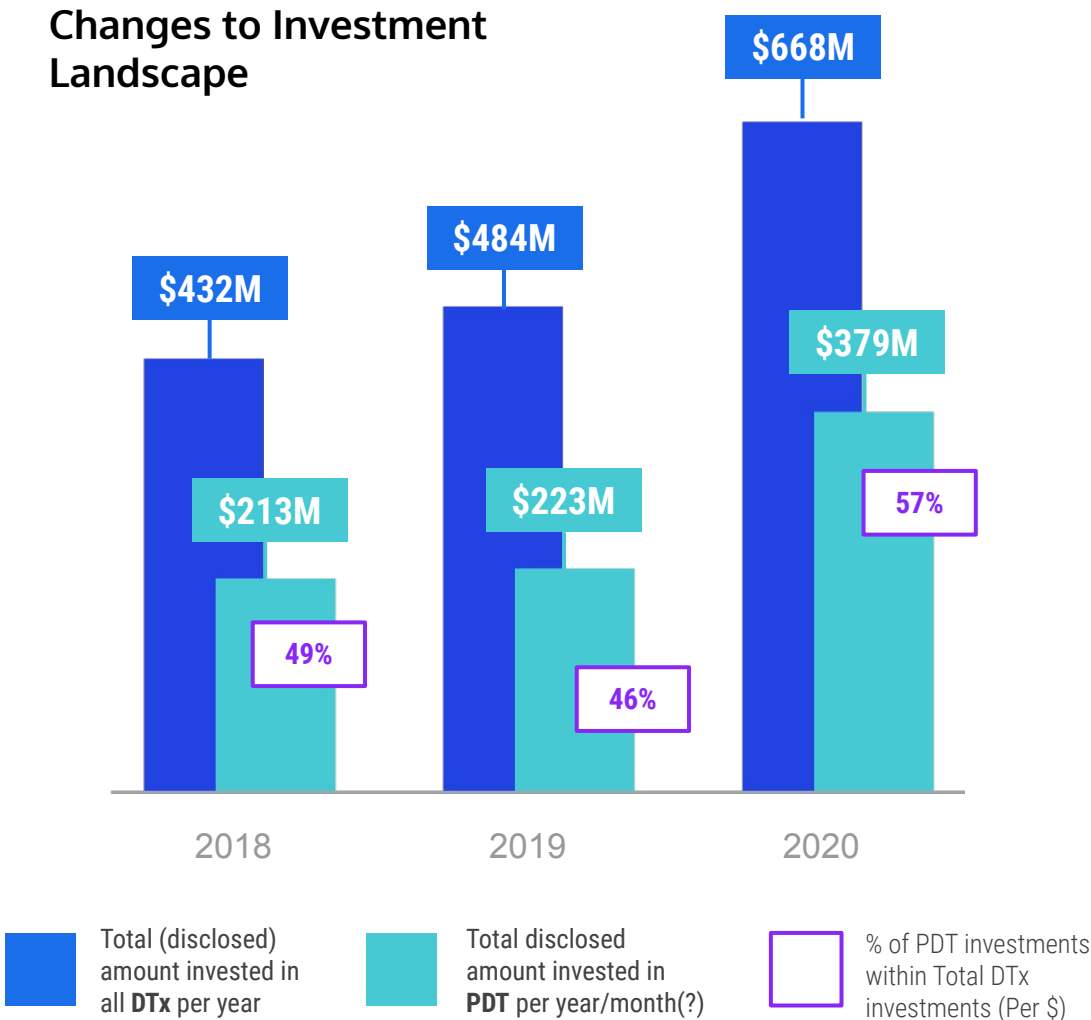
COVID has impacted our digital health investments and partnerships



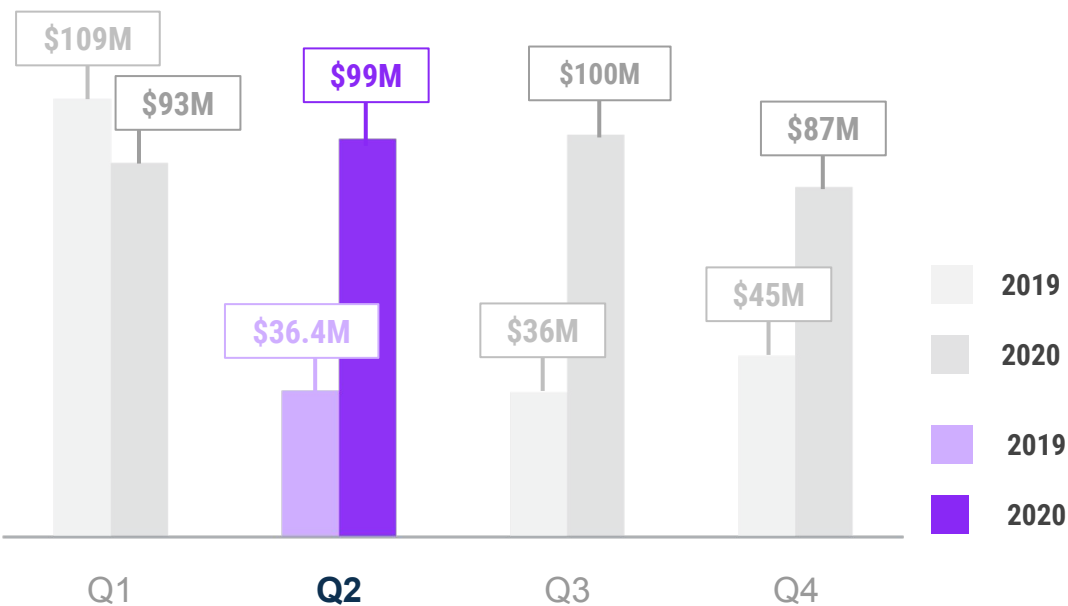
*Data obtained from HealthXL expert community meetings

Changes to Investment Landscape (2018-2020)

