

# Tendenze

*nuove*

Numero 1/2025



**Tendenze Salute e Sanità**

Materiali di lavoro di  
Fondazione Tendenze  
Salute e Sanità

## A systematic review of digital therapeutics: regulatory and business factors

*A cura di:*

**Andrea Ruggiero, Mauro Gatti,  
Pietro Leo, Cristina Mele,  
Luigi Somaini**

*Passoni*  
EDITORE

**Direttore Responsabile**

Giuseppe Recchia

**Comitato Editoriale**

Giuseppe Recchia (Direttore Editoriale)  
*Fondazione Tendenze Salute e Sanità - ETS, Verona - I*

Lucio Da Ros (Segretario Generale  
di Fondazione Tendenze Salute e Sanità)  
*Fondazione Tendenze Salute e Sanità - ETS, Verona - I*

Curatori (Associate Editors):  
Francesco Calamo Specchia,  
Sabrina Grigolo, Emanuele Torri

**Comitato Scientifico**

Elio Borgonovi, Ovidio Brignoli, Sebastiano Filetti,  
Cristina Masella, Francesco Scaglione,  
Antonio G. Spagnolo, Giuseppe Turchetti,  
Mauro Zamboni

**Direzione e Redazione**

Fondazione Smith Kline  
Via A. Fleming 2, 37135 Verona - Italia  
Tel. +39 045.505199  
[www.fsk.it](http://www.fsk.it) - [info@fsk.it](mailto:info@fsk.it)

*Tendenze Nuove*  
[www.tendenzenuove.it](http://www.tendenzenuove.it)

Personalità giuridica riconosciuta  
(D.P.R. 917 del 9. 9. 1982)  
Registrazione al Tribunale di Bologna  
numero 7150 del 14-08-2001

Per le opere presenti in questo sito si sono assolti  
gli obblighi dalla normativa sul diritto d'autore  
[http://www.mulino.it/legale/dl72\\_04.htm](http://www.mulino.it/legale/dl72_04.htm)  
e sui diritti connessi  
<http://www.tendenzenuove.mulino.it/main/info>

**Per collaborare alla rivista**

“Tendenze nuove” pubblica articoli inviati  
alla Redazione [info@fsk.it](mailto:info@fsk.it) sia su invito  
del Comitato Editoriale che spontaneamente.  
Il contenuto degli articoli dovrà essere coerente  
con le finalità e la missione di Fondazione Smith Kline

**Editore**

Passoni Editore srl  
Via Boscovich 61, 20124 Milano  
Tel. (+39) 02 2022941 - Fax (+39) 02 29513121  
[info@passonieditore.it](mailto:info@passonieditore.it)

## **Capitale umano e Intelligenza artificiale**

### *Nuove frontiere della competitività globale*

L'AI (Artificial Intelligence) sta ridefinendo non solo i modelli economici globali, ma anche gli equilibri geopolitici tra le nazioni. Mentre Stati Uniti e Cina, con Europa a distanza, si confrontano per il primato tecnologico, sta emergendo una realtà tanto significativa quanto complessa: il capitale umano qualificato rappresenta oggi il vero fattore differenziante nella corsa all'AI, in grado di condizionare la capacità dei paesi di competere nell'economia del futuro.

Il recente *Global AI Readiness Index*<sup>1</sup> di Salesforce descrive la situazione di questo nuovo scenario competitivo analizzando la preparazione di 16 economie chiave all'adozione dell'AI basata su Agenti. I dati rivelano come il successo che deriva dall'applicazione della AI non dipenda solo dalle risorse finanziarie o dalla potenza computazionale, ma soprattutto dalla qualità e dalla preparazione del capitale umano disponibile.

---

### **Nuovo paradigma di competizione tra nazioni**

L'adozione di Agenti AI - sistemi capaci di agire autonomamente per completare compiti complessi - promette di aumentare del 327% nei prossimi due anni, generando guadagni di produttività del 30%. Tuttavia, questa trasformazione tecnologica sta creando un divario crescente tra paesi preparati e quelli ancora in fase di sviluppo delle competenze necessarie.

Gli Stati Uniti mantengono la leadership con un punteggio di 39,7 su 50, seguiti da Singapore (26,5) e Regno Unito (25,8). Questi risultati riflettono investimenti strategici pluriennali nel capitale umano e nell'educazio-

ne STEM (*Science, Technology, Engineering, Mathematics*), oltre a un ecosistema universitario che continua ad attrarre talenti globali.

Un dato significativo emerge dall'analisi del capitale umano straniero nel settore AI negli Stati Uniti: nel 2022 metà dei dottorati in STEM nelle aziende della difesa americana erano nati fuori dagli Stati Uniti. Questo fenomeno - seppure per taluni a rischio, a causa delle recenti iniziative della nuova amministrazione - dimostra come il talento globale continui a confluire verso i paesi che offrono le migliori opportunità di crescita e sviluppo professionale nell'AI.

---

## Europa tra opportunità e sfide strutturali

L'Europa si trova in una posizione peculiare. La Commissione prevede di investire un miliardo di euro all'anno nell'AI grazie ai programmi *Europa digitale* e *Orizzonte Europa*, con l'obiettivo di attrarre oltre 20 miliardi di euro di investimenti totali annui in AI nell'Unione Europea (UE) in questo decennio.

Tuttavia, i paesi europei affrontano sfide strutturali specifiche: la frammentazione del mercato interno limita la crescita delle aziende AI, mentre persiste la difficoltà nel tradurre l'eccellenza della ricerca accademica in leadership industriale. A differenza degli Stati Uniti, il gap di competenze AI in Europa risulta meno acuto, principalmente perché la domanda di talenti specializzati è ancora più contenuta rispetto al mercato americano.

Il modello canadese offre spunti interessanti: il Canada è diventato la destinazione più ambita per i talenti globali, superando Stati Uniti e Australia, dimostrando come politiche migratorie mirate possano rappresentare un vantaggio competitivo nella corsa all'AI.

---

## Paradosso del capitale umano

Emerge però una contraddizione preoccupante che potremmo definire "*il paradosso del capitale umano nell'era dell'AI*". Da un lato, l'AI richiede competenze sempre più qualificate per il suo sviluppo, implementazione e governance responsabile. Dall'altro, l'uso intensivo di questi strumenti rischia di compromettere le capacità cognitive umane essenziali per gestirli efficacemente.

Recenti ricerche in ambito medico hanno documentato il fenomeno del *deskilling*: i medici abituati ad utilizzare AI, quando non possono disporne, hanno una tendenza a compiere errori maggiore di coloro che non sono abituati ad utilizzare AI. Uno studio del *Massachusetts Institute of Technology* ha inoltre dimostrato che coloro che hanno utilizzato l'AI solo per rivedere l'articolo già scritto senza utilizzare AI, ma solo il motore di ricerca, dimostrano un livello di connettività cerebrale assai superiore al gruppo che ha scritto fin dall'inizio l'articolo con l'ausilio di AI.

Questo fenomeno non si limita al settore medico o accademico. Nel mondo aziendale, solo il 55% dei *Chief Technology Officer* intervistati crede che i team esecutivi siano in grado di utilizzare le opportunità associate con le potenzialità dell'AI, mentre la mancanza di specialisti (dichiarata dal 51% degli intervistati di una recente ricerca<sup>2</sup>) rimane predominante.

