Digital Solutions and the Role of AI in Healthcare

Part 1: Recent Innovations in Digital Therapeutics

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Abstract

Digital health and Artificial Intelligence (AI) have begun to change the face of the global healthcare markets in recent years. Many different stakeholders are engaged in all aspects of the digital transformation of health and care, leading to a continuous transition from traditional processes and services to more advanced, technology-driven solutions. A wide range of emerging digital health technologies are available, opening up many opportunities not only for patients but for all involved players in the industry. Although being part of a traditionally very conservative industry and despite having initiated this transformation substantially after digitally mature industries such as financial services and telecommunications, pharmaceutical and life science companies have closed the gap and proven digital affinity via innovative product launches in mobile and telehealth as well as AI-supported process optimizations.

Building upon a previous publication on "mHealth" [1], the authors evaluate in a set of 2 consecutive articles the current landscape of AI and digitalization offers, their explicit benefits for various stakeholders as well as the challenges to be faced during development and marketing.

Zusammenfassung

Digitale Lösungen und die Rolle der KI im Gesundheitswesen

Digitale Gesundheitsanwendungen und Künstliche Intelligenz (KI) haben in den letzten Jahren Strukturen, Prozesse und Strategien der globalen Gesundheitsbranche stark verändert. Diverse Marktteilnehmer treiben die digitale Transformation in Healthcare mitsamt all ihrer Aspekte voran, wodurch ein kontinuierlicher Wandel von traditionellen Prozessen und Services hin zu fortschrittlichen technologischen Lösungen entstanden ist. Heutzutage ist eine breite Palette an aufstrebenden, digitalen Technologien verfügbar, die sowohl Patienten als auch anderen Stakeholdern weitläufige Möglichkeiten bietet.

Pharma und Life Sciences haben trotz des traditionell sehr konservativen Marktumfelds die Lücke, die durch einen gegenüber digital reiferen Branchen wie Telekommunikation und Financial Services deutlich späteren Transformationsbeginn entstanden ist, in den letzten Jahren geschlossen und ihre digitale Affinität durch innovative Produkteinführungen in Mobile Health und Telemedizin sowie durch KI-gestützte Prozessoptimierungen unter Beweis gestellt.

Aufbauend auf einer vorangegangenen Publikation zu „mHealth" [1] bewerten die Autoren in einer Serie von 2 Beiträgen die aktuelle Landschaft der KI- und Digitalisierungstools, deren Nutzen für verschiedene Stakeholder sowie Herausforderungen für Unternehmen bei der Entwicklung und Vermarktung.

Introduction

Healthcare has always been one of the largest and most impactful industries for society in the modern ages. It has been growing steadily through the discovery of novel, groundbreaking approaches to curing ever-evolving diseases. But the nature of the industry is changing. While originally, product-related innovations have mostly focused on new scientific methods in medicine, the traditionally conservative healthcare industry has become more active within the last 5 to 10 years in adapting to the global trend of digitization along the entire value chain. Digital transformation has become a focus of healthcare strategists and a paradigm shift for many stakeholders. Although being relatively late to the game – innovators in fintech, telecommunications or retail have mostly transferred entire business models into the digital space many years ago – there has been progress in healthcare and life sciences and the pace is picking up swiftly.

Nowadays, there are thousands of healthcare apps available in the app store, wearable medical devices in use and patients visiting doctors remotely via telehealth. Many new players, including large technology companies

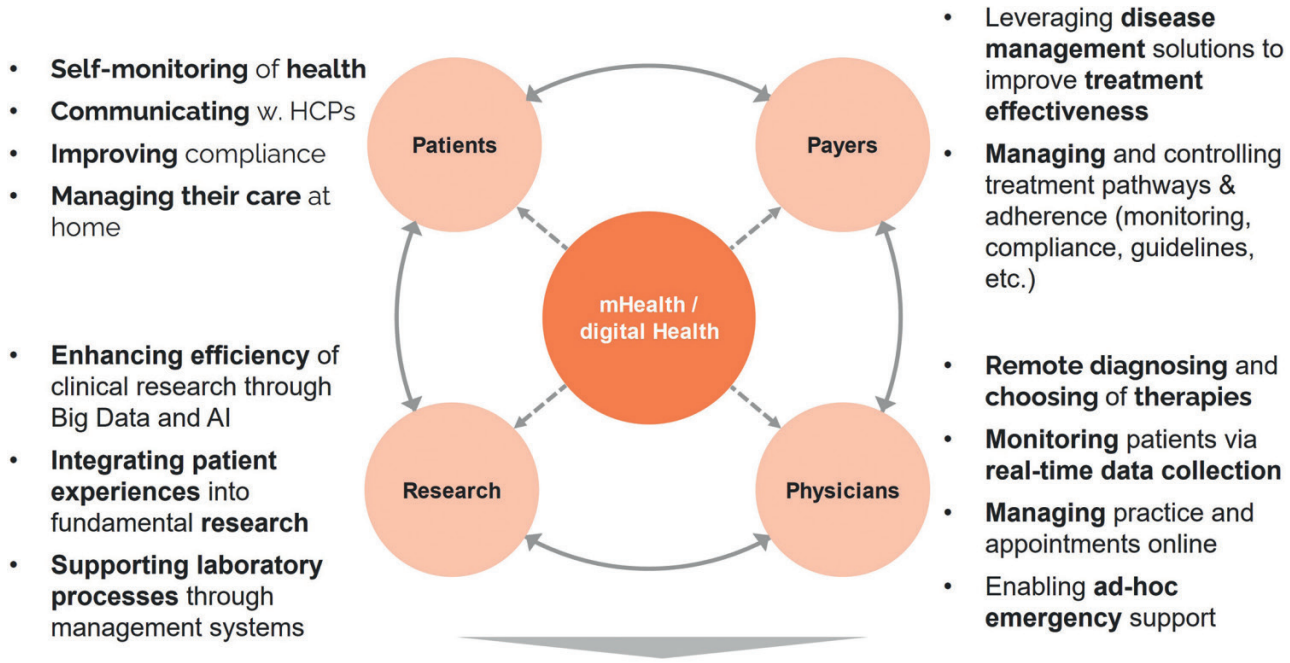

Figure 1: Stakeholders benefitting from digital health (source of figure 1 and 9: stradoo GmbH).

such as Google, Amazon & Co have pushed into the market to transform business processes, to make better use of the available data or to expand the product and service portfolio. Beyond pharmaceuticals and medical devices, the market now also offers Digital Therapeutics (DTx), Digital Diagnostics (DDx) and support tools for patients, physicians, payers, and manufacturers. Especially DTx, as a subgroup of digital and mobile health (mHealth) applications, have received plenty of attention in recent years, improving patient care and safety in multiple indications. Within that segment, the range of applications and Artificial-Intelligence (AI)-based tools is broad, with launches ranging from simple tools for patient (adherence) support to biomarker monitoring, digital and automatic learning tools for patient individual advice as well as actual medical interventions, such as closed-loop medication system based on digital sensors.

While such technological innovations for products and services are the most important factor for digitization of the industry, digital transformation goes far beyond simply transforming analogue into digital or offering new digital tools. It also implies an adaptation in mindset with a stronger focus on evidence-based decision making, the use of Big Data and automation of non-value-adding tasks. A multitude of tools that fulfill both the technological as well as the transformative requirements of a disruptive innovation is available in the market. These applications not only provide clinical benefit to the patient via digitized intervention, but also generate real world data and provide an opportunity for physicians to interact with the patient in real-time.

In this first of 2 closely interlinked articles, the authors selectively focus on latest trends in DTx as a key field of application for digitization, providing an update to a previous publication on mHealth [1].

