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Review Article

Digital Therapeutics-What they are, what they will be

Giuseppe Recchia[1,2], Daniela Maria Capuano[3], Neeraj Mistri[4,5] and Roberto Verna[6,7]*

[1]*DaVinci Digital Therapeutics, Milan, Italy*

[2]*Fondazione Smith Kline, Verona, Italy*

[3]*World Association of Societies of Pathology and Laboratory Medicine, IL, USA*

[4]*Department of International Health, Georgetown University, Washington D.C., USA*

[5]*Hepatitis Business Solutions, Washington D.C., USA*

[6]*World Association of Societies of Pathology and Laboratory Medicine IL, USA*

[7]*Department of Experimental Medicine, Sapienza University of Rome, Italy*

***Corresponding Author:** Roberto Verna, World Association of Societies of Pathology and Laboratory Medicine IL, USA and Department of Experimental Medicine, Sapienza University of Rome, Italy.

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Abstract

The convergence of health and digital technology has led to the development of Digital Health, a broad category of digital health technologies aimed at improving human health and well-being, optimising the quality and safety of care, increasing access to treatment, making health services more efficient and reducing overall health care costs. As a subset of Digital Health, Digital Therapeutics are an emerging class of medicines that deliver evidence-based therapeutic interventions. Similar to drugs, Digital Therapeutics consist of active ingredients and excipients. While the "digital active ingredient" is primarily responsible for the clinical outcome, "digital excipients" (virtual assistant, reminders, reward systems etc) are necessary to ensure the best user experience to the patient and to allow the prolonged use of the therapy. In order to allow interaction with patients, Digital Therapeutics may take different patient facing digital form, as smartphone applications, videogame, virtual reality programs and others. The research and development process of Digital Therapeutics consists of software development, pilot and full clinical development. The confirmatory randomized controlled clinical trials are critical to generate evidence of benefit for regulatory approval, reimbursement and prescription. Digital Therapeutics have the potential to transform the management of chronic diseases and to represent the first therapeutic option offered by each doctor to each of their patients with chronic disease and dependence. Since these expectations may or may not be fulfilled and potential benefits may be accompanied by unintended and/or adverse effects, the introduction, implementation, use and funding of Digital Therapeutics should be carefully evaluated and monitored.

Keywords: Digital; Therapeutics

Introduction

A combination of socio-economic growth, technological advances, evolving disease epidemiology, and demographic transitions is expected to lead to a significant change in healthcare. As a consequence of aging, healthcare costs are estimated to increase from an aggregate US$8.4 trillion in 2015 to US$18.3 trillion by 2030 [1]. Chronic disease - already the major public health emergency in developed countries - could result in US$47 trillion in lost pro-

ductivity in the same period and, the need to manage the pressure resulting from these increasing costs has created a demand for increased efficiency and outcome-based measures in global healthcare systems [1]. This scenario offers an unprecedented opportunity to address this need by enabling innovative and cost-effective digital tools and devices. Consumers have become accustomed to comparing products, services, and prices online and now they expect similar conveniences in other areas of their lives, especially in health and healthcare. In the last years, health awareness has significantly increased in people and they want to take control of their health. To seize the opportunities of this evolution, the consumer goods industry has developed a range of lifestyle products and related services to promote and support a healthier lifestyle, such as fitness devices, monitoring of physiological parameters, mental health management. These products and related services are converging with traditional healthcare, leading to a digital transformation of health and healthcare that is expected to be completed during the first years of the '20s [2]. This will ultimately change how healthcare is delivered, accessed, perceived, and reimbursed [3]. Digital health, the application of new technology in a healthcare setting, is changing the life sciences and healthcare industry from being in the hands of the practitioners to being in the hands of the patient. Since the term is used as an umbrella for many digital health technologies, it is sometimes perceived as vague and potentially confounding. The digital health field is not yet served by a standard lexicon, and the many disciplines that comprise digital health are often separated by a common language [4]. Recently a categorization framework that goes beyond the existing definitions of digital health, digital medicine, and digital therapeutics to provide clarity with examples of products and product types has been developed and published (Table 1 and 2) [4].