Per affrontare questi rischi, è necessario adottare approcci formativi che mantengano attive le capacità cognitive umane. Tre strategie si dimostrano particolarmente efficaci:

- **Pensiero critico prima dell'automazione:** prima di delegare compiti all'AI, è fondamentale sviluppare una comprensione profonda del problema. Questo approccio, simile a quello utilizzato nell'aviazione - dove i piloti devono mantenere le competenze di volo manuale nonostante il pilota automatico - preserva le capacità decisionali fondamentali.
- **AI come tutor, non sostituto:** trasformare l'AI in uno strumento di apprendimento guidato, che offra spiegazioni dettagliate e stimoli la riflessione critica, piuttosto che fornire soluzioni pronte all'uso.
- **Mantenimento dello spirito critico:** sviluppare "strumenti di forzatura cognitiva" - metodi presi dalla medicina e dall'aviazione - per spostare il pensiero dall'elaborazione rapida e intuitiva a un'analisi lenta e deliberata.

---

## L'importanza della formazione su larga scala

Il successo nell'era dell'AI richiede un approccio formativo sistemico che coinvolga tutti i livelli della società. Non si tratta solo di formare *data scientist* o ingegneri informatici, ma di sviluppare una *literacy* diffusa sull'AI che permetta a cittadini, professionisti, imprenditori e pubblici amministratori di comprendere potenzialità e limiti di queste tecnologie.

Le aziende stanno già percependo questa necessità. Oltre alla man-

canza di tecnici specialisti, emergono fabbisogni di competenze trasversali: creatività (44%), leadership (39%), pensiero critico (36%)<sup>2</sup>. Questo dimostra come l'AI non sostituisca semplicemente il lavoro umano, ma richieda nuove forme di collaborazione uomo-macchina.

Per le piccole e medie imprese, che rappresentano il tessuto produttivo di molte economie europee, l'accesso alla formazione sull'AI diventa ancora più critico. Il 75% delle PMI globalmente sta investendo in AI, ma il 90% delle PMI con AI riporta operazioni più efficienti, evidenziando il potenziale di trasformazione per le aziende che riescono a superare le barriere iniziali<sup>1</sup>.

### **La questione di genere nelle competenze AI**

Un aspetto spesso trascurato ma fondamentale riguarda la parità di genere nell'educazione STEM. La parità di genere risulta ancora lontana in materia di studio universitario sulle Tecnologie dell'Informazione e della Comunicazione, con implicazioni significative per lo sviluppo del capitale umano nell'AI. Paesi come la Turchia dimostrano che è possibile raggiungere livelli di partecipazione femminile superiori alla parità, superando non solo l'Italia ma anche gli Stati Uniti.

Questo gap rappresenta non solo una questione di equità sociale, ma anche un spreco di potenziale innovativo. La diversità di genere nei team di sviluppo AI è essenziale per ridurre i bias algoritmici e sviluppare soluzioni più inclusive ed efficaci.

---

## **Il caso Italia**

L'Italia si posiziona al 9° posto sui 16 paesi analizzati nel *Global AI Readiness Index*, con un punteggio complessivo di 18,4 su 50, leggermente al di sotto della media (22,1). Questa posizione intermedia nasconde però significative debolezze strutturali che richiedono interventi mirati.

Le performance italiane risultano particolarmente deboli in due dimensioni critiche: innovazione (1,0 su 10) e investimenti (0,2 su 10). Al contrario, il paese mostra una discreta preparazione nel quadro normativo (8,2 su 10) e nelle competenze umane (4,1 su 10), evidenziando una potenziale base solida su cui costruire.

Secondo i dati dell'Osservatorio Artificial Intelligence del Politecnico di Milano, il mercato dell'AI in Italia ha raggiunto nel 2024 gli 1,2 mi-

liardi di euro, registrando una crescita record del 58% rispetto al 2023. Nonostante questa crescita significativa, solo l'8% delle aziende italiane ha implementato soluzioni AI, evidenziando ancora un tasso di adozione limitato che può essere attribuito a competenze digitali insufficienti della forza lavoro e disparità regionali nell'infrastruttura tecnologica.

### Quali azioni?

Per ridurre il gap competitivo, l'Italia dovrebbe concentrarsi su quattro aree prioritarie:

- **Investimenti strategici nell'innovazione:** sviluppare strumenti finanziari dedicati che combinino risorse pubbliche e private per supportare startup e scale-up dell'AI. L'iniziativa IT4LIA - alla quale prende parte anche AgID - promette di creare le basi infrastrutturali necessarie, con il nuovo supercalcolatore previsto presso il Tecnopolo di Bologna.

- **Formazione sistemica:** implementare programmi di *AI literacy* che coinvolgano non solo le università e gli istituti tecnici, ma anche la formazione continua per i lavoratori già occupati. Il modello brasiliano, dove Salesforce ha avviato partnership per formare 1,5 milioni di persone, offre spunti interessanti per interventi su larga scala.

- **Coordinamento istituzionale:** rafforzare il coordinamento tra livello nazionale e regionale per superare le disparità territoriali nell'accesso alle competenze digitali e alle infrastrutture AI.

- **Attrazione di talenti:** sviluppare politiche migratorie che favoriscano l'attrazione di talenti internazionali nell'AI, seguendo l'esempio canadese, e creando al contempo le condizioni per trattenere i talenti nazionali.

---

## Verso un futuro responsabile

La competizione globale nell'AI non è solo una questione tecnologica o economica, ma rappresenta una sfida più profonda sulla capacità delle società di adattarsi al cambiamento preservando i valori umani fondamentali. L'approccio dell'UE all'AI è incentrato sull'eccellenza e sulla fiducia, con l'obiettivo di rafforzare la ricerca e la capacità industriale garantendo nel contempo la sicurezza e i diritti fondamentali.

La strada da percorrere richiede equilibrio: sfruttare le opportunità dell'AI senza cadere nella trappola del *de-skilling*, investire nell'automa-

zione mantenendo al centro il valore dell'intelligenza umana, competere a livello globale preservando i principi di inclusione e sostenibilità sociale.

Il capitale umano rimane, e probabilmente rimarrà, il fattore differenziante nell'era dell'AI. La sfida per l'Italia, come per l'Europa, è costruire un ecosistema che valorizzi questo capitale attraverso formazione sistemica a livello di popolazione e continua, investimenti strategici e politiche inclusive. Solo così sarà possibile trasformare la rivoluzione AI da rischio di marginalizzazione in opportunità di crescita sostenibile e competitiva.

---

## Bibliografia

1. Salesforce. Global AI Readiness Index 2025. <https://www.salesforce.com/news/stories/global-ai-readiness-index-insights-2025/>
2. Akkodis. What CTOs Think. <https://www.akkodis.com/en/new-sroom/news/reality-of-ai-strategy-in-entreprise-today>

## A systematic review of digital therapeutics: regulatory and business factors

---

### Abstract

**Objective:** Digital therapeutics (DTx) are on the rise, offering considerable opportunities to improve patient outcomes by complementing traditional drug-based therapeutic approaches and enabling new value co-creation practices that combine multi-industry contributions from the pharma, technology, and healthcare sectors. A growing number of studies have focused on the impacts of DTx in innovating healthcare. However, there has been no systemic and holistic synthesis of works in this area. We aim to provide a wider picture of DTx research, which will empower scholars to enrich this field, companies to formulate new solutions, and policymakers to create robust regulations and policies.

**Methods:** In line with the PRISMA methodology, we adopt a systematic literature review and conduct a thematic analysis on DTx, extracting scholarly articles from ProQuest, PubMed, and Web of Science.

---

<sup>a</sup>*Experienced professional and a researcher with a PhD in Management, Department of Economics, Management and Institutions, University of Naples Federico II, Naples, Italy*

<sup>b</sup>*Architect and Data Scientist, IBM Italy*

<sup>c</sup>*Executive Architect and member of IBM Academy of Technology, IBM Italy*

<sup>d</sup>*Full professor of Management, Department of Economics, Management and Institutions, University of Naples Federico II, Naples*

<sup>e</sup>*Business Development Manager, IBM Italy*

**Results:** We group the reviewed literature according to five themes: (1) clinical effectiveness, (2) regulatory approval, (3) economic effectiveness, (4) business model, and (5) technology. While scholars largely agree on the clinical and economic effectiveness of DTx in healthcare, there has been some debate regarding the regulatory system for DTx. DTx significantly impacts the sustainability of business models and the types of technologies used, and the development of these technologies often outpaces regulatory frameworks.