Digital Transformation Positively Impacts Multiple Stakeholders

Introducing digital elements into the healthcare space has benefits for all major stakeholders (fig. 1).

Firstly, DDx, DTx and telehealth applications contribute greatly to a better convenience not only during treatment, but also when patients are enrolled in clinical trials. Via the respective technology, patients can monitor their symptoms independently and receive medical care remotely. Smart medication devices such as pill containers possess an integrated chip to register the intake of a drug. Reminders sent to connected smartphones encourage patients to take their medicine regularly, improving their adherence. Through innovation, patients can receive care from the comfort and safety of their homes, including virtual visits by doctors.

Secondly, looking at clinical outcomes, it is not only patients who benefit from improved adherence via digital health solutions. Therapy costs and overall healthcare burden for payers can be reduced as well. Compliance with disease-specific guidelines and adherence to a prescribed treatment are essential pre-conditions to ensure that therapy is effective not only in theory but also in practice. Consequently, payers are intrinsically

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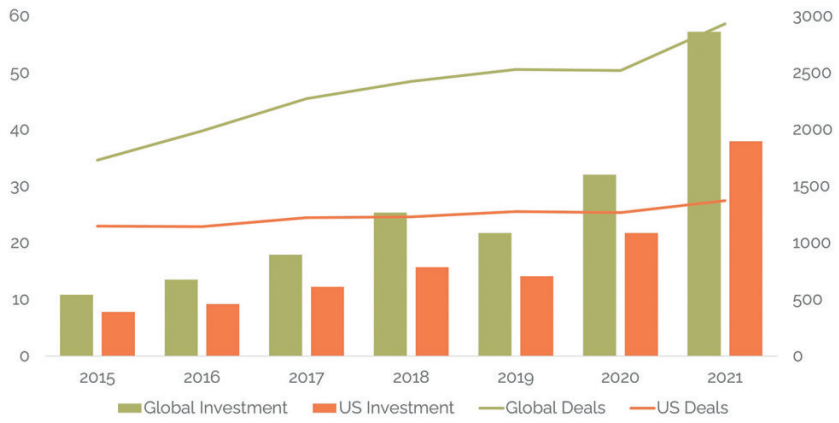


Figure 2: Increase in number of deals and deal volume [in bn US dollars] globally and in the US (Source: stradoo GmbH, CB Insights).

motivated to support patients in that process. On another note, payers can leverage data collected from wearables to predict the risk of certain severe illnesses in individual patients. Based on insights drawn from the data, payers will be able to initiate measures to better steer the system and provide recommendations to doctors for ideal treatments or pathways for patients.

For physicians, remote care via telehealth and smart medical devices facilitates clinical practice both for diagnosis and treatment. Patients can take care of standard biomarker monitoring themselves, so that no time-consuming tests need to be performed in the doctor's office. The healthcare practitioner (HCP) is also able to monitor patients in real-time using wearables in-between visits. In mental health, the number one telehealth indication in the US, virtual interactions might even replace in-office visits in most cases. Additionally, physicians have the possibility to immediately react remotely to severe conditions in patients and to provide respective ad-hoc advice and care. For administrative purposes, digital solutions can be leveraged to organize and manage appointments online.

Finally, on the industry side, almost all departments of pharmaceutical companies can benefit from digitization of processes, but the biggest potential impact lies certainly in Research and Development (R&D), the core function responsible for scientific innovation. Driven by Big Data and AI, researchers can explore a much broader field of potential drug candidates, enhancing the probability of successfully finding a suitable compound for the intended purpose. Besides, most companies have already started to use Real World Data (RWD) in R&D.

Public and private investors have acknowledged the positive impact of digitization on the global healthcare industry. Funding for digital innovation to support all stakeholder groups has expedited in many countries. According to CB Insights, more than 37.9 bn US dollars were pumped into the US digital health sector in 2021 [2]. Globally, the total investment even amounts to 57.2 bn US dollars, having increased by 79 % compared to 2020 (fig. 2).

DTx Innovations Transform the Way Healthcare is Provided

DTx, a sub-group of digital health tools, have clearly gained importance in healthcare since the introduction of chronic disease management tools like *WellDoc* in 2005. The field of application has expanded from purely coaching and patient support solutions to actual treatment interventions via digital technology. This development is reflected in the market valuation of DTx providers. Overall, DTx contribute 3.4 bn US dollars (6 %) to the digital health market. Experts predict further rapid growth to reach a total global DTx market size of roughly 15 bn US dollars by 2026 and more than 30 bn US dollars in 2030 [3].

On their website, the Digital Therapeutics Alliance defines DTx as follows:

> *Digital therapeutics (DTx) deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders* [4].

DTx can be used independently or in conjunction with medications, devices, or other therapies to optimize patient care and health outcomes.

Cognitive behavioral therapy (CBT) is the most common methodology of treatment in DTx today. CBT is primarily used in diseases such as mental health disorders, diabetes, and substance abuse, as the treatment here has a major effect on primary clinical outcomes. It also provides great benefit as a complementary treatment option for many other indications, even in complex therapeutic areas such as oncology or hereditary diseases.

As per definition, development of a new DTx requires extensive clinical evidence to obtain market approval, equal to any other therapeutic. However, despite these high market access barriers, there have been plenty of examples of successful DTx launches in new markets in the past, both in terms of hardware and software innovations. One of the most promising examples is *Hinge Health* [5]. Current valued at 6.2 bn US dollars [6], the company offers a digital care program for musculoskeletal (MSK) treatment, managing chronic back and joint pain. Hinge Health's *Enso* application combines advanced motion technology and electrical nerve stimulation to provide patients with non-invasive pain relief. Through digital sensors, the application collects real-time data and insights into clinically valid outcomes (pain, stiffness, and functional ability), as can be seen in fig. 3.

Company	HW/SW*	Location	Employees	Revenues p.a.	Net income	Funding
Hinge Health	HW + SW	San Francisco, US	~1,065	~$167 m	-	**$1 bn**

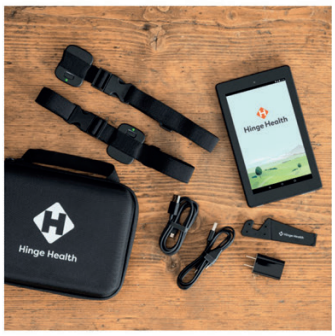
Overview on Hinge Health's Service/Product Portfolio

General Offering

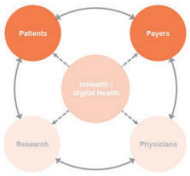
Hinge Health provides an **end-to-end Digital MSK Clinic™** offering expert medical opinion from physicians & orthopedic surgeons managing clinical programs for **prevention**, 1-to-1 Physical Therapy video visits for **acute care** as well as health coaches, wearable motion sensors, computer vision & nerve stimulation technology for **chronic disease management & surgery recovery**

Products

- **Hinge Health Enso®** (wearable electrical nerve stimulation technology)
- **HingeConnect®**



Benefits & key stakeholders profiting from Hinge Health's portfolio



- Reducing pain, depression & anxiety in MSK via **non-invasive electrical nerve stimulation**
- **Avoiding implantation** of any medical disease management devices in surgery
- **Significantly reducing overall healthcare expenditure for MSK** & **therefore payer burden by preventing surgery** either for implantation or as corrective measures

* HW = Hardware; SW = Software

Figure 3: Hinge Health's electrical nerve stimulation technology provides great benefit for patients with chronic back and joint pain (Source: stradoo GmbH, picture: Hinge Health).

Algorithms then transform the data into health coaching and education to impact the patients' behavior causing the respective health problems. A virtual platform called *HingeConnect* monitors and analyzes electronic medical records (EMR) of over 75 000 patients and flags patients which could be viable for treatment with *Enso*. The platform also connects patients with specialized physicians for virtual medical care and guidance.