Changes to Investment Landscape



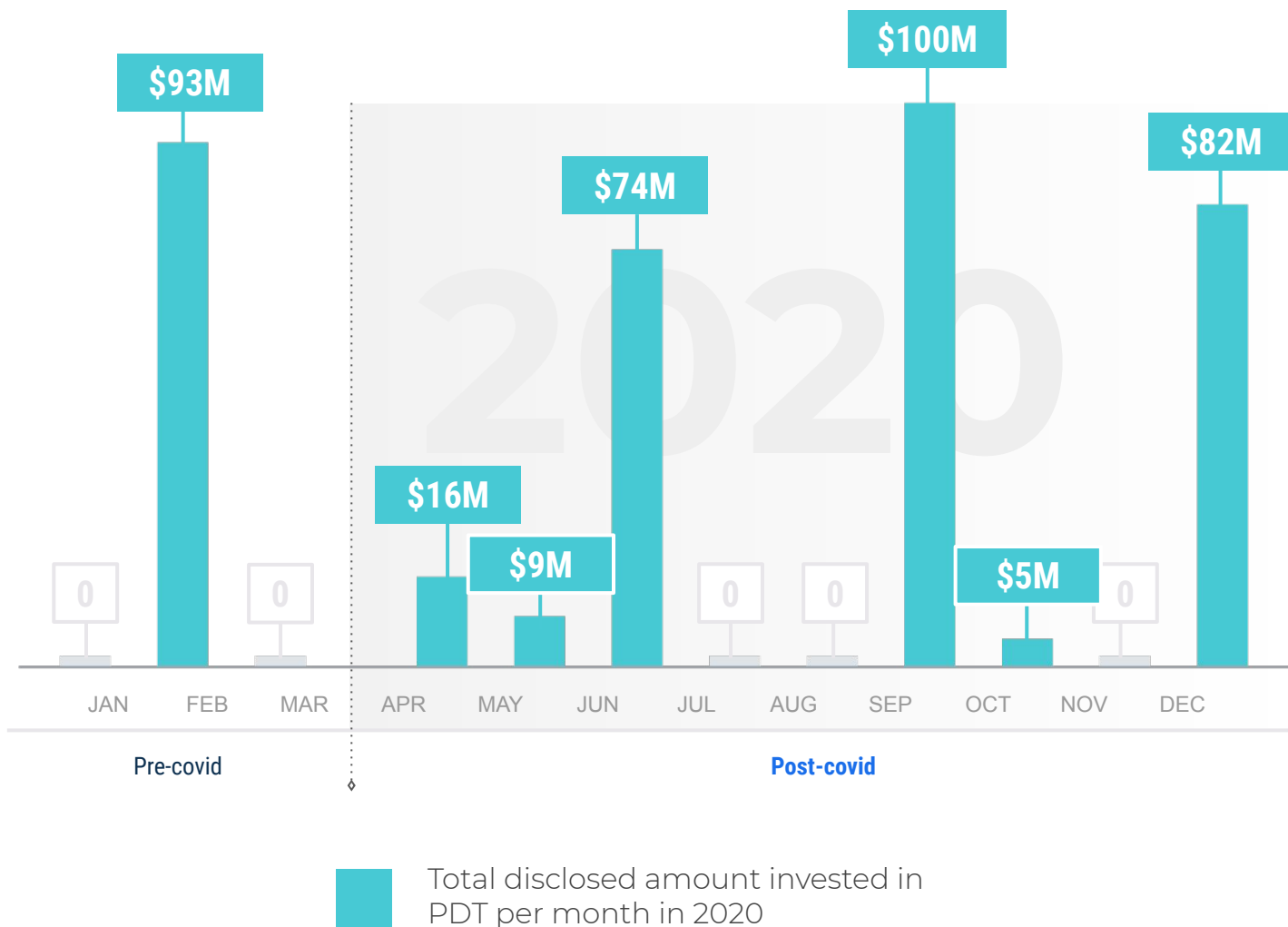
Funding Comparison between 2019 and 2020



While COVID certainly shook up the digital health landscape this year, it is clear this did not halt PDT funding, especially in Q2 where we would have likely seen the biggest impact.

Changes to Investment Landscape

2020 Timeline of PDT - Pre and Post Covid



Total funding pre March 2020
(Jan, Feb, March) = \$93 M

Total funding post March 2020
(April onwards) = \$286M



Top funded PDT company of
2020 - **Biofourmis with \$100M**

Investment Landscape (2018-2020)

TOTAL NUMBER OF INVESTMENTS IN PDT: 34 | TOTAL AMOUNT INVESTED IN PDT: \$779M

TOP INVESTORS (2018-2020)

- 1 EDBI
- 2 Jazz Venture Partners
- 3 Temasek Holdings
- 4 5AM Ventures
- 5 Arboretum Ventures

COMPANIES WITH HIGHEST INVESTMENT



TOP CLINICAL AREAS

- 1 Mental Health
- 2 Cardiology
- 3 Neurology
- 4 Female Health

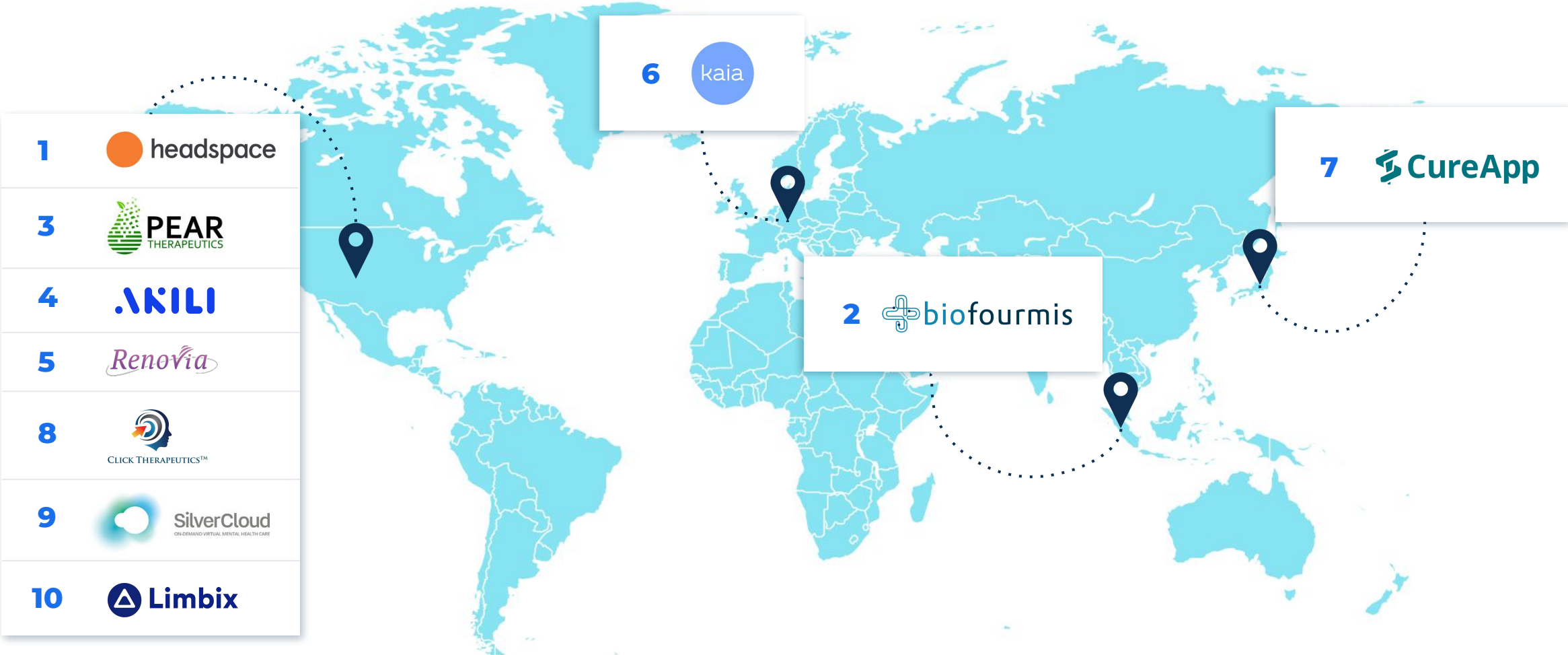
In our 2018 report on digital therapeutics (both PDT and non-PDT), we looked at the same categories, to see what has changed two years on with a narrowed in focus on PDT:

- ★ Akili and Headspace have remained in the top funded companies, with the new additions of Biofourmis, Pear Therapeutics and Renovia.
- ★ The top clinical areas are distinct to those of general DTx back in 2018, with cardiology dropping to no.2, neurology and mental health moving up the ranks, and the new addition of female health.
- ★ The top 5 investors all differ to those previously listed in 2018, showing the increasing interest in this space from a diverse range of investors.

*Our PDT definition includes companies with a PDT product on the market, in development, or in the pipeline, hence the inclusion of Headspace here.

Investment Landscape

HQ of Highest Funded PDT Companies in 2020



*Our PDT definition includes companies with a PDT product on the market, in development, or in the pipeline, hence the inclusion of Headspace here.



SECTION 3

PDT Solutions Landscape

Market Mapping of PDT | Akili: Example of a PDT Pipeline

Market Mapping - Prescription Digital Therapeutics*



*On market and in pipeline

Example | Prescription Digital Therapeutics Pipeline



Source:
[Exits and Outcomes >](#)

Like traditional pharmaceutical companies, PDT companies are beginning to show their pipeline of products.

The full list of PDT pipelines can be accessed [here](#).