**Conclusion:** Our study provides an overall picture of the DTx scholarly literature, providing valuable insights to support business model design and regulations for companies, service designers, physicians, and policymakers. This study also sheds light on the clinical and economic effectiveness of implementing DTx in healthcare.

**Keywords:** Digital Therapeutics; Digital Medicine; Effectiveness; Innovation; Business Model

---

## Introduction

In 2017, the U.S. company Pear Therapeutics received Food and Drug Administration (FDA) premarket approval for Reset, a prescription digital therapeutic for the treatment of substance use disorder. Delivered through a mobile application, Reset was designed to be used as part of a comprehensive outpatient treatment program.

The global demand for digital therapeutics (DTx) rose, showcasing a wide variety of approaches to healthcare problems<sup>1</sup>; however, it remained unclear how and when this demand would fully materialize, especially given recent changes and challenges faced by leading companies in the sector.<sup>2</sup> The DTx market was projected to reach USD 17.7 billion by 2027, at a Compound Annual Growth Rate (CAGR) of 31.6% during the forecast period<sup>3</sup>. The Digital Therapeutics Alliance<sup>4</sup> defined DTx as “health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient’s health” (see also ISO, 2023).<sup>5</sup> DTx seemed to be a potential game-changer for all stakeholders in the healthcare system.<sup>1</sup>

These solutions provided many benefits to patients who are accustomed to digital consumer applications and were thus able to utilize these convenient and informative healthcare products. DTx have the potential to transform the management of chronic diseases, and represent the “first therapeutic option offered by doctors to their patients with chronic disease and dependence”.<sup>6</sup> To date, these solutions and products were either on the market or under development. They targeted numerous intervention areas in terms of preventing, managing, and treating a broad spectrum of physical, mental, and behavioral conditions (e.g., anxiety disorder, depression, and substance use disorder).<sup>6</sup> For example, DTx could help to reduce back pain through guided exercises, manage diabetes via glucose monitoring, and control hypertension by offering lifestyle recommendations.<sup>4</sup>

Pharmaceutical and medical-device companies sought to design digital solutions aimed at improving current therapies. Payers and providers wanted digital tools that helped them serve greater numbers of patients, more effectively, and at lower cost<sup>7</sup>, and to find a sustainable business model for this (where a business model “describes the rationale of how an organization creates, delivers, and captures value”).<sup>8</sup> Finally, the health system aimed to address chronic diseases on a larger scale and lower healthcare costs.<sup>4</sup> Hence, new business models are emerging that involve startups, pharma firms, tech companies, and healthcare companies-often in combination.<sup>3</sup>

Today, DTx applications are regulated and available in several countries-such as Brazil, France, Germany, Japan, Spain, South Korea, the United Kingdom, and the United States-while in other countries they are still under regulatory development processes<sup>9</sup> or have recently been approved for the first time.<sup>10</sup> Despite an increasing interest in the need for DTx solutions, scholars highlighted overall confusion and misunderstandings regarding the applications of digital technologies in innovating processes involving health and healthcare.<sup>11,6</sup> *Table 1* summarizes the differences between DTx and other digital solutions in digital health field.<sup>4</sup> DTx were often conflated with other digital health or medicine solutions that are innovative and efficacious, but that lack scientifically demonstrated effectiveness or real-world applicability.<sup>12,6</sup> Standard digital health solutions included technologies, platforms, and systems that engage consumers

for lifestyle, wellness, and health-related purposes, but did not require clinical evidence and regulatory oversight, as in the case of DTx.<sup>13,4</sup> Unlike healthcare and wellness apps or digital medicine products, DTx required strong clinical evidence and real-world outcomes.<sup>4</sup> They needed to be reviewed, cleared, and validated by regulatory agencies, such as the FDA or notified bodies, to support claims of risk, efficacy, and intended use. Additionally, it is important to clarify the validation process when medical devices are employed. DTx solutions provided clinical results and influence clinical outcomes, as characterized by evidence-based behavioral treatments delivered via online or offline applications, which increased the accessibility and efficacy of healthcare.<sup>5</sup>

Academic literature has been paying increasing attention to DTx, in particular exploring their positive benefits<sup>4,14,15</sup>, and analyzing successful outcomes.<sup>16,17</sup> Recently, some scholars also reviewed existing DTx literature in specific domains.<sup>18,19,20</sup> Although these recent works have contributed to our understanding of the roles of DTx, several limitations in the scientific literature remained, such as the lack of an holistic approach (including management and business perspectives) or generalizable results relating to different spheres of digital health solutions. Many studies only analyzed clinical and macroeconomic features of DTx, or focused on regulatory issues. Hence, extant publications are fragmented and disconnected, and there has been little effort to review literature in this area.<sup>14,20</sup> To overcome these weaknesses, the present paper aimed to map the field through a systematic literature review. Our research question is: “*What main themes related to DTx have been discussed in literature to date?*” Our systematic literature review sought to identify gaps, key research themes, and developmental patterns. In doing so, it consolidated and integrated extant knowledge. Finally, we contributed to developing a reliable knowledge base for business practitioners to design and foster new solutions.

The remainder of the work is organized as follows. First, we summarized the methodology used to systematically select and review the literature. Second, we reported our findings. Third, we outlined the study’s contributions, and implications for practitioners. Finally, we provided limitations, suggestions for future research, and conclusions.

**Table 1 - Comparison of digital therapeutics versus other patient-facing digital health technologies**

|                                | <b>Health and wellness</b>                                                                                                | <b>Patient monitoring</b>                                                                                                   | <b>Care support</b>                                                                                             | <b>Digital diagnostics</b>                                                                                            | <b>Digital therapeutics</b>                                                                                                                |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Definition</b>              | Disease-agnostic digital health solutions that primarily capture and store general health data and promote healthy living | Digital solutions intended to monitor specific health data, which may be interpreted by a physician for clinical management | Digital solutions intended to help patients manage their care of a specific disease or medical condition        | Validated digital tools and software that deliver a diagnosis or prognosis of a specific disease or medical condition | Health software intended to treat or alleviate a specific disease or medical condition by generating and delivering a medical intervention |
| <b>Evidence requirements</b>   | Not required                                                                                                              | Non-clinical claims to assess patient data must be validated and meet a regulatory agency's quality requirements            | Any non-clinical claims (i.e., adherence) must be validated and meet a regulatory agency's quality requirements | Diagnostic accuracy must be validated and meet a regulatory agency's quality requirements                             | Efficacy claims must be validated and meet a regulatory agency's quality requirements                                                      |
| <b>Regulatory implications</b> | No regulatory oversight                                                                                                   | May require regulatory approval and labeling                                                                                | May require regulatory approval and labeling                                                                    | Regulated product with a label for indication, usage, evidence, and warnings                                          | Regulated product with a label for indication, usage, evidence, and warnings                                                               |
| <b>Examples</b>                | Fitbit, Apple Watch                                                                                                       | Dexcom, Omron                                                                                                               | mySugr, Propeller Health, CancerCare                                                                            | AliveCor's KardiaMobile, IBM Watson for Oncology                                                                      | EndeavorRx, Sleepio, Kaia Health                                                                                                           |

*Notes: Adapted from Digital Health Technology Ecosystem Categorization (2023). Examples added by the authors*

## Method

### Study Setting

Compliant with the PRISMA methodology (*figure 1*), we adopted a systematic literature review and thematic analysis method, searching and collecting articles that contained the keyword “digital therapeutic\*” in the following databases: ProQuest, PubMed, and Web of Science. These databases included a wide range of articles about DTx and allowed us to address every field of research, from business to medicine. The review protocol was not registered in any database or registry. The data were collected between January 2023 and June 2024, with appropriate updates made until June 2024. We decided to use only one keyword, “digital therapeutic\*” because, to our knowledge, there are no synonyms for it and the inclusion of other keywords would thus have resulted in including studies unrelated to our analysis. We searched in “all fields” of academic articles to avoid missing relevant studies. The first articles that explicitly referred to DTx appeared during 2013, but the timeframe 2017-2024 was deemed appropriate due to the novelty of the DTx phenomenon.