Another prominent example, *Propeller Health* (fig. 4) offers a smart sensor that can be attached to standard inhalers for the treatment of chronic obstructive pulmonary disease (COPD) and asthma [7]. The sensor collects and wirelessly transfers information about inhaler usage and biomarkers to a patient app.

Based on the data, the app provides advice for patients' daily routine and medication, reminds patients to take inhalations and displays information on medical usage trends. Supported by AI-embedded algorithms, the app learns about patient's symptoms and medication use and adapts the advice accordingly. The company also offers a portal for healthcare providers (HCPs) to monitor and obtain oversight of the generated data.

Even further beyond regular health goes *MEDRhythms*. The company's product portfolio (fig. 5), currently in clinical development, primarily targets neurological diseases and symptoms (Multiple Sclerosis, Parkinson's and Alzheimer's Disease, motion problems in chronic stroke patients), combining hardware (headphones, digital sensors), AI-supported software and music to provide Rhythmic Auditory Stimulation (RAS) for entrainment.

The solution prevents the patients from falling into harmful motional habits and thus improves neurological and motor outcomes. Patients wear motion sensors on their shoes, which collect gait parameters and send feedback to a mobile app. An AI-supported algorithm embedded in the app processes the data and adapts the music played on the patient's headphones. Via the music, the application stimulates the neural circuitry of entrainment and engages a patient's motor system, improving functional outcomes such as walking rhythm [8].

The German start-up *Dopavision,* with their product *MyopiaX* (fig. 6) offers a DTx in form of a Virtual Reality (VR) game that involves a smartphone application, a VR headset, and a Bluetooth controller [9]. *MyopiaX* is indicated to slow the progression of myopia in children and adolescents which is primarily caused by problems with dopamine signaling in the eye.

Inhibited dopamine release in the retina during growth can result in elongation of the eyeball, causing images to focus in front of the retina rather than on the retina. Via scientifically developed and validated light stimuli that activate and excite a network of photosensitive cells in the retina, the dopamine production can be modulated and enhanced, thus controlling the progression of myopia, and improving the vision of the children. The light stimulus effectively activates the signaling cascade from light exposure to dopa-

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Company	HW/SW*	Location	Employees	Revenues p.a.	Net income	Funding
Propeller Health	HW + SW	Madison, US	~116	~$24.6 m	-	**$69.9 m**

Overview on Propeller's Service/Product Portfolio

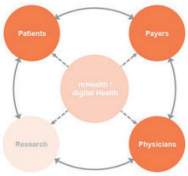
General Offering

Propeller Health aims to empower people to manage their respiratory disease self-dependently at home **via smart sensors and digital monitoring apps**, supported by algorithms interpreting collected data

Products

- Sensors for digital inhalers (medical devices)
- Propeller app
- AI-based analytical software

Benefits & key stakeholders profiting from Propeller's portfolio



- **Improving health outcomes** via continuous monitoring of biomarkers through sensors
- Enhancing **clinical decision making** via **advanced analytics** to interpret the data
- Increasing the **quality of life for the patients** by supporting the patient to manage their conditions self-dependently with support by their healthcare provider

* HW = Hardware; SW = Software

Figure 4: Propeller Health offers smart sensors for inhalers that measure inhaler usage and biomarkers (Source: stradoo GmbH, picture: Propeller Health).

Company	HW/SW*	Location	Employees	Revenues p.a.	Net income	Funding
MEDRhythms	HW + SW	Portland, US	~43	~$5.4 m	-	**$58.8 m**

Overview on MEDRhythms Service/Product Portfolio

General Offering

MEDRhythms is currently developing **Rhythmic Auditory Stimulation (RAS) technology** based on sensors & software algorithms to **measure & improve** walking speed as well as rhythm for the treatment of **multiple diseases**

Products (extract)

- Cardiology: MR-001 – Chronic Stroke
- Neurology: MR-004 – Multiple Sclerosis, MR-005 – Parkinson's Disease, MR-008 – Alzheimer's Disease/Cognitive Impairment

Benefits & key stakeholders profiting from MEDRHythms's Portfolio

- Offering **a clinically valid alternative for therapy,** backed with **strong scientific evidence**
- Reducing burden for **patients & physicians via automatic treatment adjustments by AI**
- Prevent **extensive invasive therapy & surgery**, effectively reducing **overall health care cost** for the patient and/or payer

* HW = Hardware; SW = Software

Figure 5: MEDRhythms is a leader in sensor-based healthcare applications for treatment in neurological diseases (Source: stradoo GmbH, picture: MEDRhythms).

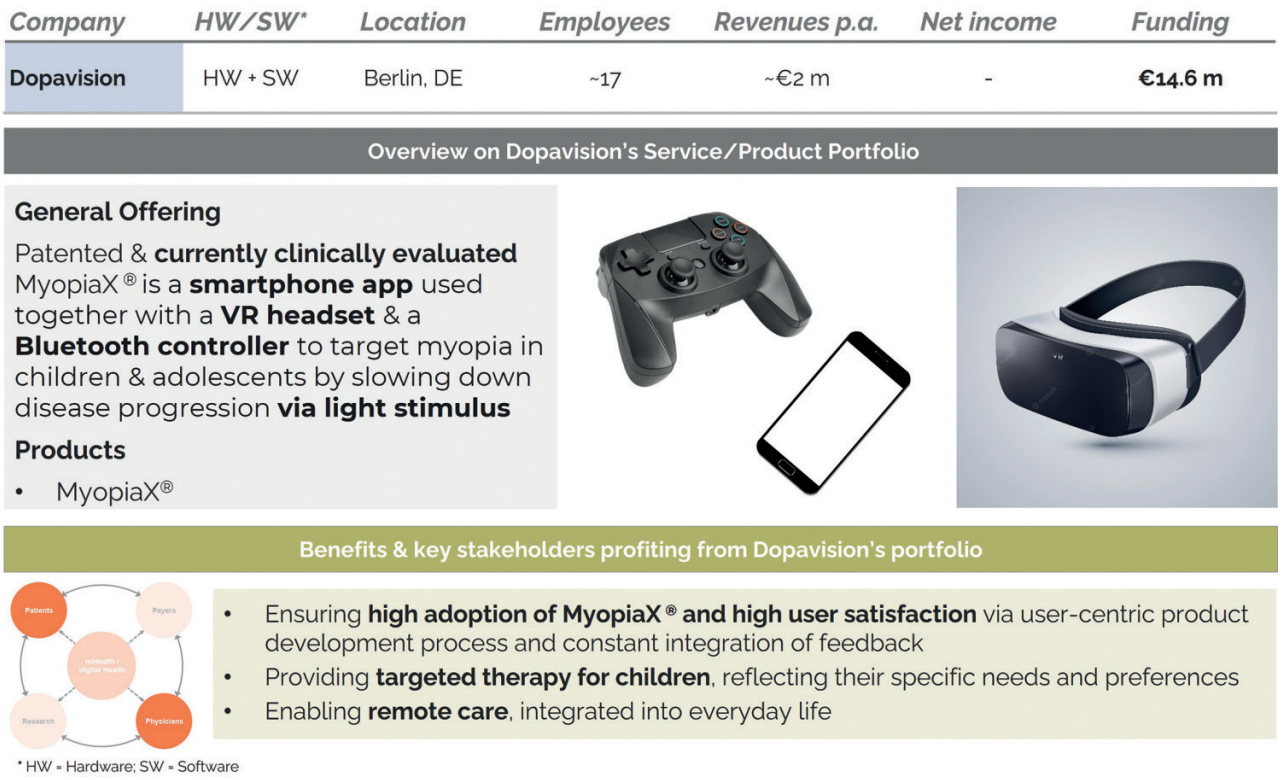


Figure 6: Dopavision leverages VR for light stimuli to treat myopia in children (Source: stradoo GmbH, picture: Dopavision).

mine production and release by dopaminergic amacrine cells. Like most DTx, the treatment by *Dopavision* is non-invasive.