Product Name	Therapeutic Area	Stage	Partner(s)	ClinicalTrials.gov Link	FDA Status
AKL-T01 Endeavor	ADHD	Commercial	-	https://clinicaltrials.gov/ct2/show/NCT02674633	De Novo https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200026.pdf
AKL-T02	Autism	Pilot	-	-	Pre-FDA
AKL-T03	Major Depressive Disorder	Pilot	-	https://clinicaltrials.gov/ct2/show/NCT03310281	Pre-FDA
AKL-T04	Major Depressive Disorder	Pilot	-	-	Pre-FDA
AKL-T03	Multiple Sclerosis	Feasibility	-	https://clinicaltrials.gov/ct2/show/NCT03569618	Pre-FDA
AKL-M01 Assessment	Cognitive Impairment	Feasibility	-	-	Pre-FDA
N/A	Traumatic Brain Injury	Discovery	-	-	Pre-FDA
N/A	Lupus	Discovery	-	https://clinicaltrials.gov/ct2/show/NCT03746197	Pre-FDA
N/A	ICU Delirium	Discovery	-	-	Pre-FDA



SECTION 4

Commercialization and Business Models

Current PDT Business Models | Pricing Strategies and
Examples | PDT and Big Pharma Partnerships



Current PDT Business Models

While there are many conceptual business models for PDTs, two paths to market have emerged in the past year among the small cadre of commercialized products:

→ Traditional pharmaceutical pathway

Early-to-market PDT products hewed closely to the same path to market that pharmaceutical therapies use. This model either relies heavily on a pharmaceutical partner's salesforce or requires the PDT company to build their own. This group includes both combination software+drug and software-based monotherapies.

Examples



→ Emerging telemedicine pathway

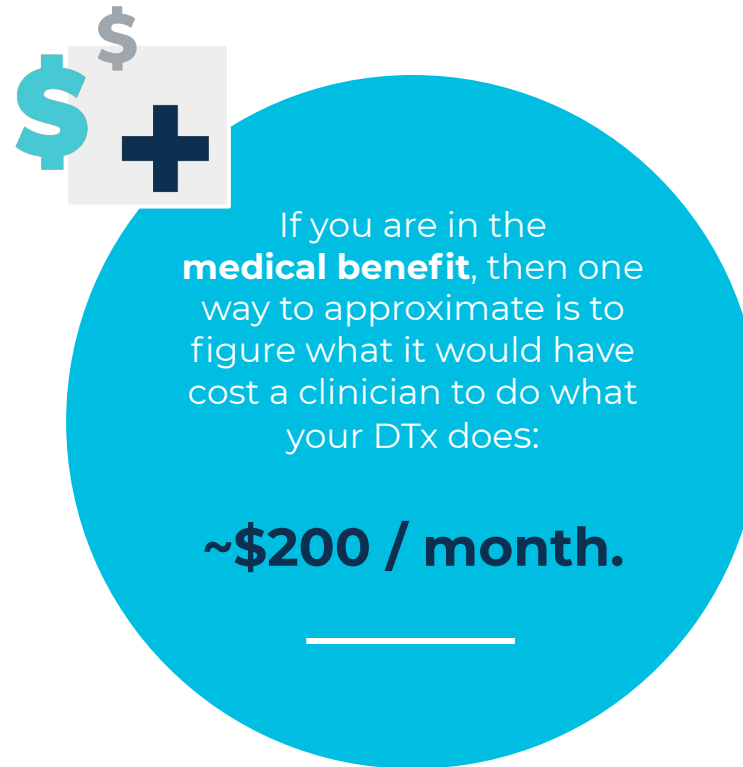
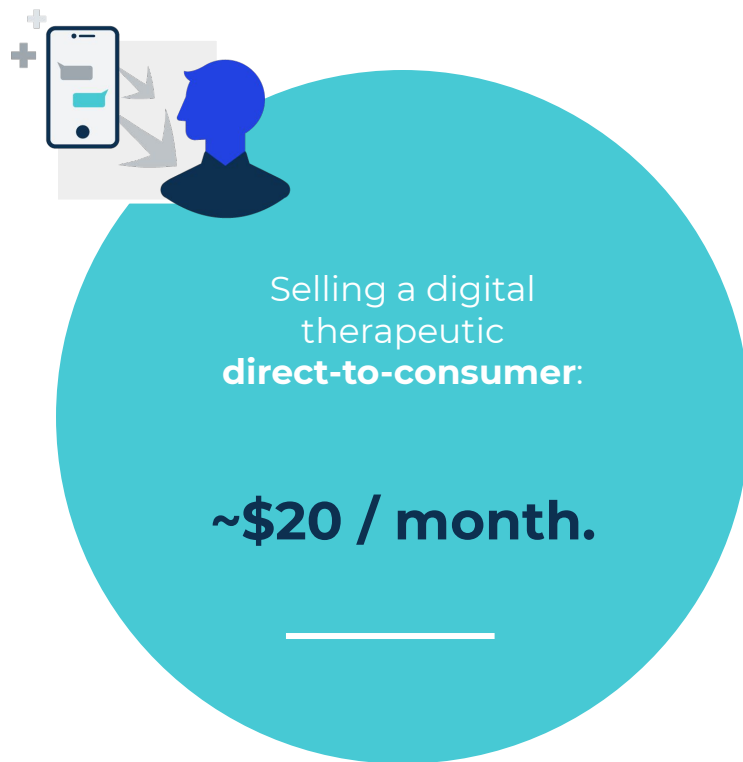
As consumer behavior has changed and telemedicine uptake has increased, recently launched PDT products have gone to market with a combination of direct-to-consumer marketing, telemedicine-accessible prescribers, and online pharmacies. This group typically includes software-based monotherapies.

Examples






Pricing Strategies for DTC vs DTx vs PDT

Advisers to digital therapeutics companies have suggested that **moving from a DTC offering, to a medical benefit, to a pharmacy benefit can 10x the price of a digital therapeutic.** Some ballpark pricing for each of those categories:







Examples of PDT Prices in Market Today

PDT pricing is typically for a three-month or 90-day period. While payer reimbursement has been slow to develop, PDT products are available via Rx and out-of-pocket pay for now. Below are some pricing examples that we have tracked over the past year:

			
EndeavorRx	Somryst	reSET-O	Vorvida
\$450	\$899	\$1,665	\$750
for three months of ADHD therapy (Rx + cashpay)	for three months of insomnia therapy (Rx + cashpay)	for three months of opioid use disorder therapy (Rx wholesale acquisition cost)	for six months of alcohol use disorder therapy (DTC pricing*)

Orexo plans to offer its **PDT offerings via a variety of business models, including via Rx pharmacy benefit channel.*

PDT and Big Pharma – Partnerships

	2018	2019	2020
	<p>Novartis - Focused on Schizophrenia and Multiple Sclerosis.</p> <p>Sandoz International - launch of reSET-O (FDA approved)</p>	<p>Ironwood Pharmaceuticals - focused on gastrointestinal disease, so Pear can expand its app-based platform to conditions outside of the brain and mental health.</p>	<p>-</p>
	<p>-</p>	<p>Novartis - commercialize a DTx for managing heart failure patients</p>	<p>Chugai Pharmaceuticals - focused on developing a DTx for pain monitoring</p>
	<p>-</p>	<p>-</p>	<p>Chiesi Pharmaceuticals - commercialize kaia's COPD pulmonary rehabilitation app in Europe</p>
 <p>CLICK THERAPEUTICS™</p>	<p>-</p>	<p>Otsuka Pharmaceuticals - create a new DTx to treat major depressive disorder (MDD)</p>	<p>Boehringer Ingelheim - development and commercialization of a PDT for Schizophrenia Treatment</p>

**Light grey = inactive partnership; black = active partnership*



SECTION 5

Clinical and Economic Outcomes

Clinical Validation: Rigor of Evidence | Validation: Current Frameworks | Case Study of Economic Validation: Pear Therapeutics

PDT Validation: **Rigor of Evidence**

We analysed 152 studies of 29 PDT companies in order to obtain the following data:

Number

There are **152 different studies** published on the validation of PDT, 27% of which are based on RCTs, considered to be the gold standard of clinical validation.

