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Digital Therapeutics: pharma's threat or opportunity

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Welcome

It is 2025 and digitally delivered therapies are now part of our regular healthcare experience. The smartphone, already our first port of call on health matters, has been elevated to the role of personal health mentor and condition management guide.

Offering us therapies and advice, both consciously and subconsciously, our device acts as our general healthcare concierge too, knowing when we've taken our medicine, showing us ways to optimize our desired lifestyle and determining medication dosages, and inviting us to visit specialists when they detect anomalous data. We are even seeing the emergence of the digital twin, a virtual version of yourself which can 'trial' treatments on your behalf before being adopted in your real body.

And clinicians, in a different role from the past, now rely on the data from your device too. They sanction or suggest technology-enabled patient services offering treatments that in many cases do not involve a chemical or biological intervention, but a digital one.

These therapies now routinely generate data in real time for deep-learning AI to interpret, enabling care providers to automate routine aspects of care, for example through alerts and 'bot' consultations, which give patients much of the information they need to stay compliant with their care plans.

Digital technologies act as a force multiplier for clinicians at all levels from consultants to nurses, who are now able to focus their time on the patients in most need and with the most complex ailments. Where necessary, the AI alerts a clinician to the need to intervene and assists them in making rapid decisions on the best and most appropriate course of action.

Meanwhile, payers rely on the rich real-world dataset that is now generated from these technologies and are used as an integral part of outcome based contracting without adding excessive burden to health systems. Digital therapeutics (DTx) are now a core part of the payer's arsenal of care delivery tools, having in many cases proven their worth in driving better care alongside analog medicines or, where they replace chemical alternatives, they do so often at a far lower cost. DTx revenues have ballooned as payers and HTAs see the value of recommending and prescribing them outright.

And in general, we now have a more proactive, voluntary health system where citizens actively prevent rather than simply manage their exposure to chronic diseases, moving the dial on population health at a global level whilst driving down costs. Healthcare systems under ever-increasing pressure from ageing populations can now do more with less. Patients are enjoying more quality years of wellness than they would have expected a decade before.

Part 1: DTx: where are we now?

A digital therapeutic is an evidence-based software product that delivers a clinical intervention and which is typically subject to regulatory oversight (depending on the claim being made for its therapeutic action). It can be standalone or in combination with drug therapies.

The Digital Therapeutics Alliance describes the category as "evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a broad spectrum of physical, mental, and behavioral conditions." And "they form an independent category of evidence-based products within the broader digital health landscape, and are distinct from pure-play adherence, diagnostic, and telehealth products."

Common features include:

- They usually involve some form of behavioural or psychotherapy
- They can integrate with electronic prescribing, dispensing, and medical record platforms directly
- Can be paired with devices, sensors, or other wearables
- They can demonstrate measurable outcomes
- Clinicians can often prescribe them; payers provide coverage for them
- The data they generate creates a feedback loop for ongoing improvements in care

In these respects, DTx differ from 'consumer grade' health related software applications. They deliver defined therapeutic interventions rather than general wellness tracking services. They also go beyond the benefits offered by related digital healthcare services such as adherence, diagnostics tools or telemedicine platforms.

Standalone, or Drugs+?

Digital therapeutics can be used independently or with medications, devices, other therapies - or all of the above.

In some cases, they may entirely replace pharmacological interventions, for example DTx designed for mental health or pain management, or offer treatments for which no drug exists (for example, tinnitus). This is not a huge leap of faith, since we know that services like counselling or Cognitive Behavior Therapies (CBT) are effective in improving depression, and digital solutions may provide a temporary (or even permanent) alternative.

When combined with drugs (for example apps that track sensors on asthma inhalers or apps used in concert with glucose monitors), DTx can deliver interventions that improve a range of patient benefits including better symptom management, efficacy, safety, adherence, proper use of medication devices, improved quality of life, better outcomes and preventative measures. They also offer an enhanced patient experience, affording easier to access services with a non-existent waiting time.

Types of Digital Therapeutics

Type	Purpose	Description	Current Use
Standalone	Digitally delivered therapeutic intervention designed to treat a condition independent of any other intervention	Standalone DTx may be used in conjunction with other prescribed treatments, but can work independently or even replace pharmacological interventions	Prevalent in the areas of Mental Health where Cognitive Behavioral Therapy can be digitally delivered to treat a range of conditions
Augment	Digitally delivered intervention to augment the effectiveness, management or treatment of a prescribed pharmacological intervention	DTx that augment an existing treatment or therapy are designed to work in conjunction with pharmacological interventions	Prevalent in areas such as Diabetes where there are complex conditions with non-linear treatment regimens
Complement	Digitally delivered therapeutic interventions designed to complement existing treatments or traditional interventions	DTx that complement existing treatment are design to improve self-management of condition and related healthcare factors	Prevalent where lifestyle and behavioral factors are significant such as Obesity, CHF and Hypertension

The trends driving DTx

Much has been written about both the promise of the nascent DTx sector and the barriers that may mean expansion at scale takes longer than hoped for. While we explore the barriers in this paper there is reason to believe that conditions are ripe for the sector to grow fast in the near term. This is due to a confluence of "trends", notes Bozidar Jovicevic, VP, Global Head of Digital Medicine at Sanofi:

- Drug treatments are insufficient for most chronic diseases, which also require support, education and monitoring

- Payers and regulators are driving towards pay-for-performance and value-based care

- Health systems are struggling to manage the rising costs of managing chronic disease as well as rising demand

- Patients want to take control of their health using smartphones and other devices that give access to knowledge and capabilities they never had before

What do regulators think of DTx?

Medical device regulation, largely conceived in the pre-digital age, has been ill-suited to DTx innovations. Since they are primarily software driven, digital therapies can be developed more quickly than pharmacological products and benefit from agile development practices with ever faster feedback loops driving rapid improvement and iteration. In other words, products are continually changing and improving, despite the ongoing need to prove clinical efficacy and health economic value (which typically requires following a rigorous clinical trial process).