Besides, there are plenty of other innovative DTx solutions. *EndeavorRx* developed by *Akili*, for instance, is a video game indicated to treat primarily inattentive or combined-type attention deficit hyperactivity disorder (ADHD) in children between 8 and 12. It is currently also under investigation for systemic lupus erythematosus (SLE) in adults and for the treatment of "brain fog" in COVID-19 patients. While coaching tools and patient support programs have been introduced to the market quite long ago, this is the first video game treatment approved by the US Food and Drug Administration (approval in June 2020) [10]. Evidence has shown that *EndeavorRx* improves ADHD-related impairments after 2 months of treatment with no serious adverse events (fig. 7) [11].

A groundbreaking improvement of available, technologically supported therapies was the recent introduction of *MiniMed*™ by *Medtronic* or *Control-IQ* as Advanced Hybrid Closed Loop (AHCL) systems for diabetes. Chronic diseases like diabetes require constant attention with measurements on a daily to hourly basis, resulting in a high burden for patients to manage their disease. Over the years, many digital innovations have proven to be useful interventions to facilitate parts of the process – from new insulin pumps to continuous glucose monitoring systems via biosensors and digital patient education programs. Smart closed-loop technologies or so-called artificial pancreas tools like *MiniMed* and AHCLs in general combine all these tools. Besides, they also analyze collected data to deliver insulin targeted to the patient's needs. While whole-scope AHCLs like *Control-IQ* imitate a human pancreas fully by automatically adjusting the insulin injections based on the current glucose levels (boluses), the *MiniMed* system – including the *MiniMed 670G or 780G* insulin pump and the *Ascensia Diabetes Care Contour® NEXT LINK* glucose meter – integrates and connects delivery of basal insulin to continuous monitoring of glucose levels in the body (fig. 8) [12]. Here, a manual intervention by the patient is still required to adjust the amount of insulin delivered. The team is currently working on removing this manual step in the process and on thereby providing a fully integrated AHCL system.

Beside these innovative treatment solutions, there are many digital health apps like *Regulora, leva, Virta, Sleepio or Happify* which focus on digital patient education, coaching and remote patient support. An overview of all evaluated DTx can be seen in fig. 9.

The Value of Digital Solutions for Healthcare is Diversifying

In conclusion, looking at the introduction of new products and services like DTx and DDx, it is clearly visible that healthcare and especially all related stakeholders can benefit massively from the digital transformation. Having said that, most of the total potential of digital health is not even exploited yet, as data shows. Accord-

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Company	HW/SW*	Location	Employees	Revenues p.a.	Net income	Funding
Akili	SW	Boston, US	~122	~$10.7 m	-	**$301.1 m**

Overview on Akili's Service/Product Portfolio

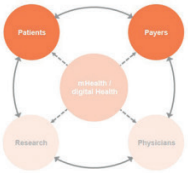
General Offering

With its digital video gaming prescription therapy (DTx), Akili is tackling the **root of cognitive impairment**. The interactive setting can be personalized to individual needs. It has been developed jointly by cognitive neuroscientists & game designers to **deliver sensory and motor stimuli** to target and activate **specific cognitive neural systems** in the brain.

Products

- EndeavorRx®, (in pipeline: cognitive dysfunction, Autism, etc.)

Benefits & key stakeholders profiting from Akili's portfolio



- Providing **targeted therapy for children**, reflecting their specific needs & preferences
- Ensuring **high adoption of EndeavorRx® and high user satisfaction** via user-centric product development processes and constant integration of feedback
- **Limiting therapy costs** due to avoidance of less beneficial medication

* HW = Hardware; SW = Software

Figure 7: Akili's virtual gaming solution provides new opportunities for treating ADHD in children (Source: stradoo GmbH, pictures: EndeavorRx).

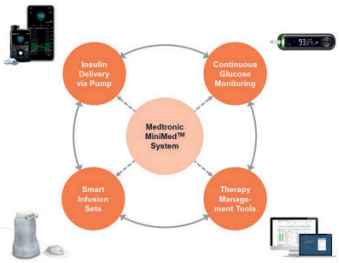
	Medtronic MiniMed system	Control-IQ
Schematic overview of the solution		
Continuous glucose monitoring	✓	✓
AI-based data analysis	✓	✓
Automated insulin injection	✓	✓
Smart dosage adaptation	✗	✓

Figure 8: While Control-IQ is a fully automated system, Medtronic's MiniMed requires manual intervention for dosage adaptation (Source: stradoo GmbH, picture: Medtronic and Control-IQ).

ing to market reports by Grand View Research, from 2022 to 2030 a Compound Annual Growth Rate (CAGR) of 26.1 % is expected globally for DTx only [3]. Growth in the past was partially hindered, as the reimbursement decision was often not clear for digital health tools in many countries as there was no general regulation.

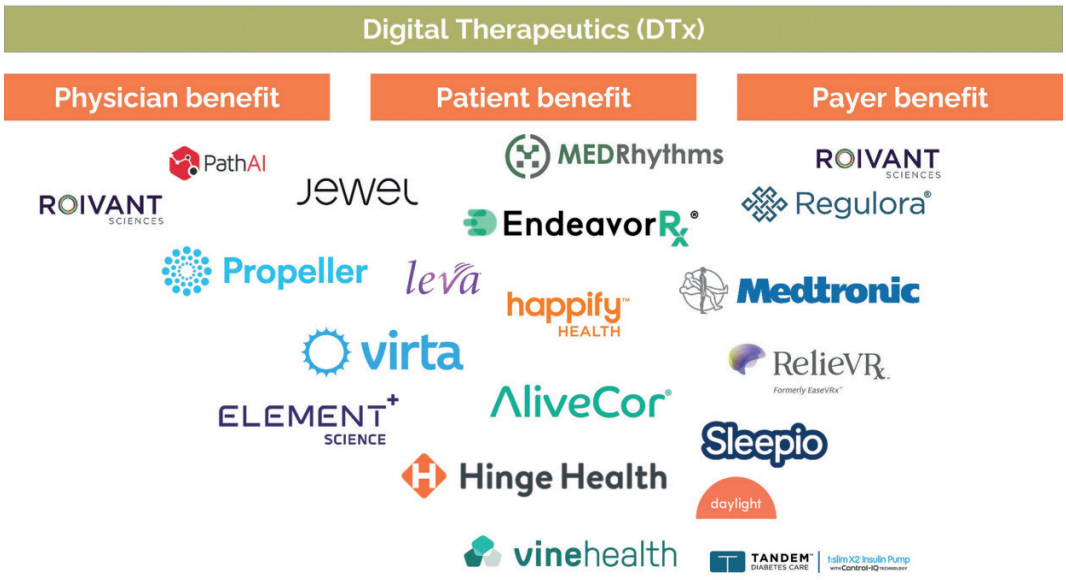


Figure 9: Overview of anallyzed DTx.

In this article, the authors have introduced several highly interesting examples of DTx and digital care solutions that are already existing and have already contributed to the digital transformation in healthcare. In general, recent innovations and upcoming launches display a clear picture of a diversifying value generation of DTx tools. On the one hand, solutions like *Dopavision* or *EndeavorRx* provide clinical benefits to patients via digital elements and software, for which previously no effective treatment was available.