Prevalence

48% of PDT companies have conducted RCTs for one or more of their products.



The Hierarchy of Evidence Pyramid, ResearchGate

PDT Validation: **Rigor of Evidence**

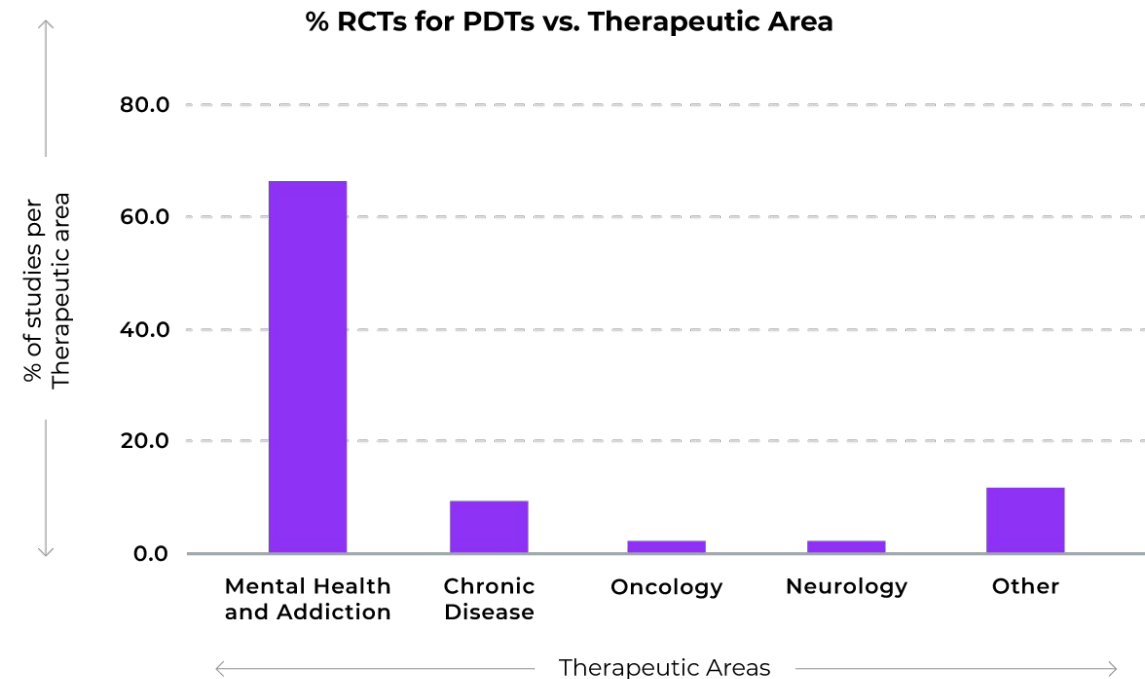
We analysed 152 studies of 29 PDT companies in order to obtain the following data:

Duration/ Length

- ★ The average study length of an RCT for a PDT is **6.3 months**, but these studies range from a duration of 1 week to 13 months.
- ★ On average, it takes **8 years** for a cancer drug to go through clinical trials and receive approval from regulatory agencies for sale to the public. Drugs for other diseases have similar timelines.

Study Size

- ★ The average study size for an RCT for PDT is **592 participants**, but these studies range in size between 39 and 1441 participants.
- ★ For the drug development process, clinical trials generally use patient cohorts of **500 -3,300 over phases I-IV**.



PDT Validation: **Endpoints Measured by PDTs are Traditional**

It is clear from our assessment of the validation landscape of PDTs that **existing clinical endpoints (albeit measured digitally) are widely being used to validate PDTs, rather than digital endpoints.**

Traditional endpoints are necessary to secure reimbursement under the current system. However, there is expectation that companies may generate novel endpoints in the future.

Some of the most common endpoints measured in these studies are listed here

Neurology



Chronic pain

Changes in patient-reported pain levels, opioid use, physical function, behavioral skills development, health outcomes, and satisfaction.

MS

Chalder Fatigue Scale

ADHD

Test of variables of attention

Chronic Disease



COPD

Change in physical activity (activity tracker) exercise capacity, health status, sleep quality, exacerbation rate, and depression and anxiety symptoms

Diabetes

Changes and education in HbA1c levels

Mental Health & Addiction



MDD

Changes in HamD for MDD symptoms, depression and anxiety scores (PHQ-9, GAD-7), self reported changes in social functioning, self-esteem, and stress.

Addiction

Continuous abstinence rate (CAR), changes in mood and physical symptoms, exhaled CO concentration, change in self-reported substance use, abstinence and relapse tendencies, treatment retention rates.

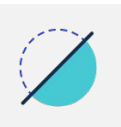
Oncology



Oncology

Improved QoL, depression and anxiety scores, No. of ER visits, survival rates

Clinical Validation: **Current Frameworks**



Distinct differences exist between regions: The allowance of comparisons to existing approved therapeutics in lieu of direct evidence and acceptance of results from overseas studies differs between regions. Otherwise, each framework has its own study design, risk assessment and security requirements.



Most established framework: The U.K.'s NICE Framework is the most established, having clear, defined categorisation and guidelines. Contrastingly, the U.S. Framework is the least complete, with a dedicated outline of the clinical validation requirements for these devices yet to be finalised.



Software iterations are challenging to validate: Software based solutions have the potential to be continuously updated following clearance or, in the case of those that incorporate AI or ML elements, have the ability to learn and adapt over time, making validation frameworks difficult to define.

Traditional medical evidence frameworks are not sufficient to effectively evaluate PDTs for which robust evidence of continued safety and efficacy is critical.

Further, clinical validation parameters must be expanded to allow for testing of the evolving nature of PDTs and their potential harm to patients, not only in a physical sense but also in terms of data protection and ownership.

Clinical Validation: Current Frameworks



Accepted Clinical Study Designs / Evidence Sources

Tier 3a DTx: EITHER High quality observational or quasi-experimental studies OR use of appropriate behaviour change techniques

Tier 3b DTx: High quality intervention studies

Prerequisite for quantitative comparative studies. Can be either of:

- Studies to verify positive care effects:**
 - Observational analytical studies e.g. case / control studies, cohort studies
 - Experimental intervention studies e.g. non-randomised/ randomised controlled intervention study
 - Meta-analyses also including evaluation of own primary data
- Studies on diagnostic quality:**
 - External sensors
 - User input on validated scales
 - Completing validated questionnaires

State that clinical evidence can be derived from:

- Clinical investigation(s) data and subsequent reports.
- A comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device
- If no clinical data available, it may be possible to provide a full clinical justification for why direct clinical evidence is either not required or only partially required. This involves referencing the performance and safety of a predicate or similar marketed device.

Evidence required may vary according to device characteristics but in general must be derived from one of:

- Well-controlled investigations, partially controlled studies, studies and objective trials without matched controls.
- Well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.

Must explain how OUS data are applicable to US population and US medical practice

Required Outcomes

Tier 3a:

- Behavioural or condition-related user outcomes such as reduction in smoking or improvement in condition management
- Evidence of positive behaviour change
- User satisfaction.

Tier 3b:

- Diagnostic accuracy
- Patient-reported outcomes
- Other clinical measures of disease severity or disability
- Healthy behaviours
- Physiological measures
- User satisfaction and engagement.