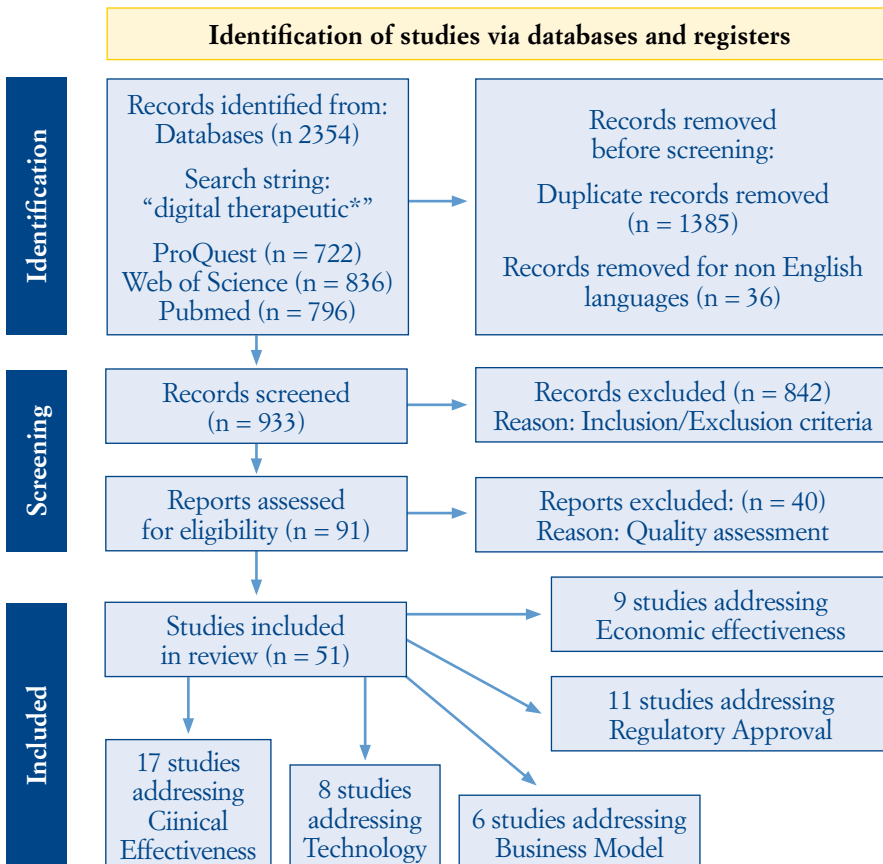
We then defined our exclusion and inclusion criteria. We excluded articles that met at least one of the following exclusion criteria: (1) DTx used as a synonym of digital medicine, digital health, patient monitoring, digital diagnostics, care support, or e-health; (2) study mentioned DTx only in subsections, such as in relation to managerial or practical implications; and (3) DTx presented only as marginal examples within a broader topic (i.e., DTx introduced as one of many actions to make medicine more personalized). Thus, we included papers that focused on DTx in both the theoretical section and the empirical study. Identified studies were analyzed separately, and two researchers assessed and compared their interpretations to reach a consensus and mutual understanding of the inclusion criteria. Differences in interpretations or doubts were discussed, through which we sharpened and refined our inclusion and exclusion criteria.

Moreover, the papers were subjected to a quality assessment alongside the inclusion and exclusion criteria. Two methodological quality checklists—one focusing on qualitative research and the other on quantitative research—were applied based on previous checklists used in various research fields.<sup>22,23</sup> During the selection process, two researchers conducted the quality assessment independently. In the initial quality assessment trial, two researchers each evaluated five papers’ methodologies and then compared their conclusions. Since there were only minor deviations (in less than 15 percent of judgments), we did not take corrective measures for assessing the methodological quality.

## Data Analysis

Given that the studies varied greatly in measuring the relevant concepts, analysis techniques, and effect sizes, we decided to conduct a thematic analysis, categorizing studies according to their shared characteristics.<sup>24</sup> We included both quantitative and qualitative studies in this stage.<sup>23,25</sup> The resulting papers were each characterized by the research field, research aim, and type of research (qualitative/quantitative data; data collection method). We then applied the theme development phase,<sup>25</sup> constructing five non-exclusive themes that were ultimately defined through the reviewing phase.<sup>25</sup> This ensured themes were distinct from each other and findings were validated.

**Figure 1 - Prisma diagram**



## Results

Using the three search strategies outlined above, we identified 2,354 potentially relevant studies (see *figure 1*). After identifying and eliminating duplicate studies (1,385) and articles written in a language other than English (36), a total of 933 retrieved studies were considered for deeper analysis. We then excluded 842 articles based on a review of their titles and abstracts. Studies were excluded if they met at least one of the exclusion criteria. We reviewed the full text of 91 articles as broadly relevant. Of these, 40 were excluded because their quality was judged to be insufficient for our purposes, according to our inclusion criteria. Our systematic review categorized 51 articles as primary references, analyzed their full text, and included them in the review. To derive our findings, we screened the 51 articles using thematic analysis—a transparent and highly flexible method that can be applied to a wide variety of unstructured information.<sup>24,25</sup> The research question, and our desire to derive interesting insights so as to contribute to mapping the field, as described previously, were used to guide the thematic analysis. The analysis results of the 51 chosen original studies produced five main themes: clinical effectiveness, economic effectiveness, regulatory approval, business model, and technology. *Table 2* presents an overview of each article, and findings regarding themes are summarized in *table 3*. Across the studies included in this review, 17 addressed clinical effectiveness, 9 addressed economic effectiveness, 11 addressed regulatory approval, 6 addressed business model, and 8 addressed technology (*figure 1*).

**Table 2 - Overview of included studies**

| Author(s)                            | Theme          | Main Findings                                                                                                                                                                                                                                                               | Method                      |
|--------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Lumbreras et al., 2024 <sup>26</sup> | Business model | DTx products require high-quality evidence, longer-term studies, and clear regulatory guidance for insurance coverage, with particular promise in mental health, while legislation and return on investment concerns significantly impact their adoption and implementation | Cross-sectional qualitative |
| Denecke et al., 2023 <sup>27</sup>   | Business model | Several aspects should be considered in risk assessments of DTx implementation                                                                                                                                                                                              | Risk assessment canvas      |