On the other hand, fully integrated, evidence-driven DTx such as *MEDRhythms* or *MiniMed* support in automating care with no further need for consultation of practitioners, while also collecting essential data on a patient's health condition at the same time. Adding that positive effect of less frequent on-site care to the reduced medication need and the products' clinical advantages not only results in better overall care because of the digital transformation of healthcare, but also significantly reduces total healthcare spending globally. Overall, it can be seen that DTx are a vital factor for evolving the industry into a more digital and data-driven field.

Part 2 of this series will be published in one of the following editions.

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All links were accessed on 14/09/2022 at last.

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Digital Solutions and the Role of AI in Healthcare

Part 2: The Role of AI and Big Data in Pharmaceutical R&D*)

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Abstract

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Zusammenfassung

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Aufbauend auf einer vorangegangenen Publikation zu „mHealth" [1] bewerten die Autoren in einer Serie von 2 Artikeln die aktuelle Landschaft der KI- und Digitalisierungstools, deren Nutzen für verschiedene Stakeholder sowie Herausforderungen für Unternehmen bei der Entwicklung und Vermarktung.

Introduction

In the first of this series of 2 articles on "Digital Solutions and the Role of AI in Healthcare", the authors extensively described the digital transformation in healthcare from a Digital Therapeutics (DTx) perspective. Yet, the recent rise of digital applications in the industry is not limited to the development of DTx tools and their related augmentation of commercial operations. There are many more dimensions to this development, starting as early as in (pre-)clinical Research and Development (R&D).

As already indicated in the abovementioned first article, digital transformation goes far beyond simply transforming analogue into digital or offering new digital tools, as it also implies an adaptation of the mindset with a stronger focus on evidence-based decision-making, the use of Big Data and automation of non-value-adding tasks. This is especially true in R&D where the industry needs to answer the question of how to cure a certain disease, which could not be treated suffiently before, by perso-

*) Part 1 of this series was published in Pharm. Ind. 84, Nr. 12, 1451–1458 (2022).

nalizing medicine. For this, the impact of individual genetic conditions on disease progression and treatment effectiveness needs to be evaluated, leading to substantial efforts required for data analytics. In total, there are over 7 000 genetically caused human disorders triggered by mutations in nearly 4 600 genes, for many of which sufficient structural data on clinical evidence has not yet been collected and evaluated [1]. Traditional drug discovery or drug design processes have reached their limitations in this context and completely new and divergent processes – using Big Data and AI-supported data analytics – are required.

As a result, many of the industry's research processes today have already adapted AI-based tools, enabling a much deeper understanding of the human biology and the nature of diseases.

Meanwhile, also development is undergoing a major change with extensive usage of Big Data and self-learning algorithms. Real World Evidence (RWE) is becoming the new paradigm in clinical development.

In this second of 2 publications on "Digital Solutions and the Role of AI in Healthcare", the authors will provide a deep-dive into the use of AI and Big Data as levers for digital transformation in healthcare R&D. The authors will also particularly address challenges that arise with the extended use of AI and Big Data and will provide solutions for players to deal with these challenges.

Big Data & AI Breaking Traditional Frontiers of Pharmaceutical Research

With returns on R&D expenditure continuously decreasing, a disruptive paradigm shift to modify or expand the traditional business model of pharma R&D, partially by simply digitizing processes and partially by making use of Big Data and AI-driven tools, has been initiated. There are many use cases for AI across multiple processes early in the pharmaceutical value chain. Often, tools can help to better analyze and identify patterns in large, complex data sets. Computational power and AI play a key role. AI and machine learning (ML) technologies have been integrated into many digital platforms transforming the way decisions in research are made. Public and private institutions are investing in better infrastructure for data management and processing. As an example, the European Commission recently launched the EU4Health program, aiming to raise 5.3 bn euros to strengthen the resilience of EU healthcare systems and their data as well as to promote AI-driven medical innovation and digital transformation [2].

The deep learning capacities of AI-supported R&D tools enable systems to detect characteristics and patterns based on historic data unrecognizable to the human eye. Via computational experiments, researchers investigate and simulate disease mechanisms that are not yet fully understood, increasing the probability of success in drug discovery. For instance, algorithms investigate the potential of drug candidates in a given area of application using in-silico based mathematical and statistical models. Such algorithms for "de novo drug design" evaluate billions of candidates in days and predict the impact of a certain candidate on the target cells [3]. Meanwhile, manual work would require lengthy laboratory experiments with a throughput of only up to 10 000 compounds evaluated in a timeframe of roughly 5 years [4]. As a result, the drug discovery and pre-clinical study phase in pharmaceutical R&D can be reduced from several years to less than 18 months, while simultaneously increasing the number of candidate compounds evaluated [5].

Not only the quantity but also the quality of research in healthcare can be improved via digital applications. While manual measurement, documentation, and evaluation of specific biomarker data can be faulty, computational tools apply constant standards in all environments and fulfill the work much more accurately without the need for real-world sampling performed by humans. When understanding correlations between compounds and related clinical outcomes early, high-potential drug candidates can be identified and followed-up on throughout the development process. Thus, AI-supported drug discovery has the potential of saving pharmaceutical companies hundreds of millions of dollars.

One of the most exciting assets in the digital pharma R&D market is *Schrödinger's* research platform. The company has only very recently closed a deal worth 425 m US dollars in milestone payments with pharma giant Eli Lilly. Through its unique setup and functionalities (fig. 1), it integrates stand-alone solutions for predictive physics-based modeling with data analytics and digital collaboration tools, enabling rapid exploration of potential drug candidate formulations in the chemical space. The platform helps to predict molecular behavior based on sophisticated mathematical models, e.g., binding activity of components with a target protein. Equipped with a constantly learning algorithm, *Schrödinger* analyzes as-is data and derives forecasts from evaluating data trends.

These forecasts are later used for modulation purposes to predict clinical outcomes in a virtual setting. As part of this process, ML techniques continuously improve the algorithm's ability to predict the unknown. On its platform, *Schrödinger* is both developing its own pipeline as well as providing access for other market partici-

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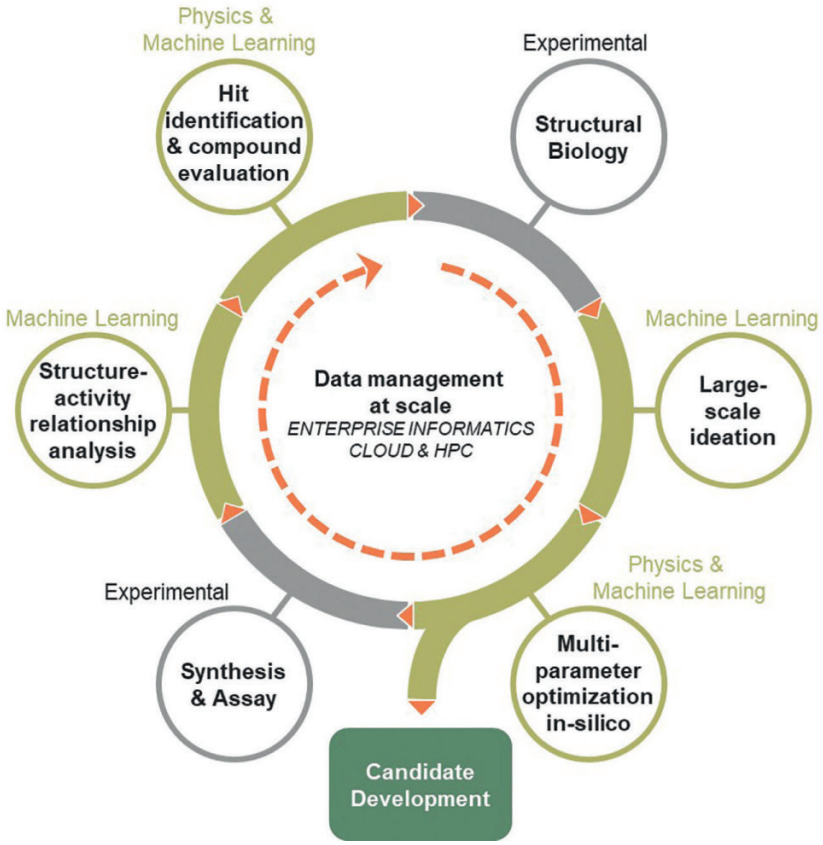

Figure 1: Schrödinger's platform massively influences the way (pre-)clinical research for candidate development is conducted (source: stradoo GmbH, Schrödinger).

pants to leverage *Schrödinger's* technology.