	Digital Health	Digital Medicine	Digital Therapeutics
Definition	Digital health includes technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes; capture, store or transmit health data; and/or support life science and clinical operations.	Digital medicine includes evidence-based software and/or hardware products that measure and/or intervene in the service of human health.	Digital therapeutic (DTx) products deliver evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease
Clinical Evidence	Typically do not require clinical evidence.	Clinical evidence is required for all digital medicine products.	Clinical evidence and real world outcomes are required for all DTx products.
Regulatory Oversight	These products do not meet the regulatory definition of a medical device and do not require regulatory oversight	Requirements for regulatory oversight vary. Digital medicine products that are classified as medical devices require clearance or approval. Digital medicine products used as a tool to develop other drugs, devices, or medical products require regulatory acceptance by the appropriate review division.	DTx products must be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use.

Table 1: Definitions and characteristics of Digital Health, Medicine and Therapeutics [4].

	Digital Health	Digital Medicine	Digital Therapeutics
Product Examples	**Data and information capture, storage, and display** • User-facing technologies - Lifestyle apps - Fitness trackers - Nutrition apps - Medication reminder apps - Scheduling apps • Health Information Technology (HIT)4 - Electronic medical record systems - Electronic prescribing5 and order entry systems • Consumer health information - Online repositories - Personal health records - Patient portals Data and information transmission • Telehealth - Telemedicine virtual visits - Remote care programs that do not include remote monitoring • Decision support software that:6 - Presents information for independent clinician review - Does not make recommendations that the user could not find through channels other than the software • Enterprise support - Clinical trial operations and management tools - Trial management software - Trial recruitment platforms • Clinical care administration and management tools - Revenue cycle management tools - Clinical staffing management tools - Length of stay monitoring and management tools	**Measurement products** • Digital diagnostics - Software-driven connected technologies that detect or confirm the presence of a disease or condition of interest or to identify individuals with a subtype of the disease • Digital biomarkers - Digital tools that measure patient characteristics that are objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention - Includes all BEST biomarkers • Electronic clinical outcome assessments - Digital measures of how patients feel, function, or survive • Remote patient monitoring - Remote monitoring tools - Medication adherence tools - Sensor technologies that measure vitals and physiologic data • Decision support software that:7 - Relies on data inputs from medical imaging or in vitro diagnostic devices - Process or analyze this information without clinician input Measurement and intervention products • Digital companion8 - Digital component integrated with either a drug or biologic - Ingestible sensors - Connected drug delivery device - Insulin pump • Digital products that both 1) measure *and* intervene, and 2) do not require human intervention to serve primary purpose - Artificial pancreas - Pacemaker - Cochlear implant - CPAP	**Software that delivers a therapeutic intervention** Medical claims include*:* • Treat a disease Digital therapeutics that deliver a medical intervention to treat a disease. • Manage a disease Digital therapeutics that deliver a medical intervention to manage a disease. • Improve a health function Digital therapeutics that deliver a medical intervention to improve a health function and/or prevent a disease. Core principles all digital therapeutics must adhere to:9 • Prevent, manage, or treat a disease • Deliver a software-driven medical intervention • Employ design, manufacture, and quality best practices • Ensure end user engagement • Implement privacy and security protections • Apply product deployment and maintenance best practices • Conduct clinical trials and publish results • Undergo applicable regulatory reviews • Make appropriate claims • Utilize real world outcomes

Table 2: Examples of products of Digital Health, Medicine and Therapeutics [3].

Digital therapeutics

The last category, Digital Therapeutics, represents an emerging and innovative area of therapy, already available to a limited extent and with potential in terms of health not yet fully defined for the treatment of many chronic diseases and addictions in particular.