Must prove one or more positive healthcare effects in either of:

- The area of medical benefit, particularly regarding:**
 - The improvement of the state of health
 - The reduction of the duration of a disease
 - The prolongation of survival or an improvement in the quality of life
- The area of patient-relevant improvement of structure and processes such as:**
 - Detection, monitoring, treatment or alleviation of disease
 - Detection, treatment, alleviation or compensation of injury or disability
 - Supporting health behaviour of patients or integrating processes between patients and healthcare providers

Clinical data may be generated for either the device or the predicate/similar marketed device. It includes:

- Documentation in relation to the design, approval, conduct and results of each investigation carried out by the manufacturer of the device in relation to the use of the device in or on a human body
- A record of qualitative or quantitative information obtained through observation, measurement, tests or any other means used to assess the operation of the device
- A written report by an expert in the relevant field, being a report that contains a critical evaluation of all the clinical investigation data held in relation to the device.

De Novo pathway:

- Clinical data (if applicable) to support reasonable assurance of safety and effectiveness.

510(k) premarket submission pathway:

- Demonstration of substantial equivalence to another legally U.S. marketed device.
- Device can be progressed to the **breakthrough pathway** having cleared 510(k) premarket submission. This requires that the device:
 - Must provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating disease or conditions.
 - Be proven to be unique or offer distinct advantage over existing devices.

Clinical Validation: Current Frameworks



U.K.

NICE Framework



Germany

DiGA Framework



Australia

TGA Framework



U.S.

FDA Framework

Evidence from Pre-Existing Solutions Acceptance

No, studies specifically designed for and carried out with the device being submitted must be undertaken.

No, in order to achieve a final listing in the DiGA directory, it is necessary to prove at least one positive healthcare effect through own data evaluation. Sole references to other primary literature and studies, even from other similar DiGA, are not permitted.

Yes, direct clinical evidence on the actual device is preferred. However, indirect clinical evidence on a predicate or similar marketed device may be used after substantial equivalence has been demonstrated through a comparison of clinical, technical and biological characteristics.

Yes, through the 510(k) premarket submission pathway that allows for a device to be compared to a substantially equivalent, legally marketed device.

Risk categorisation

Divided into three evidence tiers based on the potential risk to users. The third tier is the highest risk class. It encompasses PDTs and includes those that allow for diagnosis, active monitoring, treatment, self-management or preventative behavioural changes in relation to the patients health.

PDTs are allocated to risk classes I or IIa of the German Medical Devices Act (MPG) and are described as those that support the recognition, monitoring, treatment or alleviation of diseases or the recognition, treatment, alleviation or compensation of injuries or disabilities.

Four-tiered classification system based on risk to the human body, with ascending risk assigned to Classes I (including sterile and measuring), IIa, IIb, and III.

Divided into three evidence classes based on the level of control necessary to provide reasonable assurance of safety and effectiveness, with Class III being the highest risk.

Cyber / Data Security Requirements

State that security must be integral to the design of the offering and must prove that it meets industry best practice standards. This includes:

- Meeting the National Data Guardian's 10 data security standards.
- Ensuring that any application for an offering accessing NHS patient data and systems has completed the associated Data Security and Protection Toolkit.
- If the product is an application, ensuring that the it meets the OWASP Application Security Verification Standard.

Must complete a comprehensive checklist on data protection and IT security. This checklist contains 40 statements which take into account the technical implementation of the PDT and also the organisation of the manufacturer and its processes.

Also, if the manufacturer is a private sector company, then must comply with the German Federal Data Protection Act (BDSG).

Outline a list of 13 "Essential Principles" (EPs) that must be met in order to prove safety and performance. Suggest a set of appropriate relevant standards that can be used to demonstrate the compliance with these EPs. Other risk management strategies can be adopted alongside these standards if they are acknowledged to be state of the art.

Outlines two tiers of devices according to perceived cybersecurity risk. Tier 1 is the higher risk category defining devices that connect to wider services, a breach of which would harm multiple patients. Tier 2 defines all other devices..

However, premarket security audits for medical devices are currently not mandated by the FDA. The onus is on manufacturers to determine the level of risk and include a set of design controls to minimize it.

Overseas Studies Acceptance

No, must demonstrate that the device has a plausible mode of action and reflects current standard/best practice in the UK health and social care system.

No, studies must be conducted in Germany in order to provide sufficient evidence and an accurate representation of integration with the German Healthcare System.

Yes, devices that have been approved with recognised overseas regulators can be fast-tracked through TGA registration. Recognised overseas regulators include the EU, FDA, Health Canada, MDSAP Auditing Organisation and MHLW Japan.

Yes, the FDA requires that data from clinical investigations conducted outside the US be from investigations conducted in accordance with good clinical practice (GCP), which include review and approval by an independent ethics committee (IEC) and informed consent from subjects.

Economic Validation: Case Study

COMPANY



In Nov 2020, **Pear Therapeutics** [published a paper](#) claiming a reduction in healthcare costs of \$2,150 per patient over six months for patient's who treated their OUD with reSET-O. Soon after, Pear published their [economic modelling of reSET-O](#) in the *Journal of Medical Economics*. The retrospective study concludes that by increasing adherence to buprenorphine, reSET-o should likely lower HCRU costs in claims data at small cost to third party payers (approximately \$0.003 per member per month).

Almost concurrently, ICER (Institute for Clinical and Economic Review) published a report on the [cost-effectiveness of Pear's reSET-O](#), which included their assessment of the aforementioned studies, pre-publication.

- The report called out the lack of critical evidence in support of reSET-O's benefit in the long-term (beyond 6 months) and also highlighted Pear's inaccurate augmentation of the average healthcare resource utilization of the OUD population.
- Notably, ICER criticized the clinical validation of reSET-O, stating that Pear's evidence focused on the earlier, computer-based, clinical version of reSET-O and could not be translated to a mobile version of the DTx that could be used anywhere.
- ICER also published a companion document alongside their report that includes their responses to the public and is scathing of reSET-O and the evidence supporting it.

Only 10% of companies provide validation studies demonstrating the cost-effectiveness of their PDTs, highlighting the lack of maturity in this space.

ICERs dismissal of the economic studies for Pear's reSET-O illustrates the need for the development of standardised models for the economic validation of PDTs.

Those who watch PDTs closely wonder if Pear's reSET-O can come back from ICER's assessment.



Economic validation of a PDT is important for adoption by all stakeholders. Despite this, Pear Therapeutics is one of only three PDT companies that have attempted to do this, and their findings have been irreparably dismissed by the ICER. This example highlights the need for the development of standardised models for the economic validation of PDTs in order to progress the field of PDT.

SECTION 6



Regulatory Environment

The FDA | The EU











Regulation - FDA

DTx are most commonly regulated under the Software as a Medical Device (SaMD) framework, developed by the International Medical Device Regulators Forum (IMDRF).

DTx approvals are granted by the FDA Center for Devices and Radiological Health

In response to Covid-19 the FDA also allowed certain digital health products focused on psychiatric conditions to go-to-market temporarily.



510(k)	De Novo	breakthrough
Granted to devices if they can prove that the device is substantially equivalent to an existing legally marketed device.	Granted to novel devices of low to moderate risk that have never been marketed in the US before.	<p>Applies to medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions</p> <p>Available to products which are subject to premarket approval application (PMA), premarket notification (510(k)), or De Novo classification request.</p> <p>It may in some cases make reimbursement easier (see section on reimbursement below).</p>
<div>  </div>	<div>  </div>	<div>  </div>

FDA Digital Health Center of Excellence (DHCoE) - Focus and Activities



2020 also marked the launch of the FDA Digital Health Center of Excellence (DHCoE). The 3 principal aims of the DHCoE are to:

1. **Connect** and build partnerships to accelerate digital health advancements.
2. **Share** knowledge to increase awareness and understanding, drive synergy, and advance best practices.
3. **Innovate** regulatory approaches to provide efficient and least burdensome oversight while meeting the FDA standards for safe and effective products