US regulators recognize this and are striving to create new rules enabling the sector to develop at greater velocity. The 2016 21st Century Cures Act's attempt to foster innovation, the greater use of data and outcomes-based contracting and the FDA's 2017 Digital Health Pre-Certification (Pre-Cert) Program are steps towards this.

The latter was developed to encourage general digital health innovation by redesigning policies and processes to match the needs of technology. It selected nine firms as pilots for a new streamlined regulatory process of developing digital health products.

However, the road is uneven. There is more clarity on some aspects of regulation than others; for example, the guidelines regarding innovations involving AI and machine learning are not as permissive and the definitions relating to these areas not always clearly defined.

In Europe, the UK is forging ahead. NICE has established an 'Evidence Standards Framework for Digital Health Technologies' where it's recognized that as therapeutic digital health tools develop at an increasing pace, they are clinically effective and offer economic value. A working group led by NHS England, and including NICE, MedCity, Public Health England and DigitalHealth.London, has a way forward to address and streamline support on this issue. The project's aim is to make it easier for innovators and commissioners to understand what 'good' evidence for digital tools looks like, whilst meeting the needs of the NHS and patients and not putting the brakes on the processes that innovators, commissioners and other stakeholders use.

Clinician take-up

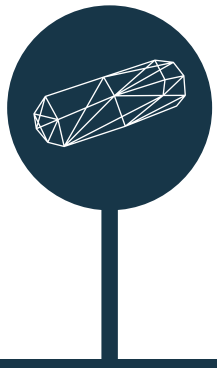
For clinicians, the issues are awareness and acceptance. These are early days for DTx so clinicians can be forgiven for not being up to speed with the latest innovations. In many cases, busy clinicians may not be thinking about DTx at all owing to a lack of knowledge about their potential.

Clinicians who are starting to embrace DTx, quickly encounter a series of issues to consider including: how well a treatment fits with existing care pathways; the additional work required to deliver multiple digital and non-digital therapies in tandem; and what to do with the data DTx generate.

Are healthcare providers and payers embracing DTx?
In the US, the Department of Health and Human Services has been reimbursing digital therapeutic programs for administering the Diabetes Prevention Program since 2016. Some insurers are also offering to reimburse for certain DTx products.

In Europe, national payers/providers are starting to demonstrate their interest in places such as Germany and the UK where a small number of DTx are being prescribed at scale, most notably therapies for mental health and pain management.

Recent landmarks in DTx

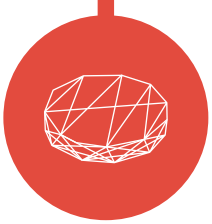


2016

- Department of Health and Human Services agrees to reimburse Diabetes Prevention Program DTx (Omada Health, Canary Health, and Blue Mesa Health)
- Sanofi and Alphabet subsidiary Verily Life Sciences launch $500m Onduo diabetes JV

2017

- US Food and Drug Administration (FDA) approves the first mobile medical application (Pear Therapeutics' reSET for substance use disorders)
- Roche acquires mySugr to form a platform for digital diabetes management
- FDA pre-certifies 9 companies for digital health fast-track pilots
- Akili Interactive posts positive clinical trial data on digital treatment for ADHD
- Digital Therapeutics Alliance formed
- The first fully integrated digital medicine, the Proteus/Otsuka Abilify MyCite, is approved by the FDA



For example, in the UK, the NHS and NICE have established a digitally-enabled therapies assessment program with a focus on 14 digital mental health therapies. The UK also has a broader initiative called Evidence for Effectiveness, developed to make it easier for innovators and commissioners to understand what 'good' evidence for digital tools looks like and to establish guidance and standards that help support the creation of DTx.

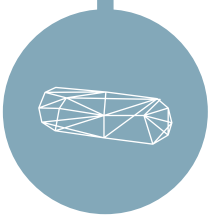
The big question for payers is the value they place on DTx. Many payers have not yet made the distinction between health and wellness products and digital therapeutics, but this is changing. As the evidence of their efficacy grows, some payers are prepared to treat DTx more like a conventional pharmacological therapy, and so reimburse for them on a comparable basis.

2018

- Apple Health Records brings together hospital and clinical records into the existing Apple Health app
- Novartis & Pear agree MS and schizophrenia DTx collaboration
- Q1&2 200 digital health deals total $3.4bn
- Several major pharma companies make strategic investments in 'pure' DTx companies, such as Sanofi spending $17m for Click Therapeutics
- UK launches Evidence for Effectiveness to develop DTx guidance and standards
- FDA plans Centre of Excellence in digital health
- FDA issues guidance offering clearer and faster routes to market in DTx
- Big Health's insomnia treatment Sleepio becomes available on the NHS
- Sandoz and Pear's commercial launch of reSET-O for opioid use disorder
- ResMed acquires digital therapeutics company Propeller Health for $225m

2019

- reSET-O launches
- Otsuka America & Click Therapeutics collaborate to develop and commercialize a prescription digital therapeutic for Major Depressive Disorder (MDD) in a deal that could be worth more than $300m for Click



Some Notable Players Making Headlines in DTx

Akili

Area: Attention Deficit/Hyperactivity Disorder (ADHD)
Product: AKL-T01
Type: Standalone
Description: Akili has completed Phase 3 trials and is awaiting FDA clearance on its digital therapeutic for pediatric ADHD. Akili's game improved attention and control in children ages 8 to 12 with ADHD after four weeks, in clinical trials.

Dthera Sciences

Area: Alzheimer's Disease
Product: DTHR-ALZ
Type: Standalone
Description: DTHR-ALZ, a digital therapeutic that is intended to mitigate the symptoms of agitation and depression associated with Alzheimer's disease, is the first product to receive Breakthrough Device designation from the FDA for the treatment of Alzheimer's disease.