Definitions

Digital Therapeutics are therapeutic interventions indicated for a specific disease and designed to modify the behaviour of a patient in order to improve the outcomes of his disease. There are some definitions proposed by bodies or associations, among which the most used is the one proposed by the Digital Therapeutic Alliance, a global non-profit association of companies in the sector and stakeholders involved in the development of Digital Therapeutics [5]:

- Digital therapeutics deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.
- Digital therapeutics products incorporate advanced technology best practices relating to design, clinical validation, usability, and data security. They are reviewed and cleared or approved by regulatory bodies as required to support product claims regarding risk, efficacy, and intended use.
- Digital therapeutics empower patients, healthcare providers, and payers with intelligent and accessible tools for addressing a wide range of conditions through high quality, safe, and effective data-driven interventions.

It is therefore an operational definition, indicating what Digital therapeutics do rather than defining what they are. To define what they are, it is necessary to describe them in their essential elements, as therapies:

- Developed through randomized and controlled clinical trials,
- Authorised for use in clinical practice by regulatory bodies,
- Subject, where necessary for the purposes of reimbursement, to assessments of HTAs
- Reimbursed in some cases knows public health services, such as in England and Germany or by insurance companies
- Prescribed - in most cases - by the doctor, although some therapy that meets all these criteria are offered to the patient directly by the manufacturer, as in the case of over-the-counter drugs.

What differentiates Digital Therapeutics from pharmacological therapies is the nature of the active ingredient, which is the element responsible for the clinical effect. This s a chemical or protein molecule in the case of the drug, an algorithm in the case of Digital Therapeutics.

Composition

In a similar way to the drug, a Digital Therapeutic is composed of digital active ingredients and excipients that constitute the application of use by the patient (patient - facing). This distinction may be relevant in clinical development and in particular, in confirmatory clinical trials, where it is not possible to modify the digital active ingredient during its development, while within certain limits it is possible to update the excipients.

In addition to the patient- facing elements, Digital Therapeutics also include a dashboard for the physician and a delivery platform from which to download the application (Figure 1).

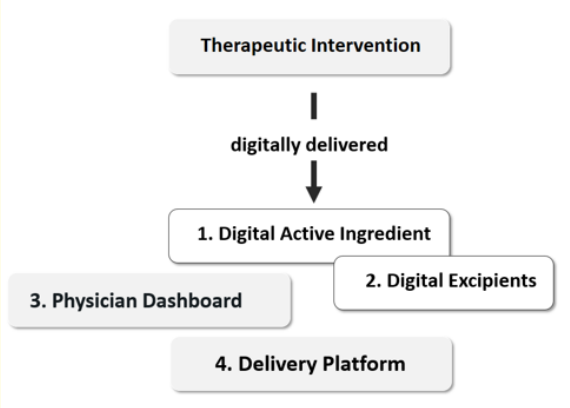

Figure 1: Composition of a Digital Therapeutic.

It is the element of therapy responsible for the clinical effect (both favourable and undesirable, as in the case of adverse reactions). It represents the entire flow of activities that are carried out from the first meeting with the patient to achieve the improvement of health outcomes: preliminary request for information on the

state of health, analysis of patient responses, provision of information to the patient on the disease and therapy, daily collection of information from the patient on his state of health, presentation to the patient of the progress of the therapy, etc..

In the development of Digital Therapeutics, a therapeutic intervention can be used as an active ingredient:

- Already available in the scientific literature (e.g. Cognitive Behavioural Therapy - CBT already undergoing clinical trials), in which case Digital Therapeutics become an alternative mode of delivery of a known treatment [6];
- Created ex-novo, using - as for example in the case of the treatment of depression - elements of different therapeutic options (CBT, Motivational Interview, Psychoeducation) elaborated on the basis of the experience of the development team (including patients, caregivers, medical specialists, family doctors).