|                                          |                        |                                                                                                                                                                                              |                                 |
|------------------------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Strauss et al., 2022 <sup>28</sup>       | Business model         | DTx are only effective if users sufficiently engage with them, and only if users meaningfully engage with the product                                                                        | Cross-functional analysis       |
| Chung, 2019 <sup>29</sup>                | Business model         | In addition to enhancing and supporting current medical treatments, DTx have the potential to provide patients, providers, and payers with novel therapeutic options for unmet medical needs | Conceptual comparison           |
| Carrera et al., 2023 <sup>30</sup>       | Business model         | Diverse rational and institutional factors drive patients' acceptance of DTx                                                                                                                 | Descriptive and factor analysis |
| Geiger and Kjellberg, 2021 <sup>31</sup> | Business model         | DTx represent a combinatorial market innovation-i.e., a synthesis of market subprocesses from two (or more) existing markets                                                                 | Longitudinal case study         |
| Biskupiak et al., 2024 <sup>32</sup>     | Clinical Effectiveness | DTx can enhance the effectiveness of pharmaceutical treatments for chronic diseases by mitigating issues such as medication non-adherence and adverse effects                                | Clinical study                  |
| Lee et al., 2024 <sup>33</sup>           | Clinical Effectiveness | Advanced-level push notifications and a human coach lead to higher completion rates for self-monitoring forms and learning courses                                                           | Clinical study                  |
| Namgung et al., 2024 <sup>34</sup>       | Clinical Effectiveness | Visual field defect-based digital therapeutics may induce clinically meaningful visual improvements in patients with post-stroke visual field defects                                        | Clinical study                  |
| Nomura et al., 2024 <sup>35</sup>        | Clinical Effectiveness | The practice-based cohort using the DTx app showed significant reductions in morning home systolic blood pressure, with a decrease of -4.9 mmHg at week 12 and -6.1 mmHg at week 24          | Clinical study                  |

|                                     |                        |                                                                                                                                                                                                                                                                                                        |                |
|-------------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Oh et al., 2024 <sup>36</sup>       | Clinical Effectiveness | Game-based DTx significantly improved attention in children and adolescents, offering a promising non-pharmaceutical treatment option vs TAU                                                                                                                                                           | Clinical study |
| Orsolini et al., 2024 <sup>37</sup> | Clinical Effectiveness | Current studies in DTx for major depressive disorder and bipolar disorder have focused mostly on feasibility and acceptability, with limited efficacy data, small sample sizes, and a lack of long-term follow-up                                                                                      | Review         |
| Seo et al., 2024 <sup>38</sup>      | Clinical Effectiveness | DTx can provide significant pivotal therapeutic impacts and offer a means to personalize treatment approaches and streamline the management of patients' treatment processes                                                                                                                           | Review         |
| Monico et al., 2024 <sup>39</sup>   | Clinical Effectiveness | DTx interventions for opioid use disorder, including buprenorphine, significantly increase opioid abstinence days, medication adherence, and overall well-being, while reducing anxiety, depression, and opioid cravings, thus supporting the maintenance of telehealth access for effective treatment | Review         |
| Kario et al., 2023 <sup>40</sup>    | Clinical Effectiveness | Patients in the DTx group experienced a reduction in Body Mass Index (BMI) and an improvement in salt intake score during the 12-week study                                                                                                                                                            | Clinical study |
| Li et al., 2023 <sup>41</sup>       | Clinical Effectiveness | DTx provide possible avenues for monitoring myopia progression and control                                                                                                                                                                                                                             | Review         |
| Sun et al., 2023 <sup>42</sup>      | Clinical Effectiveness | DTx hold potential for an adjunctive treatment in children with ADHD                                                                                                                                                                                                                                   | Clinical study |
| Joshi et al., 2023 <sup>43</sup>    | Clinical Effectiveness | DTx provide a significant improvement in glycemic control and reduction in weight and BMI                                                                                                                                                                                                              | Clinical study |

|                                       |                        |                                                                                                                                                      |                   |
|---------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Xiong et al., 2023 <sup>44</sup>      | Clinical Effectiveness | Patients with substance use disorder exhibited engagement with DTx, high rates of retention, and substantial rates of abstinence                     | Clinical study    |
| Maricich et al., 2021 <sup>45</sup>   | Clinical Effectiveness | DTx in combination with buprenorphine therapy improve abstinence from illicit opioids and retention in treatment compared with treatment as usual    | Clinical study    |
| Osborn et al., 2020 <sup>46</sup>     | Clinical Effectiveness | DTx named “One Drop” with an activity tracker for adults with type 1 diabetes significantly lowers 3-month hemoglobin A1c level                      | Clinical study    |
| Bray et al., 2020 <sup>47</sup>       | Clinical Effectiveness | The DTx platform Xploro reduces children’s levels of procedural anxiety                                                                              | Clinical study    |
| Iacoviello et al., 2018 <sup>48</sup> | Clinical Effectiveness | A digital cognitive-emotional training approach may be a feasible and effective intervention strategy for the treatment of major depressive disorder | Clinical study    |
| Davison et al., 2024 <sup>49</sup>    | Economic Effectiveness | DTx AspyreRxT plus standard of care is anticipated to dominate standard of care alone over the lifetime horizon from a payer perspective             | Clinical study    |
| Sapanel et al., 2023 <sup>20</sup>    | Economic Effectiveness | DTx interventions offer potential economic benefits                                                                                                  | Systematic review |
| Liu et al., 2023 <sup>50</sup>        | Economic Effectiveness | DTx for home-based cardiac rehabilitation is an extremely cost-effective rehabilitation option                                                       | Clinical trial    |
| Kim and Kim, 2023 <sup>51</sup>       | Economic Effectiveness | The metaverse represents an avenue for DTx trends, applications, and future perspectives in the field of urology                                     | Descriptive study |
| Nomura et al., 2022 <sup>52</sup>     | Economic Effectiveness | In treating hypertension, a DTx + TAU strategy was more cost-effective than a TAU-only strategy                                                      | Economic model    |

|                                       |                        |                                                                                                                                                                                                                                                                                       |                |
|---------------------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Velez and Malone, 2021 <sup>53</sup>  | Economic Effectiveness | DTx named “reSET-O” + TAU was economically dominant (less costly, more effective) vs. TAU alone over 12 weeks                                                                                                                                                                         | Clinical study |
| Wang et al., 2021 <sup>54</sup>       | Economic Effectiveness | Depending on the payer’s willingness to pay, DTx reSET-O may be cost-effective in increasing buprenorphine treatment retention rates                                                                                                                                                  | Clinical study |
| Velez et al., 2021 <sup>55</sup>      | Economic Effectiveness | reSET-O is an economically dominant adjunctive treatment for opioid use disorder, and is associated with an overall reduction in total incremental cost (vs. TAU)                                                                                                                     | Clinical study |
| Nordyke et al., 2019 <sup>56</sup>    | Economic Effectiveness | DTx may provide substantial cost savings, in part reducing the use of conventional medications                                                                                                                                                                                        | Clinical study |
| Carrera et al., 2024 <sup>57</sup>    | Regulatory approval    | The adoption of the framework named “M-LEAD” can potentially enhance the quality and efficiency of healthcare delivery and outcomes, benefiting patients, clinicians, payers, and society                                                                                             | Theoretical    |
| Kendziorra et al., 2024 <sup>58</sup> | Regulatory approval    | Physicians’ decisions to prescribe DTx are influenced by patient- and app-specific conditions, time constraints, and familiarity with DTx, with triggers including patient requests and company promotions, while external actors and compensation issues also play significant roles | Review         |
| Miao et al., 2024 <sup>59</sup>       | Regulatory approval    | DTx development landscape highlights challenges in designing inclusive DTx clinical trials                                                                                                                                                                                            | Review         |