Omada

Area: Diabetes/Multiple/Lifestyle
Product: Omada Program
Type: Complementary
Description: Largest CDC-recognized Diabetes prevention provider in the US have evidenced long-term weight and A1C improvements.

Pear Therapeutics

Area: Substance Use Disorders
Products: reSET & reSet-O (apps)
Type: Standalone
Description: The world's first prescribed drug replacement therapeutics, twice as effective as traditional face-to-face therapy, pave the way for new healthcare contracting possibilities.

Propeller

Area: Asthma and COPD
Products: Propeller (sensor on inhaler + platform)
Type: Augment
Description: Sensor data together with medication reminders, asthma condition forecasts and tips for reducing symptoms offer better asthma/COPD adherence and outcomes (79% reduction in rescue inhaler use, 63% increase in asthma control and 50% reduction in asthma-related ED visits). 65 commercial programs with payers, pharmaceutical companies, PBMs and health systems in 16 countries.

WellDoc

Area: Type II Diabetes
Products: Bluestar
Type: Complementary
Description: Type 2 diabetes management strategy, evidenced 2.03 point improvement in A1C levels, 58% reduction in Hospitalizations/ER visits, 2x increase in mediation changes.

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DTx opportunities for pharma companies

Capitalize on more affordable healthcare

The strongest tailwinds for DTx players are the moves towards value based care, the need to provide real-world evidence of the effectiveness of interventions and the growing consumer-driven expectation of individual patients that care should be Personalised for them.

"Digital therapeutics are perfectly placed to deliver these needs with an ability to simultaneously deliver and monitor the impact of interventions and adapt them to the needs of the individual", says Jim O' Donoghue, President, S3 Connected Health.

"DTx offer so many benefits to all stakeholders it is hard to imagine they won't become mainstream", says David Van Sickle, Co-founder and CEO of Propeller Health (who were recently acquired by ResMed for $225M). "Patient-generated health data is increasingly becoming the starting point on which we base many care decisions and conversations. Providers will simply have much more information about how their patients behave and fare outside their regular office visits. We'll see this continue to drive down the cost of care as patient-generated health data is leveraged as a form of preventive care."

Personalised medicine

With digital therapeutics, pharma companies can both boost adherence and outcomes, and compete and differentiate themselves in the marketplace.

"Digital therapeutics are a huge opportunity for pharmaceutical companies because they enable traditional medicines to treat patients more effectively," says Van Sickle. "In many cases, we already have beneficial, proven medicines but they're not being used optimally."

Digital therapeutics are tailor-made to support the delivery of Personalised medicine. "With traditional therapies the clinician often needs to wait until the next patient's visit to assess whether the therapy is working. With digital therapeutics that information can be made available on a continuous basis giving the clinician the opportunity to assess whether it's working or whether a change is required for the individual. The evidence gathering is an intrinsic part of the provision of the therapy", says O'Donoghue.

For example, if digital CBT is being delivered – and users are engaging with it on their mobile app – the DTx will know how far through the program the patient went, what elements worked for them and what didn't. "What's more, when you look at that at a population level, you can use that feedback to constantly evolve and improve the product," he adds.

A new approach to health

DTx has the potential to transform the way patients are managed. "There is an incredible power in the ability to look at trends and patterns in large amounts of data and to understand the challenges patients have in managing their chronic diseases that we have not been able to see as an industry," says O'Donoghue. "We can use these insights to predict and even prevent acute events for patients with conditions like epilepsy or diabetes."

The opportunities lie across the board in prevention, diagnostics and optimizing therapies. They also lie not just in the potential of DTx to create new product categories but also in other ways, such as market differentiation. A DTx can attract new users, retain them for longer and be bundled with conventional medicines to provide a more complete and effective treatment.

DTx also offer pharma opportunities to have their conventional medicines prescribed earlier and more effectively as well as a means of generating valuable data that would otherwise have to be purchased.

> "We can use these insights to predict and even prevent acute events for patients with conditions like epilepsy or diabetes"
>
> *Jim O' Donoghue, President, S3 Connected Health*

Opportunities for pharma

Type	Potential	Opportunity	Benefit
Standalone	Develop / deliver DTx that treat a range of conditions either as a replacement to existing therapies or potentially addressing previously unmet needs/ conditions	Development of new treatments or expanded portfolios in therapeutic categories	Service unmet needs, new patient cohorts, meet patients changing expectations, develop new revenue streams, reduced cost of new product development
Augment	Improve effectiveness of existing/new therapies	Realize efficacy and outcomes in real-world setting to match or supercede those achieved in a control / trial environment	Real-world data identifying best treatment options, evidence of adherence to improve treatment and interventions, plus outcomes for access, reimbursement and demands of value-based care
Complement	Improve management (clinician/ patient) of overall conditions to improve healthcare outcomes	Address associated lifestyle/ behavioural factors to provide a differentiated, more holistic service with the management of chronic conditions / illnesses that delivers value to patients, HCPs and payers	Capture greater data on challenges patients face and improve population health management to meet demands of value-based care, rising patient expectations and reduce health economic impacts associated with growing prevalence of chronic conditions