Digital excipients

In general, the purpose of the excipient is to shape the active ingredient and promote its intake, making it as bioavailable as possible. In the case of Digital Therapeutics, the digital excipient can include the virtual assistant able to communicate in natural language with the patient, modules for patient rewarding, reminders for the assumption of the Digital Therapeutic and complementary therapies, modules to connect the patient with his doctor and other patients and more, with the aim of ensuring the longest possible use of the Digital Therapeutics and thus to ensure maximum digital bioavailability of the active ingredient. Among the various elements of the excipient, the user interface is fundamental, able to condition the user experience, the acceptability of the therapy, the adherence to the treatment and consequently the therapeutic outcomes. Although there is no experience in this sense, it is to be expected that the same digital active ingredient may have different therapeutic effects depending on the digital excipients contained in the therapy, which may make it more or less bioavailable to the patient.

Physician dashboard

It is the web-based platform to which the physician can access both from a PC and from a smartphone or tablet to check and control - with the patient's authorisation - the patient's therapeutic evolution and the way in which the therapy is taken. Information on the different patients treated with the same Digital Therapeutic followed by the same doctor can be processed and offer the doctor new insights and new knowledge on the evolution of the therapy and the disease.

Delivery platform

This is the site from which the patient - through the code provided by the doctor in the case of prescription therapy - can download the digital therapeutic. Subject to the patient's consent, the data provided by the patient and the data relating to the progress of the treatment can be used to customize the therapy of the individual patient and allow the gradual improvement of the software.

Digital forms

As the active ingredient of a chemical drug to be used by the patient must take a pharmaceutical form (tablet, vial, cream or other), similarly an algorithm must take a digital form that allows the use and interaction with the patient. This form can be an application ("app") for a smartphone, a video game for a console, a sensor for an inhaler of drugs, a program for a virtual reality viewer.

Mode of action

Digital Therapeutics can operate in 2 distinct ways, i.e. standalone or independently of the drug or as a "plug-in" of the same. In standalone or independent mode, Digital Therapeutics are often delivering a CBT, a therapeutic approach based on the assumption that there is a close relationship between thoughts, emotions and behaviours and that provides the patient with the tools to manage emotions and change negative beliefs and misperceptions of the mind. In this case, therefore, it is a matter of modalities of delivery of therapy models already existing and in use for years in the traditional relationship between therapist and patient. In addition to the use of existing therapeutic interventions, interventions designed from scratch and combined with each other (Blended Digital Therapeutics) can be used. In the case of drug therapy, Digital Therapeutics can be an alternative, an add-on or a combination, depending on the conditions and clinical indications. The other mode is represented by the "therapeutic plug-in" of the drug, ie algorithms that extend and enhance the functions of the drug and consequently its therapeutic action. Digital Therapeutics in this case are closely linked to a drug or its device of consumption and can monitor adherence to treatment or manage side effects associated with drug therapy.

Therapeutic indications

Digital Therapeutics can be used for the treatment of many diseases. Approved or developing prescription therapies include de-

pression, Substance Use Disorder, Opioid Use Disorder, obesity and overweight, management of adverse reactions from antineoplastic drugs, ADHD - Attention Deficit Hyperactivity Disorder, Autistic Spectrum Disorders, insomnia, schizophrenia. Other non-prescription Digital Therapeutics are also indicated in asthma and Chronic Obstructive Pulmonary Disease, Hypertension, Diabetes.

Research and development

Although there are many similarities with the drug Research and Development (R and D) process, the R and D of Digital Therapeutics is characterized by some specific aspects that must be considered both in the design phase and in its execution.

Software development

The first step, performed in a "pre-clinical laboratory environment", is to develop the therapeutic intervention to be submitted to the subsequent digitization.

This intervention can be selected from the scientific literature (as for many CBTs already clinically proven in the "analogue version") and converted to digital format, as a different way to deliver an existing therapeutic intervention [6].

A different approach consists in the ex novo development of a therapeutic intervention, using elements of therapies described in the literature that are combined with each other on the basis of the personal experience of patients, specialists, practitioners involved in the team of experts. The combination of digital active ingredient and digital excipients, in a digital form suitable for the best use by a patient, is the output of this pre-clinical phase of development.