|                                        |                     |                                                                                                                                                                                                       |                          |
|----------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Schmidt et al., 2024 <sup>60</sup>     | Regulatory approval | DTx's journey in Germany underscores the need for improved reimbursement strategies, enhanced user engagement, and updated legislative frameworks, all in response to recent regulatory modifications | Review                   |
| Kim et al., 2024 <sup>61</sup>         | Regulatory approval | The DTx framework named "RWE" helps in developing and deploying DTx in real-world contexts, including those in industry, healthcare, public health and academia                                       | Theoretical              |
| Recchia and Gussoni, 2023 <sup>6</sup> | Regulatory approval | DTx can represent the first therapeutic option offered by doctors to their patients with chronic disease and dependence                                                                               | Theoretical              |
| Wang et al., 2023 <sup>21</sup>        | Regulatory approval | A real-world, evidence-based validation system, supported by cooperative/regulatory frameworks, can overcome engagement barriers in DTx                                                               | Review                   |
| Kumar et al., 2023 <sup>62</sup>       | Regulatory approval | There is a need for a more rigorous and inclusive approach to clinical research supporting prescription DTx                                                                                           | Cross-sectional analysis |
| Mantovani et al., 2023 <sup>17</sup>   | Regulatory approval | Regulatory systems for DTx are complex and vary among countries in terms of requested evidence, payment approaches, and overall reimbursement landscape                                               | Scoping review           |
| Smits et al., 2022 <sup>63</sup>       | Regulatory approval | A transition from evidence-based healthcare toward evidence-based well-being would improve the successful implementation of DTx                                                                       | Theoretical              |
| Carl et al., 2021 <sup>64</sup>        | Regulatory approval | The traditional "prescription-based" model of DTx for mental health can undermine and limit its broad accessibility                                                                                   | Theoretical              |

|                                        |            |                                                                                                                                                                                                                                          |                    |
|----------------------------------------|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Bolpagni et al., 2024 <sup>65</sup>    | Technology | Stakeholders perceived AI-based data processing as beneficial for personalized treatment in a secure, privacy-preserving environment                                                                                                     | Review             |
| Rheinberger et al., 2024 <sup>66</sup> | Technology | DTx offer personalized coping strategies, integration with hospital records, and inclusivity features to support young people who are in suicidal distress and to improve hospital care efficiency                                       | Clinical study     |
| Weimann and Gißke, 2024 <sup>67</sup>  | Technology | Reinforcement learning in DTx benefits from diverse data sources, simple algorithms, privacy-preserving AI, and patient safety considerations, but requires larger studies and further exploration beyond physical activity optimization | Quantitative study |
| Fougère et al., 2023 <sup>68</sup>     | Technology | Sensory stimulations can enhance the effectiveness of DTx in pain control                                                                                                                                                                | Review             |
| Stanojevic et al., 2023 <sup>69</sup>  | Technology | Socially assistive robots can be a beneficial asset to DTx since data gathered from sensors onboard the robots can help identify in-home behaviors, activity patterns, and health status of patients remotely                            | Descriptive study  |
| Yoo et al., 2023 <sup>70</sup>         | Technology | Digital therapeutics require various technical supports and methods                                                                                                                                                                      | Descriptive review |
| Adler et al., 2022 <sup>71</sup>       | Technology | Digital biomarkers have the potential to revolutionize mental health diagnosis and treatment                                                                                                                                             | Theoretical        |
| Hong et al., 2021 <sup>16</sup>        | Technology | Only a tiny fraction of medical apps in the market are likely to be considered DTx, as they do not meet relevant criteria (i.e., integration, interoperability, intelligence, socialization, outcomes, and engagement)                   | Review             |

**Table 3 - Thematic analysis findings**

| Theme                  | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Current State                                                                                                                                                                                                                                                                                                 | Key Drivers and Indicators                                                                                    |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Clinical effectiveness | <ul style="list-style-type: none"> <li>• DTx positively contribute to preventing, managing, or treating medical disorders or diseases, especially compared to TAU</li> <li>• DTx can enhance the effectiveness of pharmaceutical treatments for chronic diseases</li> <li>• DTx offer promising non-pharmaceutical treatment options in some settings</li> <li>• DTx can provide significant pivotal therapeutic impacts and personalized treatment approaches</li> </ul>                                      | - Scholars are adopting retrospective and prospective studies, which are often required as clinical studies for DTx companies                                                                                                                                                                                 | - Clinical effectiveness                                                                                      |
| Economic effectiveness | <ul style="list-style-type: none"> <li>• DTx may provide substantial cost savings, in part reducing the use of conventional medications</li> <li>• There is still a need to prove value compared to current interventions, and to demonstrate potential cost savings for payers</li> <li>• DTx, with their ease of implementation, may help overcome the difficulty in health care systems of deploying intensive behavioral interventions at the large scale needed to improve population outcomes</li> </ul> | <ul style="list-style-type: none"> <li>• Literature is scarce, and it is questionable whether cost savings can indeed be achieved when using DTx, and whether the benefits provided by DTx are in line and feasible with healthcare expenditure from the perspective of patients and public payers</li> </ul> | <ul style="list-style-type: none"> <li>• Cost-effectiveness</li> <li>• Health resource utilization</li> </ul> |

|                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                         |                                                                                                                     |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Regulatory approval | <ul style="list-style-type: none"><li>• Regulatory processes are seen as a gold standard to differentiate DTx from other digital health solutions</li><li>• Reimbursement can be a barrier to scaling interventions</li><li>• Technology literacy, age, and other socioeconomic factors (e.g., income, nationality) may play a more significant role when conducting reimbursement decisions</li><li>• Physicians' decisions to prescribe DTx are influenced by patient- and app-specific conditions, time constraints, and familiarity with DTx</li></ul>   | <ul style="list-style-type: none"><li>• There has been discussion in multiple countries and between scholars about how to regulate DTx solutions in terms of how they are developed, evaluated, reimbursed, and delivered</li></ul>     | <ul style="list-style-type: none"><li>• Reimbursement</li><li>• Prescription</li></ul>                              |
| Business model      | <p>Revenue streams:</p> <ul style="list-style-type: none"><li>• Reimbursement plays an essential role; “risk-sharing” revenue models are on the rise, in which the price paid by the health care provider depends on the clinical impact of the solution</li><li>• With regard to business-to-business (B2B) contexts, pharmaceutical companies can offer DTx for a fee to the patient (business-to-business-to-consumer) or the health service (business-to-business-to-government), or offer it for free when the incremental margin is positive</li></ul> | <ul style="list-style-type: none"><li>• DTx market is divided into business-to-consumer, B2B, and business-to-government, including DTx offered through employers, health plans, health systems, and pharmaceutical companies</li></ul> | <ul style="list-style-type: none"><li>• Reimbursement</li><li>• User engagement</li><li>• User acceptance</li></ul> |

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                     |                                                                                                                                                                       |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Business model | <ul style="list-style-type: none"> <li>• DTx players are experimenting with consumer-led subscription models to reduce reliance on intermediaries and increase consumer access</li> <li>Value proposition:</li> <li>• DTx include automated, cost-effective, and flexible solutions</li> <li>• DTx can make medicine more personalized for patients and allow for remote patient engagement, and better capturing/tracking of outcomes</li> </ul>                                                                                                                                                     |                                                                                                                                                                                                                                                     |                                                                                                                                                                       |
| Technology     | <ul style="list-style-type: none"> <li>• DTx need high-quality software to be cleared and certified</li> <li>• DTx should adopt advanced technologies to enable data exchange across at least one other platform, and provide customized and adaptive algorithms and interventions</li> <li>• DTx producers should possess advanced datasets, effective communication across IT platforms, and standardized data formats</li> <li>• Digital biomarkers can revolutionize mental health diagnosis and treatment by providing near-continuous, unobtrusive, and remote measures of behaviors</li> </ul> | <ul style="list-style-type: none"> <li>• Literature is scarce and scholars have questioned which technologies can better enhance the usage and success of DTx, such as sensory stimulations, the metaverse, or socially assistive robots</li> </ul> | <ul style="list-style-type: none"> <li>• Software</li> <li>• Intelligence</li> <li>• Interoperability</li> <li>• Datasets</li> <li>• Advanced technologies</li> </ul> |