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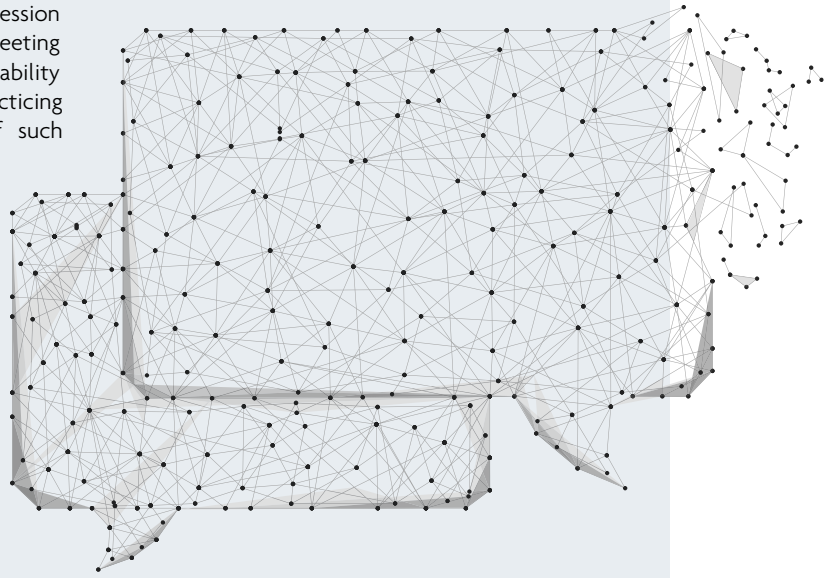
Mental health DTx show the way

Mental health offers the most immediate opportunity for the emerging DTx marketplace and the pioneers here are already getting traction. Mental health DTx also demonstrate clearly the potential for DTx in general to offer treatments at scale for certain conditions that simply have not been possible before.

The opportunity is vast, says John Docherty, VP, Clinical Sciences, Digital Medicine, at Otsuka, which in January 2019 announced a deal with Click Therapeutics to collaborate on the commercialization of its CT-152 app which combined with Click's patient engagement platform is designed to treat patients suffering from major depressive disorder.

Globally, patients currently lack access to non-drug-based treatments in mental health. "The need in depression is so great, [the industry] comes nowhere near meeting it," says Docherty. "There is a deficit in the availability of psychotherapists trained and rigorously practicing evidence-based therapies. Sufficient numbers of such therapists are hard to find apart from some of the big cities and they are expensive. We are vastly undertreating depression; we are probably only diagnosing and treating a third of people currently and that problem replicates across all categories of psychiatric illness."



That potential to address the behavioural healthcare market, estimated to be worth more than $40bn in the US alone, is being realized by Silvercloud Health. By the end of 2018 it had attracted 220,000 end users to its 30+ behavioral health program since its 2012 spinout, adding half of those in the last year, primarily in the US and UK.

"The platform enables healthcare organizations to digitally deliver mental health while achieving the same levels of clinical outcomes as they would see with low intensity face-to-face care and offer great potential in integrated care", says SilverCloud's CEO Ken Cahill. "There is a very significant co-morbidity between mental health and chronic care, with between 30% and 70% of end users with chronic care conditions experiencing clinical levels of depression and stress that as well as causing misery in their own right also reduce adherence and compliance rates."

They promise both short and long-term benefits for payers and patients. They offer the potential to provide treatments earlier and with greater ease as well as the longer-term impacts that stem from lasting behavioral change as well as better insights into the patient population. Accepted non-pharmacological treatments (particularly first-line treatment options) are often not possible to prescribe, monitor and standardize at scale, across care practices e.g. non-pharmacological treatments for aggression and agitation in dementia. Companies like Dthera Health have created digital therapeutics that offer these interventions in a scalable and standardize manner.

Change will be rapid from here, predicts Cahill. "We are starting to see a steep change in terms of adoption by pharma and payers. There is both push from end users who realize they can gain access to a treatment right away and pull from payers and physicians who see alternatives to pharmacotherapies."

DTx threats for pharma

If DTx become an integral part of the healthcare system, which we expect, their eventual ubiquity will mean that a failure to engage with the sector is the greatest threat to traditional pharma. The onus, after all, will be on every participant to deliver services and products that impact outcomes, irrespective of the route taken to get there.

What's more, the early providers of DTx will develop a deep, persistent and trusted relationship with patients, says Kaia Health's Mehl. "The threat for today's pharma is that there are new players like us who own the patient relationship and who cut pharma out of the whole picture. Pharma is like hardware suppliers; they might supply our patients with medication but in the end, the patients use our app to track medications. Maybe we'll end up telling them they are taking the wrong medication."

"A key action, therefore, is for companies to identify the right partners with whom to develop DTx", says Propeller's Van Sickle. "It's important to partner with digital therapeutics companies with a track record of proving their impact on patient outcomes. Starting with clinical trials gives you a foundation of evidence on which to base a commercial program."

Threats to pharma

Type	Potential	Threat	Outcome
Standalone	DTx become a widely adopted prescribing option for unmet patient needs or as a replacement to existing therapies	Ability to readily demonstrate use & effectiveness leads to DTx becoming the preferred prescribing option for physicians and patients	DTx companies develop deep data-sets, understanding of and relationship with patients and physicians, along with meeting rising expectations around how treatment/healthcare is delivered
Augment	Therapies that integrate DTx to augment current treatment demonstrate improved effectiveness and patient outcomes	Pharma companies that don't look to understand, support and deliver digital interventions to improve real-world outcomes lose patient understanding and market share	Pharma companies fail to appreciate full understanding of real-world challenges and don't implement solutions. DTx companies own the relationship with patients on a pharma company's treatment.
Complement	DTx effectively address lifestyle/behavioral factors to provide improvement in management of conditions and population health	Pharma companies become medical suppliers that are used as just one element of multi-modal treatments and holistic condition management	Pharma companies miss the opportunity to provide more holistic services; meanwhile DTx and condition management companies take ownership of disease/population health management, gaining reimbursement based on demonstrating outcomes of their more holistic solutions

Part 2: Making DTx mainstream

In this rapidly developing space, there are many aspects for pharma companies to consider. These include the pathway to patients, whether to partner or develop DTx internally, pricing strategies and strategies for incorporating new DTx into existing Drug+ packages.

Pathways to patients

There are two commercial pathways available to the makers of digital therapies; the regulated prescription-only route (with FDA/EMA approval, paid for by health payers) or the non-prescription, direct-to-consumer route. Both are currently operating, and can even do so alongside one another.