Berg Health is taking a different approach to enhance pre-clinical and clinical research by deriving potential drug targets and candidates for individual patiens not only from clinical outcomes but also from human biological profiles. Often, insights drawn from the use of the solution are first-in-class molecular entities. The company's solution contains 2 sets of AI-based platforms that can be leveraged for drug candidate and biomarker identification as well as for patient stratification, especially when no clear research hypothesis is available. In a first step, in vitro cell cultures are produced to mimic diseased and healthy cell environments. From these cultures, samples containing information on lipids, metabolites, proteins, and genes are taken and OMICS data from various biofluids are measured. Based on the obtained biological data, *Berg*'s *Interrogative Biology* ® platform employs several high-throughput technologies for in-silico molecular profiling and modelling, incorporating clinical information from electronic medical records (EMRs) (fig. 2).

These molecular profiles are then fed through the second analytical platform, *bAIcis* ®. The tool, which is based on Bayesian models, creates cause-and-effect networks for investigated diseases and the respective biomarkers as well as a map of healthy and diseased cells in order to identify discriminators, drivers, and risk factors of the disease. These networks can then be used to develop drug candidates targeting the drivers of the disease or to define predictive and prognostic biomarkers. Like *Schrödinger, Berg Health* is both developing their own product pipeline as well as enabling access for other drug developers in the form of strategic cooperations.

DeepMind's AlphaFold solution aims to solve one of the most fundamental and challenging problems of pharmaceutical research and drug discovery: determining the structural biology of potentially targetable proteins in the human body. In 1961, American biochemist Christian B. Anfinsen first discovered the relationship between the sequence of amino acids within a given protein and its 3D structure. Other researchers have made progress in understanding the role of each amino acid in general. However, up until today, it is still unknown for most proteins how the two-dimensional sequence induces its structure and what that final structure looks like. This is mainly due to the impact of attraction and repulsion forces causing the string of involved amino acids to fold in seemingly spontaneous ways. Finding adequate ways to solve this problem significantly enhances the possibilities for researchers to develop suitable drug candidates.

With rational drug design on the rise in the recent years, the importance of understanding the protein target structure has massively increased even further. In the past, time-consuming experiments were required, which could take several years to yield results for each individual protein. Today, *AlphaFold* accelerates scientific discovery by leveraging computational models to build 3D protein structures in seconds. The company's solution analyses the underlying amino acid sequence and predicts the structure based on data on the expected impact of individual amino acids on a protein's shape, derived from fully developed protein models. In essence, *AlphaFold* creates the foundation for all remaining in-silico & AI-based tools supporting pharmaceutical research. Due to its significant importance for the pharma-

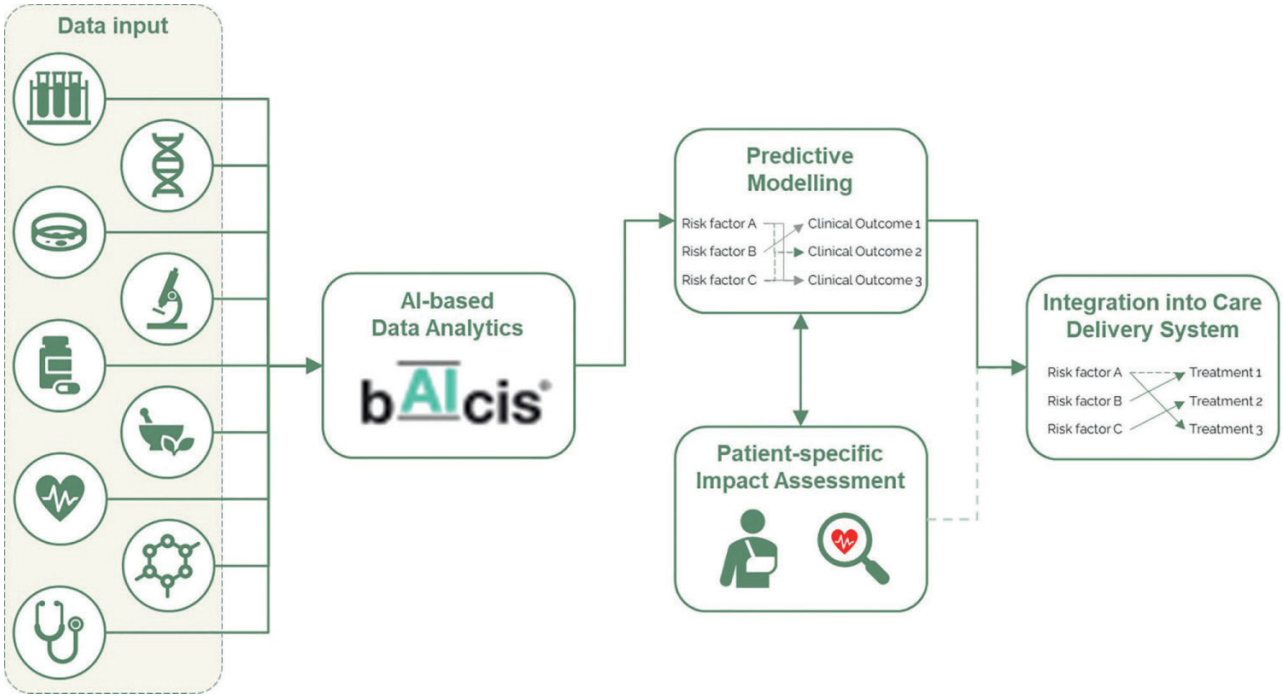

Figure 2: bAIcis enables researchers to predict clinical outcomes of treatment with investigated drug candidates based on multi-sourced data models (source: stradoo GmbH, Berg Health).

ceutical industry, the Google-owned company provided its protein structure prediction algorithm as open-source software in 2021, with the database now containing 200M+ protein structures across different organisms.

Using a very different approach, the unique selling proposition (USP) of the *Syntegra Medical Mind* platform (fig. 3) is the generation of artificial records. *Syntegra,* just like its competitor *Owkin*, is addressing the pressing data security issue in healthcare. Based on real-world samples, the application reads and analyses the underlying statistical distribution of several types of structured and unstructured healthcare data (EHR, genomics, etc.) in an anonymized way. An embedded algorithm with machine learning capabilities reflects on this data input in form of a temporal sequence of medical events and generates completely new patient records derived from the learned distributions, with advanced language recognition models constituting/providing the underlying technology.

The format of the resulting synthetic data matches the format of the original data. Furthermore, all statistical properties are maintained, even rare cohorts and outliers. Creating synthetic patient records enables pharmaceutical companies to undertake their research effort without the need to retain or continuously access any actual patient information. Once an entire dataset is re-created, the algorithm self-dependently checks the quality of the results and thus learns from deviations within the originator dataset. Thereby, the application continuously improves its functionality with every dataset it works with.