Pilot development

Once the first version of the software in its digital form is available, the pilot development aims to produce the data and information that will allow an appropriate assessment of the opportunity to continue the development of the therapy. Since full development is by far the most expensive phase in terms of resources and time, the decision to continue or stop development must be based on data to avoid wasting money and time in a therapy that does not have the opportunity to offer a real benefit to the patient. The first test to perform in this phase concerns the evaluation of the usability and acceptability of the application by the patient. This test may be performed on healthy volunteers or on patients with the disease to be treated, in order to have a better representativeness of the result and must involve subjects with different levels of culture and aptitude for the use of technology. Following this test, the first pilot clinical study is performed on a limited number of patients, in which the candidate Digital Therapeutic is administered to the patient under controlled conditions of use, both with and without control, using - in the case of the treatment of depression - self-administered evaluation parameters. The objective of this study is to obtain preliminary indications on the efficacy and tolerability of the candidate Digital Therapeutic and subjective evaluations of the patient on its use.

Full development

The results of the pilot phase may lead to a review of the algorithm and a change in the digital active ingredient in order to improve the expected therapeutic outcome. It is also possible to upgrade the excipients with new value-added utilities to improve the user experience. On the basis of these results and activities, the decision to commit to full development can be taken, considering both technical aspects (quality of the software, interface, utility, etc.) and strategic and commercial aspects (competitors, costs, probability of inclusion in medical practice, etc.). The full development phase consists of one or more confirmatory randomized controlled clinical trials (RCTs) that must generate the evidence of benefit of the candidate Digital Therapeutic for its approval by the regulatory authority, reimbursement by public health systems or insurance companies, prescription by the doctor and use by the patient.

Clinical trials

The design of the RCTs varies with the expected use of the Digital Therapeutic. If used in combination with a specific drug, the trial should demonstrate the therapeutic superiority of the combination over the drug and not inferiority with respect to tolerability. In the case of standalone use, in addition (add-on) to the patient's usual therapy, the trial should demonstrate the therapeutic superiority of the candidate Digital Therapeutic over digital placebo, both added to the usual therapy. In these trials, the digital placebo is represented by an app (or the appropriate digital form) similar to the Digital Therapeutic app, providing only generic and descriptive information on health. In our opinion, the digital active ingredient tested in the confirmatory clinical trial cannot be changed or modified, except within "windows of possible modification" [7], identified among the standards and ethical principles of the development of these therapeutics.

Both observational research and clinical trials in the real life setting are the most appropriate ways of performing clinical studies. They may be much easier to perform - at least from the logistical and organizational point of view - and allow to progressively and continuously test the therapeutic effect of the subsequent changes and evolutions of the Digital Therapeutic.

Post marketing surveillance

After marketing, post-marketing surveillance is necessary in order to identify potential adverse effects of the Digital Therapeutic. Dependence from the Digital Therapeutic may be an expected adverse effect.

Role of patients

In the research and clinical trials of Digital Therapeutics, the role of the patient and the caregiver, in particular if they are experts (expert patient) [8], is essential, alongside the experts in the treatment of the disease (whether they are specialist doctors or family doctors) and the experts in information technology. In the development of Digital Therapeutics, the patient can take on different roles. In the role of user, the patient contributes to the research and development process using technology while the researcher can observe video record or test his skills. As a tester, the patient tests the prototypes and is observed using the technology to capture his or her experiences. Finally, in the role of design partner, the patient is considered on a par with other experts involved in the design of the new Digital Therapeutic [9]. The evolution of the role of patients "from tester to development partner" is crucial for the quality of use of Digital Therapeutics and to ensure the best adherence of patients to the therapy thus developed.