"There are now enough deals to demonstrate that the prescription model offers scale", says Bozidar Jovicevic of Sanofi. While there may have been some doubt about the financial worth of DTx in the early days, payers' attitudes to reimbursement are becoming clearer.

The direct-to-consumer model followed by the likes of Omada, which runs clinical trials but does not go to the FDA to be regulated as a medical device, is not dependent on the current health/prescription system, but there is still virtue in effectively proving to employers, insurers and payers.

"Both models are viable and no one knows which will win out," says Jovicevic. "For me, by far the biggest determinant is the price. How much will payers pay for these solutions?"

DTx pricing strategies

While the future may well herald alternatives, currently DTx pricing strategies vary widely depending on the nature and progress of the therapy.

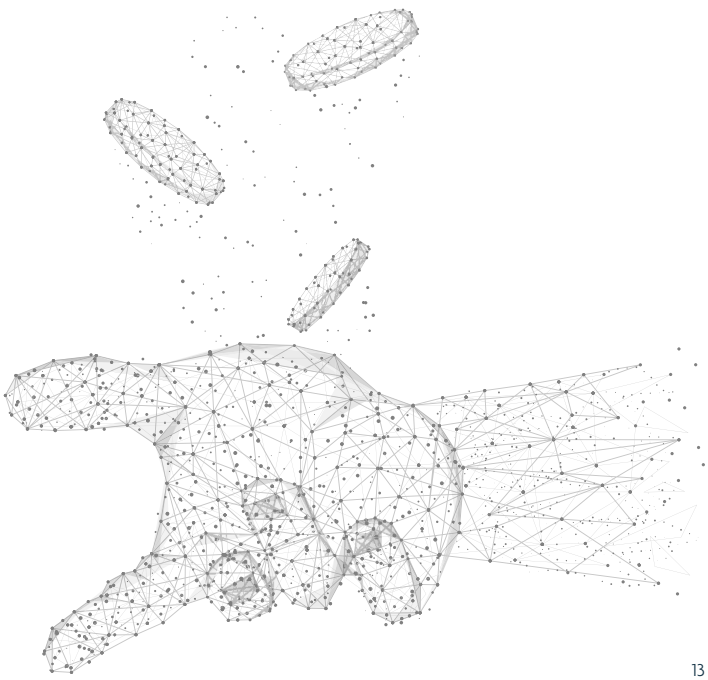
For example, VC-led creators of DTx may prioritize building a user base, datasets and efficacy ahead of profits. In these cases, 'freemium' type models on a B2C basis enable the vendor to build experience of working with patients and to create a large user base. Over time these will command higher prices once a solid clinical evidence base is established.

Others focus on agreeing population-level deals with large providers, providing blocks of licenses that can then be used by clinicians to prescribe therapies to patients.

Deals struck by Pear Therapeutics and Akili recently – which are thought to have secured reimbursement along the lines of conventional medicines – have been seen as paving the way for the sector when it comes to pricing.

"There is evidence that payers are open to paying appropriately," says Jovicevic.

> "There is evidence that payers are open to paying appropriately"
>
> *Bozidar Jovicevic, VP, Global Head of Digital Medicine, Sanofi*



The path to payment

Type	Regulatory Path	Clinical Pathways	Pricing/Reimbursement
Standalone	Clinical Trials to demonstrate efficacy. Regulatory approval for specific indication	Prescribed by Physician / HCP	Reimbursement achieved by pricing in line with conventional treatments with similar outcomes. Provided directly to payers
Augment	Requires regulatory approval for use in conjunction with approved medicine	Prescribed by HCP for use in conjunction with specified treatment	Priced as part of a Drug+ offering. Provided by pharma
Complement	Either seek regulatory approval, or use as a complimentary tool to support patient self-management. Greater datasets are obtained and subsequently used to demonstrate effectiveness	Direct to patient, but recommended by physician. Provided as part of patient support services to prescribed treatment	Lower cost pricing. Provided direct to patients, HCP, payers & employers. Offered by pharma as part of support services with prescribed treatment

The Drug+ approach

As well as offering a potential source of direct revenue, DTx have the potential to shape wider strategies for pharma. They offer the chance to cultivate even closer relationships with patients, as well as better patient engagement thanks to regular updates and upgrades.

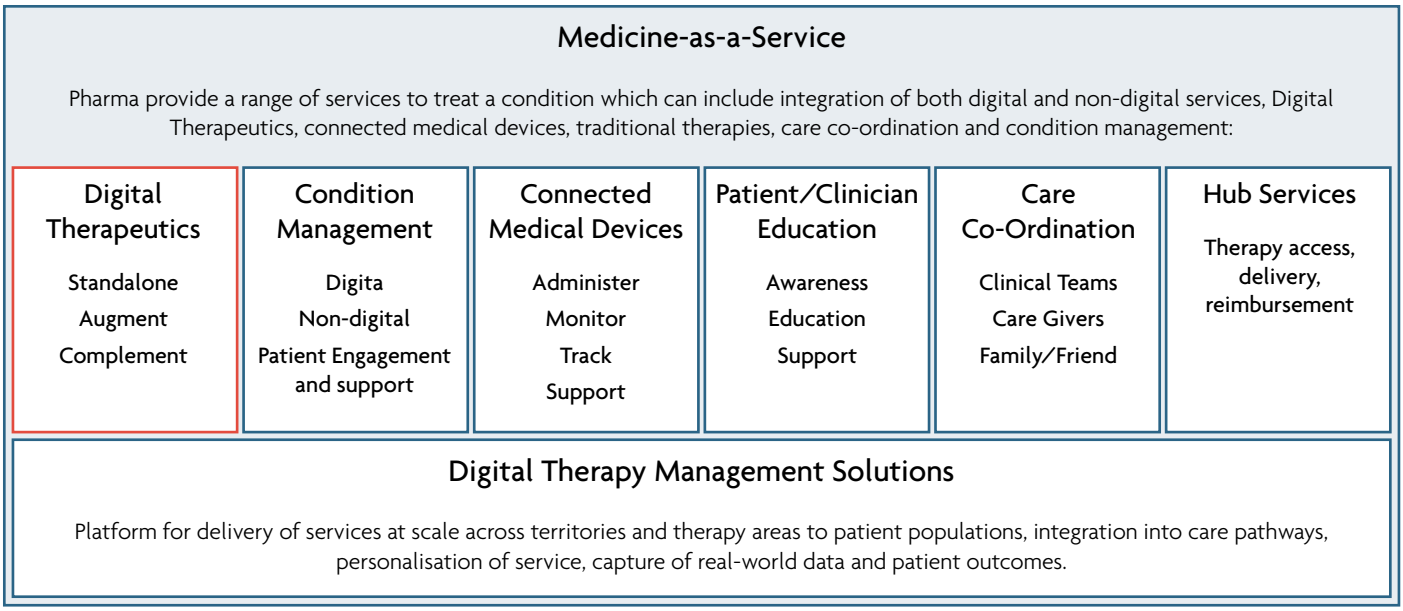
There is also the potential to gain competitive advantage by establishing proprietary sources of data for training, input and feedback and for deploying AI to yield better results and greater value from data.