Phase	Focus	Activities
Phase 1 (Fall 2020)	Raise Awareness and Engage Stakeholders	<ul style="list-style-type: none"> • Conduct listening sessions with stakeholders • Develop resources for FDA staff • Begin operationalizing the DHCoE outcome measurement • Amplify FDA's digital health work
Phase 2 (Winter 2020 - Winter 2021)	Build Partnerships	<ul style="list-style-type: none"> • Build strategic partnerships for policy, regulatory science, and fellowships • Develop resources for external stakeholders • Create a digital health community of practice • Assemble FDA and CDRH advisory groups
(Winter 2021 and onward)	Build & Sustain Capacity	<ul style="list-style-type: none"> • Continue to build strategic partnerships • Update and implement regulatory framework for digital health • Continue harmonization with other regulators

EU - MDD for SaMD (Software as a Medical Device)



Software intended to monitor physiological processes is classified as class IIa

The European Commission recently published guidance on the qualification and classification of medical device software under the new EU Medical Devices Regulation (MDR)

Medical Devices Regulation (MDR)

- Was adopted in May 2017 but will become fully in force in all EU Member States from May 2021
- Software can be considered standalone or embedded
- Medical software that falls under the scope of the MDR is considered a medical device and needs CE marking
- Software must have a medical purpose on its own to be qualified as Medical Device Software (MDSW)
- Medical devices to be re-classified against new risk criteria
- Nearly all software medical devices to be classed as class IIa, or even class III (where previously the majority were class I)
- A European database on medical devices (EUDAMED) will be introduced in order to strengthen the market surveillance and ease traceability

The MDR bring more clarity to address the differences between software incorporated within devices and stand-alone software



Rule 11 - *“Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa”* (with exceptions)



SECTION 7

Reimbursement and Cost Coverage

Highlights of the Previous Two Years | Reimbursement in the US
| Reimbursement Outside of the US | Prescription Pathways



Regulation & Reimbursement - 2019 highlights

REIMBURSEMENT

JANUARY

CMS considered and rejected a request to create a new Level II HCPCS code for 'Computer Based Training for Cognitive Behavioral Therapy' (CBT4CBT).

MAY

Express Scripts announces it will launch a digital health formulary for self-insured employers in early 2020

JUNE

CVS Caremark launches a digital health formulary for self-insured employer clients

SEPTEMBER

First US Senate bill that mentions prescription digital therapeutics and calls for more info on their use in behavioral health

DECEMBER

US House bill proposes Medicare reimbursement for all Breakthrough devices -----
Express Scripts reveals which programs made it into its digital health formulary, which launches weeks later

2019

REGULATION

JANUARY

FDA publishes more documents about its Pre-Cert Pilot and says it plans to conduct a test case this year

JANUARY

Cognoa Receives FDA Breakthrough Designations for Autism Diagnostic and Digital Therapeutic Devices

APRIL

FDA announces it may develop a new regulatory framework that address the use of artificial intelligence and machine learning in regulated digital health products

MAY

NightWare, a prescription digital therapeutic for nightmares that accompany PTSD, receives breakthrough status from the FDA

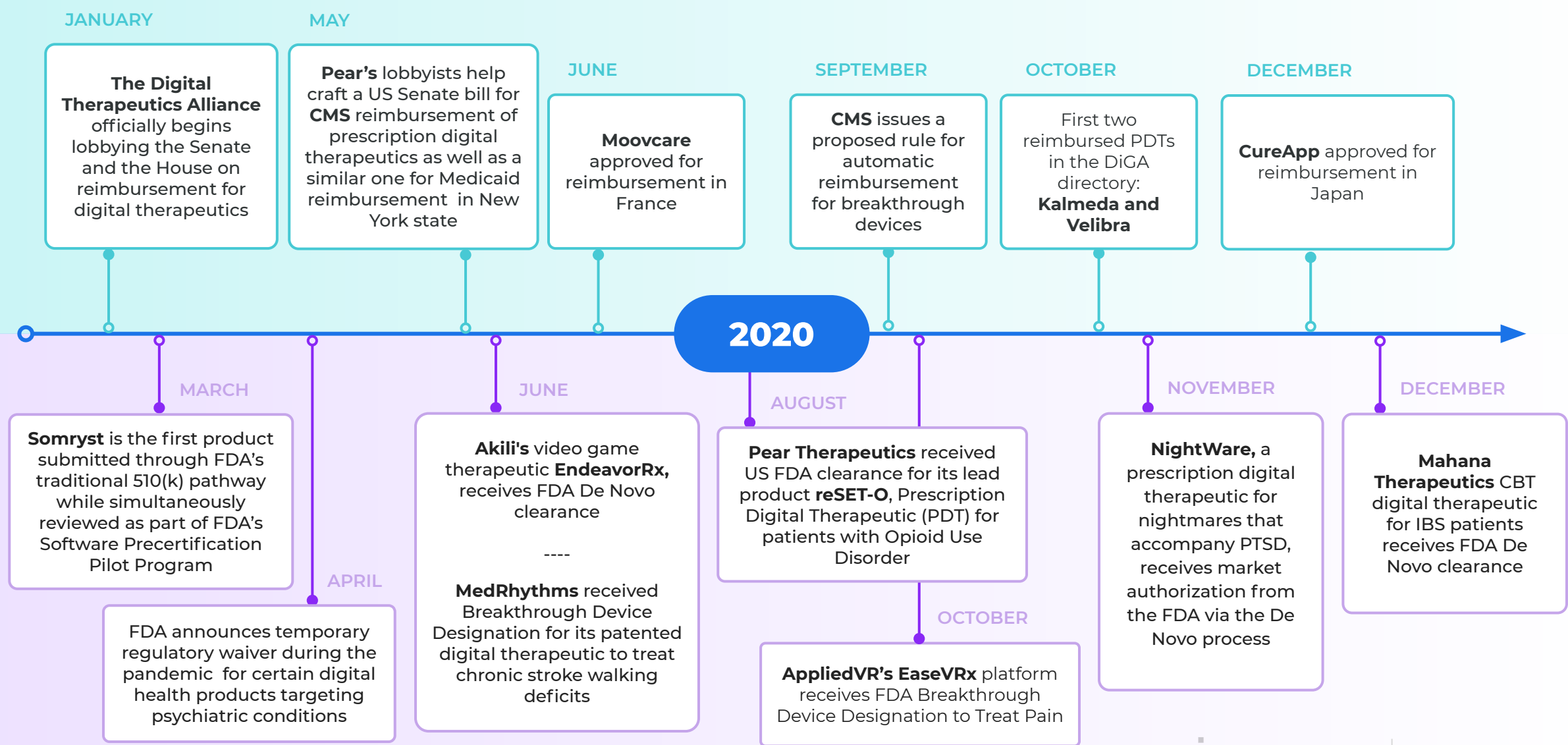
NOVEMBER

Renovia received FDA 510(k) clearance for its next-generation Leva pelvic digital therapeutic for urinary incontinence (UI) in women

Regulation & Reimbursement - 2020 highlights

REIMBURSEMENT

REGULATION



Reimbursement of PDTs (US)

As we enter 2021, **reimbursement for PDTs remains thin in the US**, however, efforts to secure reimbursement only began in earnest in 2020.



March 2020 Senate bill called for Medicare reimbursement of PDT: the Senate Finance Committee reviewed a bill entitled, "S.3532 Prescription Digital Therapeutics to Support Recovery Act". The bill, which never left the committee, called for the establishment of a fee schedule to reimburse for "prescription digital therapeutics" within 180 days of their clearance or approval by the FDA. Pear Therapeutics' lobbyist helped craft the bill as well as a similar one that went before the New York state legislature to consider a similar fee schedule via Medicaid.



Breakthrough Designation pathway to reimbursement: CMS proposed a streamlined path to reimbursement for FDA-cleared medical devices that received a "Breakthrough Designation" status from the FDA. However, CMS' final rule excludes most PDTs from the proposed reimbursement because the devices would need to fit into a pre-existing Medicare benefit category. Some PDT companies asked CMS to consider striking that caveat from the final rule, but they did not.