### Clinical Effectiveness

Most of the literature on DTx has highlighted DTx's positive contributions to preventing, managing, or treating medical disorders or diseases compared to therapy as usual (TAU). These studies have typically employed quantitative methodologies and retrospective or prospective designs, often serving as necessary clinical trials for third-party approval. A common indicator used is "clinical effectiveness," which is frequently measured in terms of "quality-adjusted life-years" (QALYs).<sup>53</sup> Primary intervention areas included drug abuse,<sup>21,44</sup> major depression<sup>48</sup>, diabetes<sup>40,43</sup>, Attention Deficit Hyperactivity Disorder (ADHD)<sup>42</sup>, sleep problems, and chronic insomnia. For instance, the DTx reSET-O showed promising results for patients with opioid use disorder,<sup>44,55</sup> while "One Drop" DTx demonstrated efficacy in diabetes management.<sup>46</sup>

### Regulatory Approval

DTx companies launched solutions that, in order to be sold, require a medical prescription and reimbursement to be economically sustainable.<sup>17</sup> There has been extensive discussion in multiple countries about how DTx solutions should be regulated, and this has considerable implications for how DTx are developed, evaluated, reimbursed, and delivered.<sup>17,62,63</sup> Studies in this sample have viewed regulatory processes as gold standards to differentiate DTx from other digital health technologies-namely health and wellness and care support solutions.<sup>6,62,72</sup> However, despite the many positive aspects of prescription and reimbursement (e.g., the validation of a health claim by a third party), some scholars raised concerns about current regulations regarding reimbursement as a barrier to scaling interventions.<sup>17</sup> Moreover, other scholars viewed the prescription-based model as inappropriate, since no consensus exists on the ethical acceptability of prescribing interventions based solely on their placebo effect.<sup>63</sup> Moreover, one leading player in DTx has been pursuing regulatory approval for over-the-counter labeling of its products, shifting its strategy to a non-prescription model so as to increase patient access to clinically validated non-drug treatments.<sup>73</sup>

Contrary to pharmaceutical drugs, whereby consideration of human biological factors (e.g., ancestry, genetics) is necessary to assess potential therapeutic effectiveness, in DTx, technology literacy, age, and other socioeconomic factors (e.g., income, nationality) may play a more significant role when making reimbursement decisions.<sup>74</sup>

### **Economic Effectiveness**

Studies in this area explored the economic impact of DTx compared to traditional therapies, using quantitative analyses to assess costs and benefits.<sup>20,35,50</sup> Such studies investigated whether DTx can provide cost savings and are sustainable from a healthcare expenditure perspective.<sup>74</sup> For instance, in some intervention areas (e.g., mental health), DTx, with their ease of implementation, may help to overcome the difficulties healthcare systems face in deploying intensive behavioral interventions at the large scale needed to improve population outcomes. Measures such as incremental cost per QALY have often been used.<sup>53</sup> For example, the use of DTx in treating chronic heart failure and hypertension showed potential economic benefits, reducing healthcare resource costs and improving quality of life.<sup>35</sup>

### **Business Model**

Studies in this cluster analyzed how DTx impact business models, highlighting opportunities for pharmaceutical companies and start-ups.<sup>16,27,75</sup> According to the company's revenue model and channels, the DTx market is divided into business-to-consumer (B2C), business-to-business (B2B) and business-to-government (B2G), including DTx offered through employers, health plans, health systems, and pharmaceutical companies.<sup>16,75</sup> With regard to B2B, pharmaceutical companies in turn can offer DTx for a fee to the patient (B2B2C) or the health service (B2B2G), or offer it for free when the incremental margin is positive. Regarding revenue streams, reimbursement may play an essential role;<sup>17</sup> "risk-sharing" revenue models are on the rise, wherein the price paid by the healthcare provider depends on the clinical impact of the solution.<sup>31</sup> However, some DTx players were experimenting with consumer-led subscription models to reduce their reliance on intermediaries and increase consumer access.<sup>73</sup>

The DTx value proposition for patients included automated, cost-effective, flexible, and convenient solutions that are available to patients 24 hours a day. Providers need to promote users' engagement<sup>28</sup> and ensure patients' DTx acceptance.<sup>30</sup> DTx can make medicine more personalized for patients and allow for remote patient engagement,<sup>28</sup> enabling better capturing and tracking of outcomes.<sup>27</sup>

In terms of key activities and essential resources, Denecke et al.<sup>27</sup> analyzed the complexities and challenges related to DTx, which often involve a combination of technology, healthcare processes, patient engagement, and data management. For DTx and their reimbursement processes to be

widely diffused and accepted, it is fundamental to fully involve various stakeholders, especially patients and physicians, who can serve as essential allies in the complex development process of DTx.<sup>21,27</sup>

### Technology

Technology represents the essence of DTx, yet few scholars have addressed this theme. It is generally agreed that DTx require high-quality software, which must also be cleared and certified.<sup>4</sup> In this domain, some scholars questioned which technologies can most effectively enhance the usage and success of DTx.<sup>70</sup> These technologies may include sensory stimulations,<sup>68</sup> the metaverse<sup>51</sup> socially assistive robots.<sup>69</sup>

The technology used in DTx can be viewed from the perspectives of developers and actual service users.<sup>70</sup> Scholars in this vein, in fact, have shown the essential steps from the DTx service developer's point of view on the one hand, and the technologies to be considered for each implementation step and those utilized from the service user's point of view on the other.<sup>70</sup> DTx producers should possess advanced datasets, ensure effective communication across IT platforms, and provide standardized data formats.<sup>16</sup> These requirements, however, do not have to substitute the characteristics of DTx of being safe and straightforward enough to ensure broad-based adoption.<sup>16</sup>

DTx also need to be clinically validated and connected to the flow of clinical work, and should enable data collection and an instantaneous feedback loop.<sup>4,5</sup> Finally, for developers of DTx, digital biomarkers can revolutionize mental health diagnosis and treatment by providing near-continuous, unobtrusive, and remote measures of behaviors associated with mental health symptoms, and may represent a way to better understand which variables within the therapeutic are most predictive of clinical outcomes.<sup>71</sup>

---

## Discussion

This study shed light on the effectiveness and features of DTx in healthcare. Our analysis of 51 studies showed that papers within the clinical effectiveness and economic effectiveness themes adopted mainly quantitative methodologies, with prospective and open-label clinical trials enriching data supporting the validity of DTx. This finding can be explained by the fact that DTx companies often seek clinical validation for their products and services.

We also found that DTx may represent a solution to the failure to ensure quality and safety control by providers.<sup>17</sup> Ultimately, this may boost healthcare systems if DTx serve to improve patient care by preventing diseases and reducing healthcare costs.<sup>20</sup> In addition to existing pharmacological, non-pharmacological (surgical, radiation, and physical), and psycho-behavioral therapy, DTx can cover therapeutic areas that have previously not been well addressed.<sup>29</sup>

In terms of different research fields, our findings provided three insights related to the current state of DTx literature, as well as some gaps (which we address in our section on future research). First, the challenges related to DTx mainly pertained to the medical context, which was remarkably varied and divided concerning DTx. While many doctors supported these healthcare innovations, some were reluctant to do so and have concerns about their reliability.<sup>27</sup> In fact, while they might cut costs and assist in increasing business and profits, DTx can also undermine the need for in-person clinical visits and the human dimension of clinical care, and care in general. Many doctors were not clinically familiar with these solutions and perceive difficulty in use and inconvenience in prescribing DTx. There was also an absence of standards and processes for providing prescriptions in some cases.<sup>17</sup> Moreover, doctors received little money for DTx, despite the effort required to explain them to patients.<sup>16</sup>