In addition to the examples listed above, there are multiple other companies with similar business models who are still in the build-up phase of AI-driven algorithms to support research. One of them is *AICure*, who have developed the *AiCure platform* which is characterized by the dynamic bundling of disparate data sources into one database to correlate previously unrelated endpoints and translate them into meaningful, actionable insights for large-scale research projects. Not to forget *Evidation's App*, a tool that continuously tracks health parameters and connects individuals and healthcare companies for research purposes. It encourages patients to participate in projects and studies to design, test, and deploy digital health programs on the one hand and functions as a source for real-world data for healthcare companies on the other. The near-term evolution of companies such as *Cellarity*, *Deep Genomics*, *Komodo Health, Atomwise*, *Path AI,* and many others, which are all aiming to digitally enhance pharmaceutical research, will equally be interesting to follow closely.

Digital Transformation Solves Problems in Clinical Development

Similar to processes in early research, also clinical development is currently undergoing a major change with extensive usage of Big Data and self-learning algorithms.

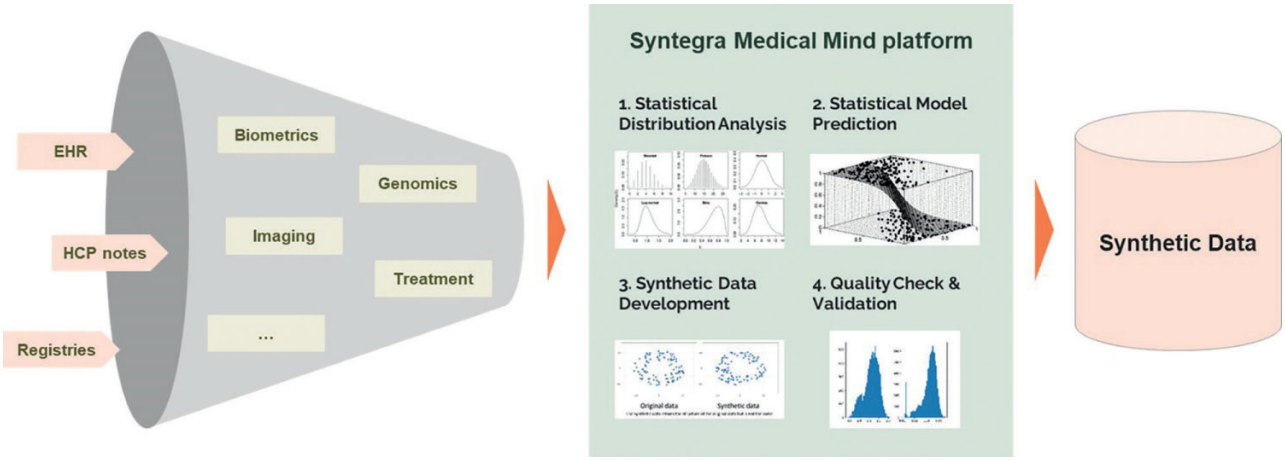

Figure 3: The USP of Syntegra's software solution for R&D is the possibility of synthetic data generation (source: stradoo GmbH).

RWE is becoming the new paradigm in clinical development. Numberless digital platforms are being built to facilitate decentralized processing and analytics of Big Data. Improved data analytics based on AI models support developing companies in designing in-silico clinical trials and in providing high-quality clinical decision support (CDS) to enrolled clinical centers. In the modern ages, AI-integrated technologies will replace older control-arm trial approaches and will resolve problems encountered in many areas like trial formulation design, patient enrollment, and quality control. In the following, some innovative companies which have the potential to re-shape the industry shall be introduced.

Medable, for instance, a company last valued at 2.1 billion US dollars in Oct 2022 provides Software-as-a-Service (SaaS) solutions to solve common issues in decentralized clinical trials in the cloud (fig. 4). In essence, the company is offering a platform for researchers, startups, pharmaceutical companies, payers, and academia to centrally manage and administer clinical trial data generated in multiple clinical sites across the globe. The platform can be used to create and provide secure, compliant healthcare applications in the cloud. These applications are hosted directly on the platform. To name exemplary use cases, *Medable's* solution may contain applications that support patient engagement in the clinical context, targeted to the client's need with access for all involved stakeholders (e.g., local clinics). Alternatively, personal health information may be stored on the *Medable* platform in a secure environment in the cloud without violating the US Health Insurance Portability and Accountability Act (HIPAA) and other compliance regulations [6].

Generally, the company aims to connect multiple patient data sources relevant for clinical development purposes by storing the respective data in a platform accessible to all involved stakeholders in real-time. Meanwhile, the tool also safely protects the raw data from unauthorized use. Via their solution, *Medable* intends to simplify the trial experience by offering an intuitive data experience for all trial stakeholders. Although the platform itself is not based on any self-learning algorithms, many of the add-on tools leverage AI for individual tasks. These primarily include solutions to convert patient data from multiple sources into one data set. *Reify Health* follows a similar business model. Via their cloud-based software solutions like *StudyTeam* (a technology platform for optimizing patient recruitment and enrollment) and *CareAccess* (a support application to conduct decentralized trials at scale), the company aims to break up existing paradigms on how clinical trials are run.

When talking about software providers for smart data management solutions in pharma R&D, *VeevaSystems* needs to be mentioned as one of the most impactful players in the industry. The company's solutions have been implemented in almost all Big Pharma organizations across the world, ranging from customer relationship management (CRM) systems for commercial purposes to quality management, regulatory intelligence, marketing material management, drug application management, and clinical operations tools for R&D and Medical departments. Through their targeted expertise in the pharmaceutical industry, *Veeva* enables users to streamline workflows and processes involving multiple R&D functions. Especially with regards to drug application submissions, the company's tools also leverage the power of AI. During the creation of dossiers, the software is capable of reading unstructured data (e.g., clinical trial result reports), deriving the key messages, and converting those into usable text or graphical ele-