Data safety and privacy

Smartphones based sensor data such as global positioning system (GPS), voice, keyboard usage, photos, video and overall phone usage behaviour are features that many health apps collect, posing new and significant privacy challenges. As a result of the increased perception of the risks of misuse of online data (email, social media), health apps and in particular Digital Therapeutics must ensure that data storage, use and sharing practices fulfil health care standards for handling patient health information data [7]. Recommendations from an international panel of experts were recently proposed and concern: a) agreed upon standards for data storage, use and sharing are needed; b) data storage, use and sharing policies must be made transparent to users of the app; c) if data are shared with external partners (e.g., researchers), the partner's storage, use and sharing plans must be shared with the end user; d) the end user must have the option to "opt out" of sharing his/her information; e) any language regarding data storage, use and sharing must be written at a maximum of a 6th grade reading level; f) technical security reviews and data audits are necessary to guarantee that apps follow the standards they set out and ensure that new vulnerabilities are quickly identified [7].

Approval

From a regulatory point of view, Digital Therapeutics are considered Medical Devices. Their CE classification is variable, being Class I as in the case of Deprexis or more frequently Class IIb as in the case of Voluntis Insulin Therapy Manager. The modalities of approval in the United States are described in the table 3 [8].

Regulatory Pathway	510k	*De novo*	Premarket approval
Product risk levels	Class I and II	Class I and II	Class III
FDA decision type	Cleared	Granted	Approved
Requires a predicate	Yes	No	No
Decision criteria	Product demonstrates "substantial equivalence" to a predicate (e.g., no independent assessment of the product required)	Probable benefits of the product outweigh probable risks	Requires independent assessment of the product's safety and effectiveness

Table 3: Risk based classification of Medical Devices in USA [8].

Technology assessment

Each new health technology, after regulatory approval, must undergo a technological assessment to determine its therapeutic value and position in therapy with the aim of informing and supporting decision-makers at different levels in decisions regarding purchase, reimbursement and use. In the case of emerging health technologies, such as Digital Therapeutics, the need for a comprehensive and systematic multidisciplinary assessment of the welfare, economic, social and ethical consequences determined by their adoption in health practice, becomes even more critical and relevant. Experience to date is limited and in Europe mainly concerns the assessments of the National Institute for Health and

Care Excellence (NICE) of Deprexis [6], a Digital Therapeutic for the treatment of depression and Sleepio [11] for the treatment of insomnia.

Reimbursement

The modalities of reimbursement of Digital Therapeutics are one of the most debated areas, still poorly defined. A scheme on possible reimbursement channels has recently been proposed [12].

Price

Information on the cost of Digital Therapeutics is still scarce. For the German-language version of Deprexis, access to therapy costs approximately €297.50 (including taxes) per person for 90 days of access [6]. Sleepio, a non-prescription Digital Therapeutic reviewed by NICE, costs £200 per user per year (£3.85 per week) in the UK for individual purchases (i.e. without the discounts offered for bulk purchases) [11].

Use

To date, no prescription digital therapeutic is medically prescribed and used by the patient in Italy and most European countries. Experience, however very limited, is present in Germany (where Deprexis has been reimbursed for the treatment of depression for years), the United Kingdom (where NICE has approved a conditional reimbursement in clinical trials for Deprexis and Sleepio) and France.

Digital therapeutics, what will be

It is expected that the impact of digitalisation on health, healthcare and health systems will be profound, affecting all the different phases of health care delivery, including health promotion, prevention, primary care, specialised care, long term care, social care, and self-care [3,13]. The digitalisation on health and healthcare has the potential to change the way health systems are organised and financed, the type of health professionals needed, the role of those professionals and of patients, as well as the health services provided and the process of delivery [14].

As a result, we expect a very different healthcare system, which will move to a 'consumer-centric' model, based on patient empowerment, self-management, shared decision-making and goal orientation towards the achievement of life goals of individuals. These changes will allow citizens to have much more responsibility for managing their health and healthcare [15].

Digital Health, Medicine and Therapy are likely to entail important shifts from diagnosis and treatment, to prevention and management. The location of health care delivery is expected to shift from hospitals and other treatment centres to home and the community [13,14,16].