DTx could also play a key part in future creative contracting approaches, for example risk-sharing around adherence, quality of life improvements and outcomes (which have traditionally been difficult to monitor and provide evidence around).

Rolling DTx into a wider package of supporting therapies has great potential as an attractive commercial path forwards for pharma companies, enabling them to complement and add value to their existing drug portfolios.

There is great potential to prove the efficacy of DTx therapies used in this way in certain conditions, such as in treating MS, RA or other autoimmune diseases, since they typically involve a complex set of challenges and symptoms that could benefit from a range of pharmacological and digital interventions.

"Rather than looking for the silver bullet to replace an expensive therapy with an inexpensive DTx, pharma may provide a range of services around specific conditions – almost like a transition to medicine-as-a-service," says O'Donoghue.



Other likely parallel paths for some vendors will be 'DTx lite' solutions, where patients pay out of pocket, or licensing DTx (or selling DTx data) to other manufacturers.

"Rather than looking for the silver bullet to replace an expensive therapy with an inexpensive DTx, pharma may provide a range of services around specific conditions"

Jim O' Donoghue, President, S3 Connected Health

Prescribing and reimbursing DTx

Prescribing and obtaining reimbursement for DTx is new, relatively haphazard and until recently there was little supporting infrastructure either to properly account for them in existing reimbursement codes.

Traditional reimbursement models for DTx are being used in some cases, such as for reSET or WellDoc's BlueStar real-time type 2 diabetes coaching. National health provider/payers in the UK, France and Germany are also already prescribing and paying for DTx in pockets, notably in mental health, diabetes and chronic pain.

Established reimbursement frameworks and device codes have tended to be ill-fitting for DTx, but some progress is being made in adapting them. In the US new Current Procedural Terminology (CPT) codes that include DTx are being introduced, and in 2018 the Centers for Medicare & Medicaid Services (CMS) issued new reimbursement policies and codes for telehealth, remote monitoring, and other uses of digital tools.

Meanwhile, digital medicine platforms designed to help healthcare providers deliver DTx at scale are emerging from the likes of AppScript, Solera Health, RX.Health and Xealth. These platforms integrate with EHRs, clinical health data and CRMs to automatically pair the best therapies to the appropriate patient populations.

Rx.Health's Bulk Prescription, for example, allows healthcare teams to prescribe digital therapeutics to entire cohorts of patients. Initially launched to help treat and monitor chronic diseases, including respiratory, cardiovascular, and gastroenterological illnesses, it will give patients access to education, digital therapeutics and remote monitoring via smartphone or email. Incoming patient data is then integrated into electronic health records (EHR) and care management dashboards.

"The time and skill demanded of clinicians in analyzing the data DTx provide is a major potential barrier to their adoption and there is a push to account for this work", says Kyle Rose, Vice President, Partnerships and Strategic Projects at MySugr.

"It is very intimidating for a physician's office to suddenly have all these reports to sift through. The reality is they have only so much time with each patient. It's great that we are seeing reimbursement codes in the US evolve when it comes to remote patient monitoring. Care Innovations, our partner, are trying to get healthcare professionals to get their time reimbursed for interpreting data."

"Over time, AI and other forms of automation are likely to take on some of the legwork for care providers when it comes to interpreting data, cutting the burden on them", adds Rose.

"It is very intimidating for a physician's office to suddenly have all these reports to sift through"

Kyle Rose, VP, Partnerships and Strategic Projects, MySugr

Developing DTx: Internally or with partners?

Pharma organizations need to think hard about how they approach the development of their presence in the sector.

"Companies that try to develop DTx competencies internally are ill-advised", says Kaia's Mehl, who also says that going it alone carries a high risk because if such a strategy fails, shareholders and internal stakeholders will be reluctant to explore the sector any further in future. There is also a difficult cultural fit.

"Some pharma players talk to us to understand the process we went down to develop our digital therapy in order to estimate the cost of doing it themselves internally, but those who want to build something internally will fail," he says.

"Pharma companies are not internet startups; they are almost the opposite of how naturally agile companies work. Imagining you can hire top talent from tech to work in pharma is so unrealistic. The people who build digital therapies don't want to work for a pharma company. None of my friends would come and join you."

For companies determined to focus inward, it would be a mistake to give responsibility for the developing of DTx to internal pharma tech groups, says Pear Therapeutics CEO, Corey McCann. "The tech groups have a mandate to investigate but not develop new assets," he says.

The sector has evolved so rapidly there is a lack of understanding of this. A technology group with a digital mandate is more likely to develop products that deliver efficiencies, such as a social platform to more rapidly recruit patients for clinical trials, than a revenue earning product.