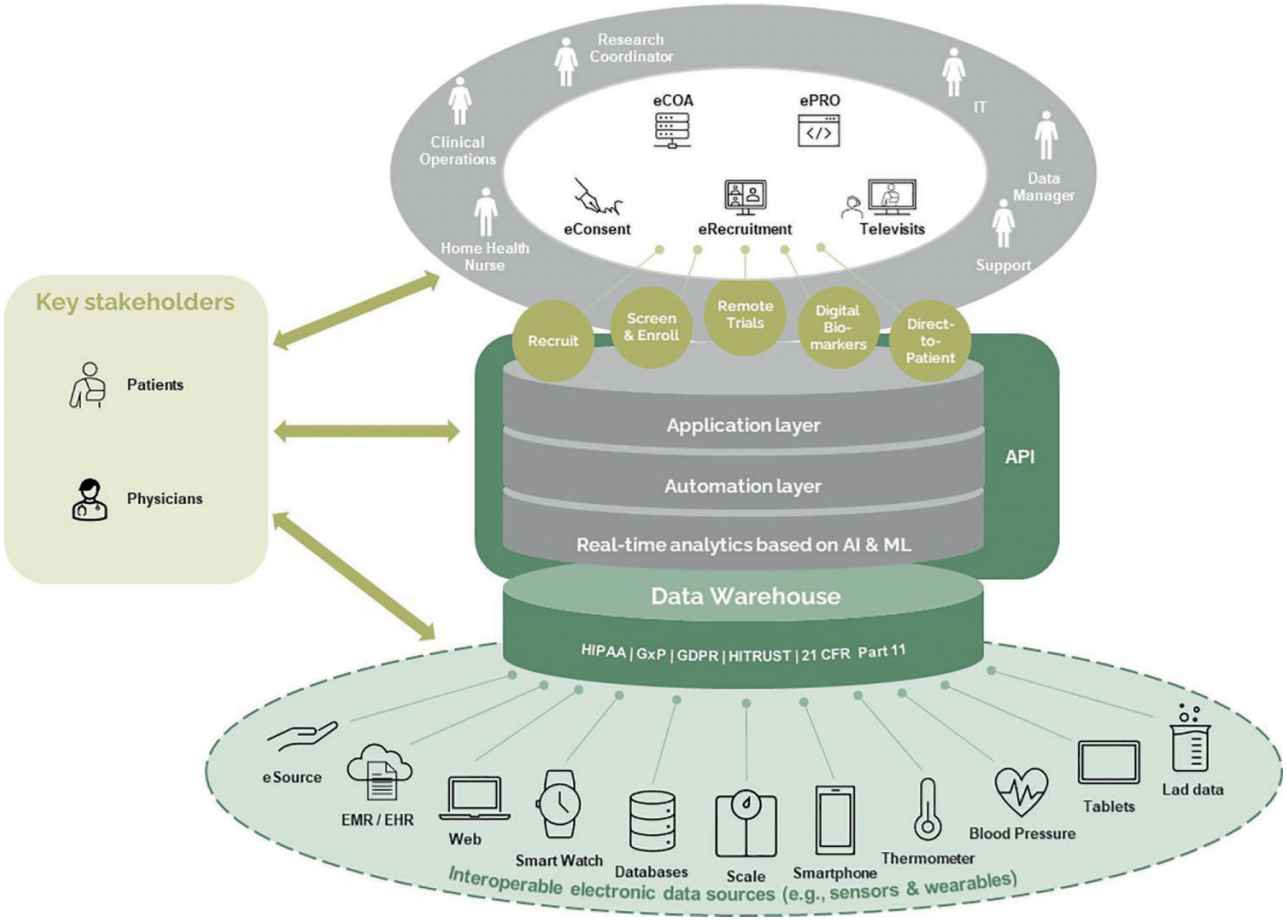

Figure 4: Medable provides a holistic environment for data management in clinical development (source: stradoo GmbH; innovationsoftheworld.com).

ments for a standardized dossier structure. However, most companies have implemented *Veeva* for its simplified data management in R&D (fig. 5).

Benchling, a US-based company last valued at 6.1 billion US dollars in Nov 2021 is also active in this segment providing an informatics platform to centralize and standardize all R&D data.

GNS Healthcare's product portfolio builds upon the increasing availability of multi-OMICS and clinical data to create virtual patients (digital twins) for clinical development. Based on historic, real-world training data on patient characteristics, the company's algorithm generates randomized, in-silico representations (*Gemini*) of patient records, which reflect multi-folded patient characteristics (incl. complex genetic and molecular mechanisms and pathways). For that, *GNS Healthcare* leverages reversely-engineered causal networks connecting gene expressions, metabolites, and clinical data.

Due to their artificial nature, digital twins can be used to investigate and simulate entire disease models even at an individual patient-phenotype level without causing data privacy issues. Such disease models based on a completely virtual study population may even include information about disease progression and drug response depending on the biometric profile of the respective patient. Clients using *GNS Healthcare's* technology are capable of discovering novel, personalized drug targets without the need for extensive clinical studies. *GNS Healthcare* can also simulate entire clinical trials using these *Gemini*.

The company *Unlearn* follows a similar business model, organizing small clinical trials with digital twins, addressing recruiting hurdles and constraints (e.g., number of available patients, ethical limitations to include).

However, digital twins are not the only solution to the problem. Software providers like *Deep 6 AI* and *Trials.ai* support healthcare companies in regular site selection and patient finding for real-world clinical trials, especially in specialty care. Similar to the solutions of *GNS Healthcare* and *Unlearn*, their precision research tools leverage registries and other sources of real-world data (e.g., patient records) to generate representative, sufficiently sized populations for clinical trials, customized to the research question of the client. The software screens and mines mil-

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Figure 5: Veeva's clinical solution provides a network for all stakeholders to collaboratively optimize clinical operations (source: stradoo GmbH; pictures: Veeva Systems).

lions of datasets, mapping structured and unstructured data to gain a clear understanding of each individual potential participant, all of which is done by AI algorithms in real-time so that no extensive pre-planning of study populations for clinical trials is required. Already today, *Deep 6 AI* and *Trials.ai* are offering solutions to problems many stakeholders are facing in clinical development.

Apart from such established companies, there are numberless early-stage start-ups like *Castor EDC*, *Circuit Clinical*, *DQueST*, *Flywheel*, or *Overwatch* which are pushing into the market. Although showing promising potential, it is still too early to evaluate their impact on global clinical operations, which is why they will not be presented in further detail in this article. An extensive list of companies offering AI-based solutions in healthcare, partially with focus on R&D, can be found in the graphic below (fig. 6) [7].

Overall, AI in R&D Can Offer Great Potential to Re-shape The Market if Challenges Can Be Overcome

In conclusion, the use of AI in R&D clearly provides great benefits to the healthcare industry. But again, similar to DTx, the full potential of technologies has not yet been exploited so far.

One of the reasons for the lack of digital maturity in the industry is that until recently, providers struggled to find solutions to comply with the regulatory and legal requirements, while developing new digital health applications. Often, such tools require to collect, to process, and to store health data. Meanwhile, authorities are primarily concerned about data security and data protection, given that health information involves a lot of sensitive and personal data. This has resulted in a number of legislations such as the EU General Data Protection Regulation (GDPR) which applies independently of pharma or healthcare environments and is binding for all companies across industries. These legislations restrict the space in which data processing tools can operate. Especially sharing the data among researchers is difficult, as it requires the individual consent of all patients represented in a specific data set in most cases. Therefore, despite having the technological capabilities of building up large data platforms for R&D, limited benefit of such tools has yet been achieved. In the past, providers often could not find enough data donors for the platform to become meaningful. In the very recent past first data platforms, such as OPTIMA or PIONEER, have increased their efforts in anonymizing and de-personalizing data for common use. Nevertheless, there is still a long way to go to remove all skepticism and hesitation with regards to data privacy.

On another note, healthcare authorities are still hesitant to approve medications for which clinical evidence was generated with the help of in-silico clinical trial control arms. Although this attitude is currently evolving, as the introduction of the Digital Health Application (DiGa) pathway in Germany in 2019 and a few recent approvals by the US Food and Drug Administration (FDA) have shown, in-silico is not expected to become customary practice in the next few years. Players in the healthcare industry will first have to increase the confidence level in in-silico data.

For applications of AI in R&D, the quality of collected data is also an issue that is preventing broader application of innovative AI-re-

Figure 6: Landscape of AI solutions in healthcare and especially in healthcare R&D contains many more tools that are worth analyzing in more detail (source: DataRoot Labs).

lated tools. Tech start-ups work on improving their algorithms in terms of processing structured and unstructured data.

Despite these challenges, new, advanced technologies have been developed to not only diversify treatment opportunities for patients and healthcare professionals (HCPs), but also support players in managing the massive amounts of data that are available in the market. Through these additional capabilities more evidence-driven and target-oriented decisions can be made. Researchers are enabled to investigate the biological, chemical, and physical structure of the human body on a much deeper and more sophisticated level. Computational experiments allow for comparison of healthy and diseased cells on a large scale over time. AI-driven algorithms combine the results of these experiments with real-world Big Data to derive meaningful conclusions for drug development. This not only increases the likelihood of successful product development. It also ensures that a new medication in complex therapeutic areas is personalized to the needs of different patient groups. The same holds true for clinical decision support based on real-world data models.

If not already the case, Life Sciences and healthcare companies are inclined to be open to this change in order to utilize innovative approaches for their own benefits. Building up capabilities internally or via strategic partnerships certainly helps!

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