While such developments hold the promise of reducing pressure on the workforce, lowering costs and improving patient centeredness and goal-orientation of care, this does not reduce the need for evaluation. However, such promises and expectations may or may not be fulfilled and in any case potential benefits may be accompanied by unintended and/or adverse effects in the short or long term [3,16]. Therefore, the introduction, implementation, use and funding of digital health technologies should be carefully evaluated and monitored. In the context of public healthcare, such evaluation and monitoring are necessary and must be performed in relation to the goals health systems pursue [3,16].

Conclusion

Digital Therapeutics are going to play a major role in this transformation. Today, Digital Therapeutics present even more open questions than certain conclusions. In any case, they are not future therapies or futuristic, but therapeutic interventions already in use for years, evaluated positively by NICE in England [6,11], reimbursed by public and private health institutions.

The implementation in Germany of the new Digital Health Law (Digitales Versorgungsgesetz - DVG) which provides for the reimbursement of Digital Therapeutics and other digital health technologies for German citizens covered by public health insurance will represent in 2020 a turning point for the entry of Digital Therapeutics into European medical practice [16,17].

Digital Therapeutics have the potential to transform the management - both clinical and economic - of chronic diseases, which represent the real health emergency (both public and private) for our country and most countries in the world and to represent the first therapeutic option offered by each doctor to each of their patients with chronic disease and dependence.

What will it take, how long will it take to turn this vision into a real situation? Commitment by all the actors of the system, first of all the institutions, to a systematic research and clinical experimentation activity, in order to give assurance and confidence on the real therapeutic value of these therapies, some years.

Bibliography

1. Schulz F., *et al*. "The Race is on. Taking advantage of digital platforms for medical technology". *Accenture Life Sciences* (2018).

2. Frederix I., *et al*. "ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardio-vascular medicine". *European Journal of Preventive Cardiology* (2019): 1-12.

3. EXPH - Expert Panel on Effective Ways of Investing In Health. "Opinion on Assessing the impact of digital transformation of health services". Luxembourg, Publications Office of the European Union (2019).

4. Goldsack J., *et al*. "Digital Health, Digital Medicine, Digital Therapeutics (DTx): What's the difference? (2019).

5. Digital Therapeutic Alliance. Digital Therapeutics: Combining Technology and Evidence-based Medicine to Transform Personalized Patient Care (2018).

6. National Institute for Health and Care Excellence. "Digital psychological therapy briefing". Deprexis for adults with depression (2019).

7. Torous J., *et al*. "Towards a consensus around standards for smartphone apps and digital mental health". *World Psychiatry* 18.1 (2019): 97-98.

8. Grosjean S., *et al*. "The Design Process of an mHealth Technology: The Communicative Constitution of Patient Engagement Through a Participatory Design Workshop. ESSACHESS". *Journal for Communication Studies* 12.1 (2019) 5-26.

9. Duncan MJ and Kolt GS. "Learning from community-led and co-designed m-health interventions". *The Lancet Digital Health* 1 (2019): 248-249.

10. Purnama A and Drago D. FDA regulatory pathways for medical devices (2019).

11. National Institute for Health and Care Excellence. Health app: Sleepio for adults with poor sleep (2019).

12. Powell AC., *et al*. "Reimbursement of Apps for Mental Health: Findings from Interviews". *JMIR Ment Health* 6.8 (2019): 14724.

13. Gardiner R. What is digital health? (2019).

14. World Economic Forum. Building the healthcare system of the future (2019).

15. De Maeseneer J and Boeckxstaens P. "James Mackenzie Lecture 2011: multimorbidity, goal-oriented care, and equity". *British Journal of General Practice* 62.600 (2012): 522-524.

16. Ricciardi W., *et al*. "Lehtonen L on behalf of the Expert Panel on Effective Ways of Investing in Health (EXPH). How to govern the digital transformation of health services". *European Journal of Public Health* 29.3 (2019): 7-12.

17. Deutscher Bundestag. Digitale-Versorgung-Gesetz-DVG (2019).