No major commercial payers have covered PDT: While a few PDT products have been in the market for more than a year, no major commercial payers in the US have announced plans to cover them.



Patchwork of small PBMs and payers: Instead, early PDT reimbursement has largely been from small PBMs and other small payers.



CMS/AMA CPT codes: At the American Medical Association's CPT Editorial Meeting in October 2020, a set of five CPT codes were adopted for "Remote Therapeutic Monitoring Treatment Management Services", which may signal CMS fee-for-service reimbursement in future years for PDTs.

Employer Coverage Continues: Employers are increasingly seeing the benefits of prescription digital therapeutics for their employees and one route to reimbursement that has shown success is coverage for PDTs by employer plans.

Reimbursement of PDT: European & Global (Non-US) Markets

In the **European and Asian markets**, examples of more defined pathways to PDT reimbursement are beginning to emerge. **Germany has paved the way** with the DiGA act being passed into law in 2019. In the **UK**, the NHS approved reimbursement for prescription of Oviva while in **France**, Moovcare has been approved as the first PDT for reimbursement.

The regulatory approval of CureApp for reimbursement by the **Japanese** Public Healthcare System marks the **first PDT reimbursement milestone in Asia**.

GERMANY



kaia health



velibra®

FRANCE



UK



OVIVA

JAPAN



CureApp



SECTION 8

Enablement and Adoption

Digital Health Formularies, Registries and Health App Libraries
| Prescription Capabilities | EU Landscape

Differences in Prescription Pathways

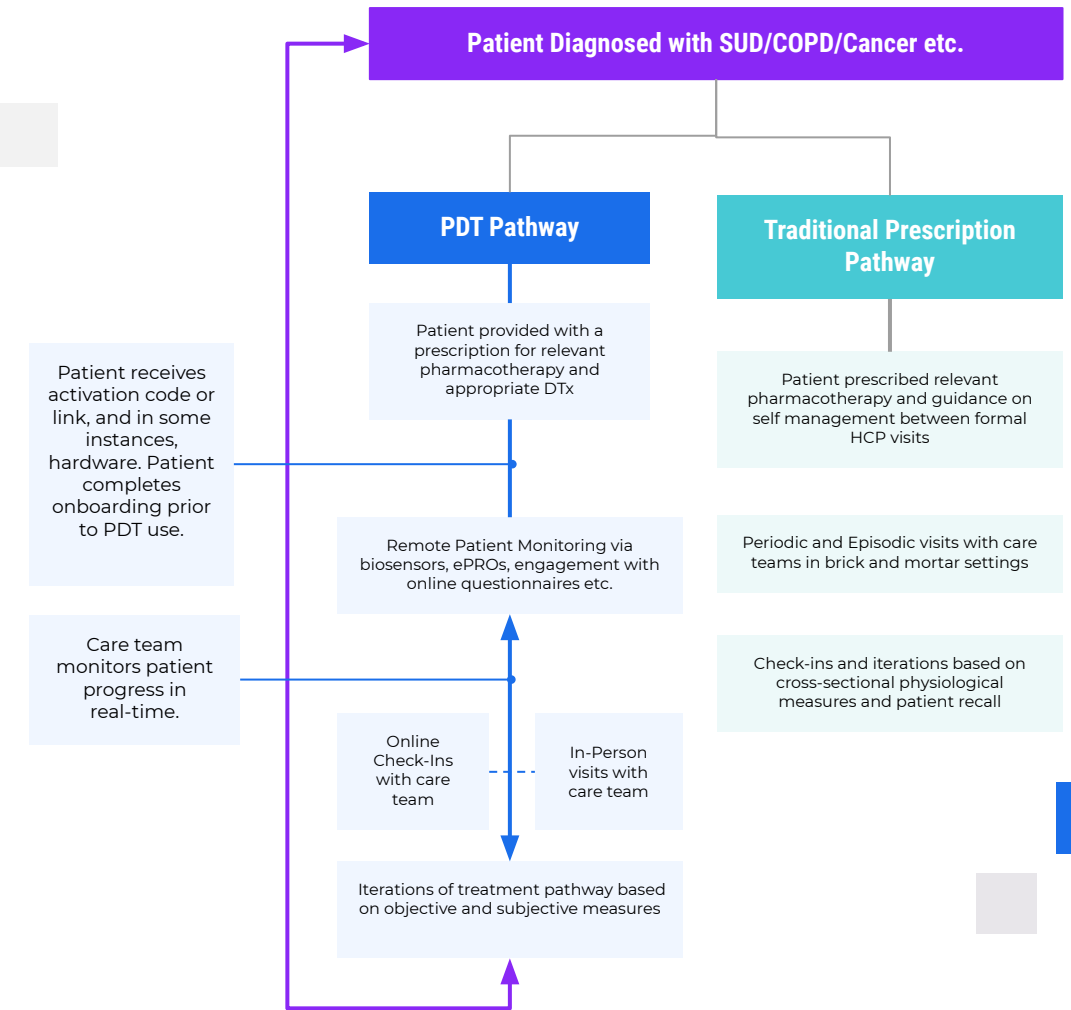
The development and commercialization pathway of PDTs are in many ways akin to that of a pharmacologic agent – as such they are subject to review, clearance and approval by regulators.

The prescription pathway for PDTs differs to that of drugs. Some crucial differences to the traditional prescription pathway are:

- ★ The PDT manufacturer often plays a role in the onboarding process.¹
- ★ The care team has access to a portal to monitor and track patient progress in real-time.¹
- ★ The treatment pathway is iterated based on continuously collected objective and subjective measures.

As PDTs are edging closer to becoming incorporated into therapeutic arsenals, the seamless integration into conventional pathways still needs to be ironed out. The rise of digital health formularies and prescription platforms is certainly a move in the right direction.

1. [Patel & Butte \(2020\)](#)



Engagement and outcome measures leveraged to optimize overall DTx intervention for future users

Enablement and Adoption of PDTs – What Has Changed?

Digital Health Formularies, Registries and Health App Libraries

- Standalone digital health formularies are beginning to emerge, providing a curated list of vetted digital health solutions to health plans.
- In 2019, [two leading PBMs](#) in the US, Express Scripts and CVS Caremark, announced the creation of digital formularies.
- In 2020, CVS Caremark also expanded access to 5 digital health platforms including Hello Heart, while Kaiser Permanente added a new feature allowing physicians to prescribe mental health apps such as SilverCloud using EHRs.
- Despite these promising initiatives, [research](#) has shown that payers in the US do not anticipate that a formulary approach will be widely adopted for another 3-5 years.
- In Europe, examples of DTx (and other applications) listings are the NHS App Library in the UK and the digital health application (DiGA) directory in Germany. While both initiatives were designed to [facilitate patient access to DTx](#), the DiGA directory not only facilitates the prescription of digital health applications but, unlike in the UK, also secures their reimbursement.
- In the absence of universally accepted evaluation frameworks, health app evaluation organizations such as [ORCHA](#) in the UK and [TherAppX](#) in Canada conduct valuable, independent and objective assessments to guide physicians in prescribing health apps. This information in turn can guide formulary compositions. ORCHA has prescription capabilities, while TherAppX is currently building this capability in addition to its curated lists of clinician-evaluated health apps.



Physicians will decide the destiny of PDT. They will need to see evidence for the efficacy, cost-effectiveness and safety of PDTs. While much has to do with building trust and educating physicians on digital treatment modalities, ensuring that doctors have the capability to prescribe DTx in the first place seems like an important roadblock to tackle first.