"The key success factor is moving DTx into a part of the organization with a P&L," says McCann. "There needs to be an acknowledgment that these products are directly revenue generating. DTx are contributing to the top line of the company and need to be treated as an asset."

> "None of my friends would come and join pharma."
>
> *Konstantin Mehl, Founder and CEO, Kaia Health*

The traditional split between R&D and Commercial is also a potential stumbling block. With far shorter timelines compared to pharmaceuticals (typically three to five years), there are question marks over each side's ability to cooperate effectively.

"Digital therapeutics touch every aspect of a Pharma organization from R&D through to Medical Affairs and Commercial. These groups, however are often siloed across therapy areas and territories. Creating buy-in and a common approach is a challenge and doing this in a changing regulatory environment with fast-moving technology is an even bigger one.," says O'Donoghue. "When it comes to operationalizing these services on a global scale, Pharma companies typically need help".

Bypassing pharma

In some cases, even if they go down the prescription route, DTx creators may opt to bypass pharma altogether. These vendors, such as Kaia Health and Akili, see payers and insurers as the end market and are already bypassing pharma as a channel, able to offer alternatives to payors that deliver similar or better outcomes.

Akili Interactive Labs CEO and co-founder Eddie Martucci mentioned during the 2019 CES Digital Health Summit that his company would be bucking the trend of its contemporaries by building its own distribution platform for the video game-based therapeutic, as opposed to relying on relationships and sales channels of an established pharmaceutical company.

"There's a little bit of a psychological assumption that the pharmaceutical industry must partner and deliver this for it to be a legitimate medicine. I disagree vehemently. We may partner with pharmaceuticals or medical device manufacturers, but we are building today the end-to-end [prescription and procurement] process, the entire backend for digital medicine that doesn't exist today — the sales force, the medical affairs, the insurance processing — that will enable a platform for scalable digital medicine. It's expensive; we haven't launched the product, we've raised $120 million. But it's an investment worth making, and it's something that I'm very passionate about."

In an email to MobiHealthNews, who reported on this statement and reached out for further information, an Akili representative confirmed that this project is underway, and noted how such an approach could improve the connection between the therapeutic maker and its users.

"Akili is definitely looking at building a very different type of commercial model than traditional pharma. And building it ourselves. We believe it's the only way to build meaningful relationships with patients we feel our products enable, if not demand," the representative wrote.

Partnering with pharma

Despite this, most DTx companies believe that partnering with pharma will make sense given what each player can offer the other – in the case of pharma, access to global scale and existing patients and clinicians, and in the case of DTx, an iterative, nimble approach to development and innovation. For Propeller, there is a strong argument for this.

"We believe partnerships with pharma companies, payers and healthcare organizations, which are incentivized to manage costs and drive better outcomes, are currently the best route for getting affordable digital medicines to patients," says Van Sickle. "We see that routes to market are being increasingly integrated into ordinary clinical workflows and are more and more tightly coupled with medications."

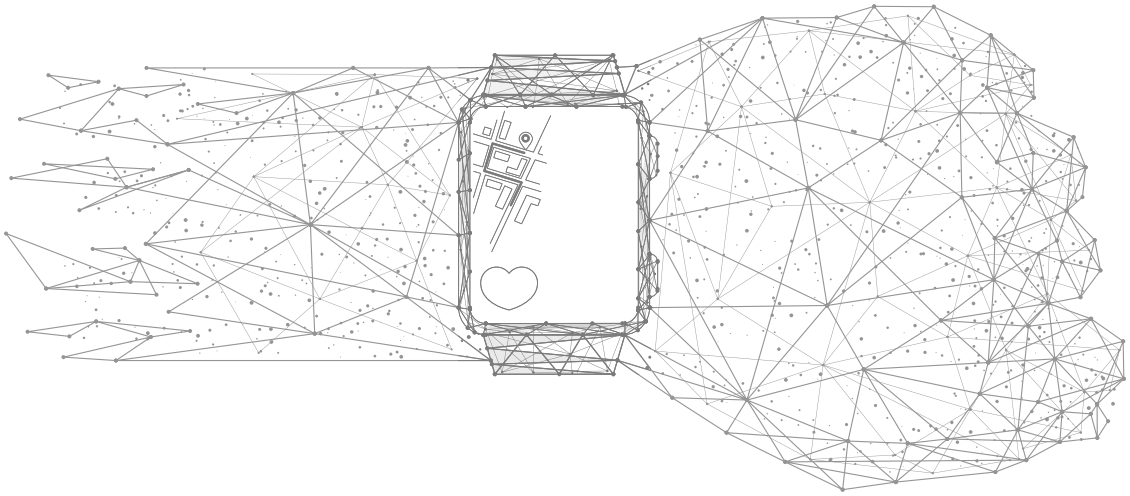
Acquire or license?

Acquisitions are a more natural route for pharma, which has proven its abilities in M&A as replacement for R&D, for example buying biotech startups during Phase 3 clinical trials, says Mehl.

"If I was the chief digital officer in a pharma company and working out whether to buy, partner or build in-house, I would acquire startups and let them continue as before, rather than try to subsume them within the corporate culture."

The challenge pharma faces when it comes to acquisitions is that it is still very difficult to put valuations on DTx startups.

"Licensing deals with DTx players are another opportunity for pharma to get to grips with the sector while minimizing the risks. Such deals enable them to test products in certain countries, pursue outcomes-based contracts, get a feel for the value of the data generated and the potential for greater loyalty", adds Mehl. "It's not far away from what pharma companies already do."



Barriers to DTx success

Traditional pharma players were not set up to operate digitally, and many are still dealing with the many legal, regulatory and organizational challenges it brings.

As the new kid on the block, Drugs+ DTx are often viewed by people in pharma as a sideshow. After all, clinical trials have so far been relatively small-scale and best practice is still being developed (for example in establishing the equivalents of control arms and placebos).

Involving patients

"A risk for every player in the DTx space, but especially pharma, is a failure to recognize the importance of the end user in developing the therapy", says MySugr's Rose. "They are so often left out of the design process or too often it is an afterthought. When patient influencers are invited into the process it is usually too late. We need to involve them early in the process and ask, 'What can we do for you?'"

Involving patients is an ongoing challenge in pharma that has persisted for more than a decade, with many pharma resistant to go through the often complex and regulatory-fraught areas of patient participation. However, the transparency of DTx, the ubiquity of smartphones and other devices upon which to run software, and the comparatively more straightforward nature of clinical trials (with the possibility of more remote trials being easier) provides an opportunity for pharma companies to involve patients in design more closely than previously.
In most industries not involving end users in the design of a product would be unthinkable, and so it should be with Digital Therapeutics. Organizations like NICE have recognized this in their December 2018 document "Evidence Standards Framework for Digital Health Technologies" where they identify as a key evidence requirement that users, patients, and HCPs, have been involved in the design of the product and that where there are behavioural interventions that a user behavioral analysis has been carried out and evidence based behavioral techniques have been used.

On a pure practical level, involving patients in the design of Digital Therapeutics is no-brainer. No matter how good the clinical evidence is, the product will only be successful if it is embraced by patients and clinicians. Surely we have learned from companies like Apple that user experience is the real differentiator.

Engaging HCPs

DTx may also require new ways of thinking around how they are communicated as a viable option, taking into account all parties in the prescribing chain, from carers to clinicians and nurses.

"Each party will need to benefit and that is not a simple thing to deliver," says McCann. "DTx might in some cases present greater complexity and claims on time that may prevent them from gaining traction."

For instance, a digital therapeutic may promise much but if it needs more management from HCPs – or more attention from patients (who may want to simply forget about their disease) – than they are prepared to give, it will fail.

The evidence generated by DTx, sometimes in the span of a day or two, may mean that clinicians are expected to make decisions they are not accustomed to.

"Data needs to go somewhere and to be actionable," says McCann. "Quite often it will be about making that data available to the care team, but does it make the care job easier or harder? Do they get paid for it? Does it mean they can look after more patients or spend more time with patients they did not previously spend time with? If the answers to those questions are wrong, it can prevent adoption."

"It is the responsibility of those working in the digital space to curate reports so that they are easy to interpret and are in line with standards of care and so avoid overwhelming HCPs with data", says MySugr's Rose.

Kaia, M-Sense and Silvercloud offer early examples of DTx that were developed with a care provider-centric model in mind, seeking to anticipate these challenges.

Prescribing SilverCloud is as simple and streamlined as a physician writing a scrip for a medication, claims Cahill. "We had to make it simple. From a design point of view, we focused on end users and clinicians, with the aim of making it `low touch and high reward'. Low touch for the clinician while being high reward for the end user, so that they don't feel it is robotic. As a patient, I want to feel there is a human in the loop helping me even though, being a voice that cares."

> "When patient influencers are invited into the process it is usually too late, we need to involve them early in the process and ask, 'What can we do for you?'"
>
> *Kyle Rose, VP, Partnerships and Strategic Projects, MySugr*

Conclusion

The growth of the DTx market will inevitably be linked to the trends driving the consumerization of healthcare. These include the ubiquity of smart devices and sensors and an increasing acceptance by patients of app-based healthcare delivery. The march of real-world evidence and value-based contracting will also act as growth catalysts for the DTx sector.

"The biggest change we'll see over the next three to five years is an explosion in scale," says Van Sickle. "Interest and investment in digital therapeutics from pharmaceutical companies, payers, health systems and pharmacy benefit managers are growing rapidly. I believe digital therapeutics will start to seem like a much more standard part of the healthcare experience all around the world."

Pear's McCann likens the DTx market to the early days of the biologics revolution. "We are right at the beginning – it is a whole new therapeutic modality and we have the opportunity to create upwards of 100 products to increase efficacy across a range of disease conditions."

"Given their low cost and quick development cycles, DTx will come to be seen as 'solutions without side effects", says Jovicevic. He predicts that some form of digital treatment will be universal within 10 years and the overall market worth $50-100bn.

DTx developers are already proving to be among the most nimble and entrepreneurial actors in the health sector. They will be as comfortable carving out direct relationships with payers and healthcare providers as forming partnerships with pharma. Their agility will lead them to set the pace in terms of growth as well as product development across the span of diseases and conditions.

The success rate of pharma in developing internal DTx will be low and its most common pathways into the market will be through partnerships, early-stage start-up funding, and outright acquisitions.

It's all about the patient

Pharma players will come to see DTx as both revenue earning products whether standalone, augmenting or complementary, and important vehicles to drive them to become ever-more patient centric organizations.

DTx will enable the nimbler pharma players to own, or at least co-own, their relationships with patients. They will come to covet the precious digital real estate they occupy on patients' smartphones. This presence in the patient's pocket will engender deeper trust and more abiding direct patient relationships, particularly with chronic conditions.

It will also generate data from whichever more value can be unlocked and will enable pharma and DTx developers to identify new products and services. DTx will then meet hitherto unmet needs and achieve new milestones in managing conditions.

"Already, we're seeing patients and providers use digital therapeutics to keep better track of their medication use and symptoms between appointments, communicate about exacerbations and changes to their treatment plan, and identify previously unobserved triggers based on symptom patterns," says Van Sickle. "In the next five years, we will see digital therapeutics become increasingly ingrained in healthcare workflows and in the patient-provider relationship."

Longer-term DTx will begin changing healthcare on a larger scale with growing applications in prevention, keeping patients out of the emergency room and hospital for longer.

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S3 Connected Health design and develop 'Digital Therapy Management Solutions', 'Digitally Enhanced Patient Support Services' and 'Digital Therapeutics' that increase patient engagement, enable patient-self management and improve healthcare outcomes.

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