PBM Digital Health Formularies: *Not for PDTs Yet*

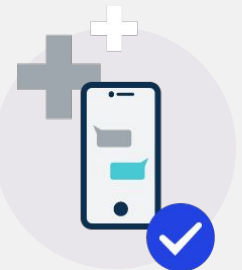
Express Scripts Digital Health Formulary

1. **Livongo** (Diabetes)
2. **Propeller Health**
3. **Omada Health** (Diabetes & joint pain management)
4. **LifeScan** (powered by Welldoc)
5. **Learn to Live**
- ★ 6. **SilverCloud Health***
7. **Wildflower** (Women's Health)
8. **Quit Genius** (Smoking cessation)
9. **Prevail Health** (Caregiver support)
10. **Back with Care** (COVID19 back to work platform)
11. **Hinge Health** (muscle & joint pain management)
12. **RecoveryOne** (muscle & joint pain management)

CVS Caremark Point Solutions Management Service

1. **Sleepio** (insomnia)
2. **Daylight** (anxiety)
3. **Hinge Health** (Musculoskeletal conditions coaching)
4. **Hello Heart** (CVD management)
5. **Torchlight** (Support for families of patients)
6. **Whil** (Mindfulness/meditation)
7. **Vida** (Personalised health coaching and anxiety)
8. **Naturally Slim** (Weight management)
9. **Weight Watchers** (Weight management)
10. **Kurbo** (Teen/youth lifestyle management)

★ Prescription DTx



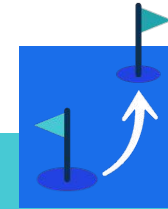
The two largest US PBMs launched digital formularies at the end of 2019. This important milestone paves the way for employers and health plans to reimburse DTx using the same infrastructure currently used.

*Note - Silvercloud does not require a prescription when sold through Express Scripts

Enablement and Adoption of PDTs – What Has Changed?

Prescription Capabilities - Distribution, not Reimbursement

- ★ A clear challenge to the prescription model, however, is the fact that many health systems are unable to prescribe DTx, notably because many [lack the supporting software](#) to do so.
- ★ Prescription platforms such as Xealth, Appscript and Rx Universe have been developed to fill this gap.
- ★ Despite the rise in enabling software, designed to simplify the DTx onboarding and patient engagement process, it is currently unclear to what extent physicians are prescribing DTx to their patients. Overall, DTx prescription appears to be low and at present occurs in isolated - mostly academic - centres.
- ★ Regional differences exist in terms of **capability to prescribe**, with physicians in the US much less likely to be able to electronically prescribe a DTx compared to their English counterparts where [58% of general practitioners are able to find, recommend or prescribe a digital health app](#) through the EMIS App Library by AppScript. And yet, it is unclear to what extent General Practitioners are aware of this feature.
- ★ In Germany, despite widespread prescription capability, research has found that since the first DiGAs have been listed, only [2% of physicians](#) have prescribed a DTx so far. It is still early days and current prescription rates are unlikely to be indicative of future trends.
- ★ DTx adoption does not solely rely on provider distribution. Many DTx providers, including PDTs, are contracting with insurance companies (and PBMs) directly. In 2020, Pear Therapeutics announced that reSET & reSET-O would be offered and administered as standard pharmacy benefits by [Remedy One](#) and [Serve You Rx](#).
- ★ Pear Therapeutics and Voluntis are shaking up the PDT distribution chain altogether. Pear Therapeutics has launched a fully virtual end-to-end prescription and dispensation program while Voluntis has partnered with Salesforce to launch a [full-service platform supporting DTx prescription and reimbursement](#).



While things are certainly moving along, ultimately, not very much has changed since we last wrote about DTx adoption in 2018.

Enablement and Adoption - EU Landscape



GERMANY

November 2019 - the federal parliament in Germany passed the **Digital Care Act (DVG)**:

- DVG allows doctors to prescribe apps, which can be reimbursed by German statutory health insurance.
- Physicians and psychotherapists in Germany will have access to a library of these apps, which they can prescribe to a patient
- Prescriptions can be renewed after 3 months.
- **Fast track market entry pathway** from Q2 2020 made available for Class 1 or 2a CE-marked low risk devices
- So far, 10 DiGAs approved for reimbursement with about 5,000 prescriptions.
- Max reimbursement prices are still being finalized and the process is in arbitration.
- Prevention-based digital interventions are excluded from DiGA process but are reimbursed already - at 200 Euro/Year/Insuree.

July 2020 - the German parliament passed a draft bill (German language) for patient data protection and for more digitalisation in the German healthcare system

- From 2021, statutory health insurance providers will be obliged to offer their insured persons electronic patient files (ePA)
- From 2023 onwards, patients will have the option of voluntarily making the data in their ePAs available to researchers as part of a "data donation"

While initial guidance was that evidence required for approval would be low, the reality is that BfArM appear to in practice expect more data as part of the application. This could be some of the reasons for the 18 withdrawals from the BfArM assessment so far.



BELGIUM

- **In 2018** - The Federal Belgian Government developed the mHealthBelgium platform to support integration of mHealth applications in Belgian healthcare
- **In 2018**, public authorities introduced the mHealth pyramid
- Belgian federal government rolled out a new **eHealth action plan 2019-2021**

- In Jan **2021**, the three tiered **mHealthBelgium validation pyramid** was finalized, meaning that medical applications (mobile health applications or mHealth applications) can now be reimbursed by the National Institute for Sickness and Invalidity Insurance (INAMI). MoveUP Coach app is the first solution to secure reimbursement under this pathway.

So, What Does This All Mean?

Where are we now?

- Early PDTs have had to cobble together creative go-to-market strategies that result in customized contracts on a deal-by-deal basis.
- New consumer-focused telemedicine approaches to PDT distribution have recently entered the market.
- PBMs have created “formularies” for their employer and payer clients to manage the growing number of digital health programs, but we have a long way to go.
- Despite the impact of COVID-19, investments in PDTs have not been halted, and in fact appear to be increasing year on year.
- Clinical validation frameworks for PDTs are still being developed globally with some regions, such as the UK, leading the charge.
- In the US, lobbying for CMS reimbursement of prescription digital health has just begun, with early wins like MCIT.
- Elsewhere, strides in reimbursement strategy are being achieved with Japan, France and the UK all having approved their first PDTs for reimbursement.

Where are we going?

- While PDTs have a clear application within chronic diseases and neurology, we are seeing applications in emerging clinical areas like ophthalmology and female health.
- An increasing number of PDTs with novel, neurological mechanisms of action will come to market alongside the current crop of mostly CBT-based PDTs.
- Key challenges remain to be tackled in clinical validation, most notably the establishment of concrete methods allowing for the continuous assessment of the safety and efficacy of PDTs.
- PBMs' early digital health formularies will evolve to include PDTs covered under the pharmacy benefit.
- CMS's new MCIT reimbursement program could pave the way for wider reimbursement of PDTs.
- Germany is paving the way in Europe for reimbursement with the DiGA act being passed into law.
- Congress will decide the fate of the FDA's Pre-Cert Program.

Authors



Sarah Cronin, PhD
Senior Digital Health
Consultant



Tessy Huss
Head of Market
Research



Sophie Madden
Digital Health Strategy
and Insights Manager



Kate O'Reilly, PhD
Senior Digital Health
Consultant



Alette Ramos Brinth, PhD
Senior Digital Health
Consultant



Laura Ardill, PhD
Digital Health
Consultant



Sabrina Mendes
Business Intelligence
Analyst



**Chandana Fitzgerald,
MD MPH**
Chief Medical Officer



Brian Dolan
Founder and lead writer
at *Exits and Outcomes*

Reviewers



Francesca Wuttke
Chief Digital Officer
Almirall



Robert Garber
Partner
7Wire Ventures



Lisa Suennen
Group Leader of Digital and Technology
Manatt Ventures



Kal Patel MD
CEO & Founder
Bright Insight

A special thanks also to **Shrawan Patel, MD** and **Michaël Cardinal, Pharm D**
for their insights on adoption and enablement of DTx.



Prescription Digital Therapeutics (PDT)

THE FUTURE OF DIGITAL THERAPEUTICS

FEB 2021