Second, the generation of clinical evidence was critical for efficacy and safety.<sup>63</sup> Pioneering companies (e.g., Kaia Health, Sleepio, and many more) firmly emphasized on their websites and in their promotions the randomized and controlled clinical studies that their DTx have undergone, thereby validating the comparison between pharmacotherapy and DTx.<sup>31</sup> Nevertheless, the need to revise methods to demonstrate clinical effectiveness has also been highlighted.<sup>62</sup> Some scholars raised doubts about current policies, and suggested moving away from randomized clinical trials and heading toward pivotal studies.<sup>64</sup> Other concerns have also been raised, such as technical characteristics of DTx being rapidly upgraded throughout a trial, and the fact that the technology itself may become outdated before the trial ends.<sup>29</sup>

Third, there was a need to consider the complex world of regulatory approval in healthcare, which often fails to keep pace with the development of new technologies.<sup>16,62</sup> Our review emphasized the need and opportunities to revise DTx regulations, and suggested that countries should seek to move together toward common models.<sup>17</sup> Some countries are lagging or have not

provided clear or specific regulations for DTx, making it more difficult for doctors and companies to foster this healthcare innovation.<sup>6,17</sup>

In addition, to promote patient engagement and clinical outcomes, DTx may form part of a digital therapeutic ecosystem, supported by other digital health solutions, patient monitoring, and care support tools. It is essential to consider the prospects and challenges of the Internet of Things (IoT) in DTx solutions because this offers significant opportunities for real-time monitoring and personalized treatment. Moreover, DTx may be combined with the application of biosensors administered as part of small-molecule drugs to monitor adherence with drug therapy.<sup>76</sup>

DTx can also become part of the trend of emerging technologies playing the role of patient companions, such as cognitive assistants or companion robots,<sup>77,78,79</sup> enabling conditions and contexts that promote smart behaviors by amplifying capacities for self-understanding, control, and action.<sup>78</sup>

---

## Practical implications

This work, particularly the identified and discussed themes, provided helpful information regarding the implementation of DTx to address different types of medical disorders or diseases.

The clinical effectiveness theme provided DTx companies, physicians, and policymakers with an overall picture of DTx clinical studies in many fields (diabetes, drug abuse, ADHD, etc.), alongside the methods utilized to obtain these data. Multiple avenues of work remain open and critical elements concern how the clinical effectiveness of DTx should be demonstrated and propagated to end users. Demonstrations of DTx's clinical effectiveness can be provided by utilizing regulatory protocols, but the co-creation of value necessarily involves multiple parties. As developers of DTx obtain regulatory approval, the next step is to gain widespread adoption.<sup>17</sup> Here, it is essential to overcome the barriers set by clinicians, such as concerns regarding personal privacy, equal access, and safety.<sup>6</sup> This study identified many studies that have clinically supported DTx, but few related to privacy and equal access issues.

The economic effectiveness theme provided policymakers with valuable insights on the validity of DTx for the health system. Many studies have shown how DTx can reduce health resource utilization costs compared to TAU.

The regulatory approval theme provided policymakers with a picture of norms and practices to date, along with their critical issues and related academic discussions from different points of view (pharma companies, physicians, other companies, and psychologists). This theme suggested that practitioners must carefully address the complex world of regulatory approvals, which are now essential for market entry. This study acknowledged that DTx represent a heavily regulated industry. Companies need to be aware of existing restrictions and pay particularly close attention to recent changes in the regulatory environment, which can either create opportunities or force every actor in the industry to adapt. Shedding light on regulations, and the economic and clinical efficacy of DTx, represents an opportunity for the health system.<sup>40</sup> Then, by understanding the value that DTx can generate and distribute to the overall ecosystem, policymakers should design rules and policies that keep pace with rapid technology innovations.<sup>16</sup> To ensure broad adoption, policymakers must facilitate the process, guaranteeing ease and clarity in obtaining certifications and reimbursement.

Little has been discussed in the reviewed articles about the specific technology DTx companies should adopt. However, the technology discussion indicated that DTx designers should consider the state of clinical effectiveness and the careful adoption of appropriate technology.<sup>16</sup>

Alongside the technological characteristics DTx should possess, this study underlined several key components of the business model followed by DTx companies. These companies should design innovative and feasible solutions so as to effectively penetrate the market. As with non-digital medicine, it is essential for DTx companies to gain doctors' trust and educate them regarding DTx to allow for appropriate prescription and to promote adoption.<sup>30</sup> DTx success may depend on doctors and caregivers taking active roles in promoting new practices in using technologies, and patients being engaged. To capture and harness this growth market, managers must be able to understand patients' complex and diverse needs.

This study also helped policymakers, healthcare professionals, and DTx manufacturers to devise effective products and services tailored at fostering well-being, the possibility of accessing care, and risk-reduction of treatments that, to date, have had no or little adherence.

Finally, this study presented guidelines and opportunities for healthcare providers and physicians, first arguing that DTx interventions do not wholly displace the human contact that is an essential part of healthcare. Armed with technology and DTx monitoring and treatment of patient

symptoms, physicians will have a greater opportunity to perfect the “human touch” element by spending time with patients for emotional, empathetic, and personal reasons. Nevertheless, at the same time, general practitioners must be able to understand and manage new concepts that are competing in the technological sphere. To this end, adequate training must be provided to integrate clinical skills.

---

## Limitations and further research

Our study is not without limitations, and these could serve to guide further research and future DTx literature reviews.

First, we utilized only three databases for our literature search, which may have restricted the breadth of the reviewed literature and excluded relevant studies available in other databases. Future research should include more databases from diverse disciplines, such as social sciences, humanities, and interdisciplinary studies. This broader approach would capture a wider range of perspectives and findings. For instance, incorporating JSTOR, PsycINFO, and Sociological Abstracts could enrich the literature and provide a more holistic view of DTx research.

Second, our technocratic approach to DTx may have neglected sociological, political, and historical dimensions, leading to an incomplete understanding of its implications and effectiveness. This limitation arose partly due to the limited availability of literature that has integrated these perspectives with DTx. For example, there is wide research from the field of critical sociology on how diagnostic categories, such as ADHD, have been constructed and expanded over the past few decades.<sup>80</sup> Future studies should integrate these perspectives, examining power dynamics, social constructionism, and historical contexts.<sup>81</sup> Additionally, insights from anthropology, ethics, and cultural studies are essential to understand how cultural beliefs, ethical considerations, and human behaviors influence DTx. This should include exploring data privacy issues<sup>82</sup> and how cultural variations affect the user experience and the effectiveness of digital health interventions.

We also proposed several avenues for further research, which we addressed according to each theme (see *table 4*). With some governments taking initiatives and launching programs to increase the adoption rate of digital health solutions, future studies should carefully analyze DTx regulations and the role of the public sector in addressing these, since the needs

of companies in producing and launching DTx solutions on the market in a short time must go hand in hand with specific regulation and policies.

Regarding technology, scholars could seek to develop a comprehensive picture of the roles of IoT, sensors/devices, and hardware in DTx solutions and whether they can help monitor treatment adherence in complement to a traditional therapeutic approach. So far, companies such as Voluntis and Kaia Health have not used hardware in their solutions, while others, such as Omada and Propeller, have based their solutions on the selling of wearables and hardware components. There are articles (see systematic review in Cornet and Holder<sup>83</sup>) that extensively discussed technological aspects that could be related to the DTx field. In terms of business model, with the rise of chronic diseases, research may also examine the motivations and needs of doctors and healthcare providers. Regarding DTx effectiveness, literature may also proceed to separately address economic and clinical aspects. In some countries (e.g., Germany), randomized controlled trials represent the gold standard for assessing the efficacy of therapeutic interventions,<sup>17</sup> as they provide a high degree of internal validity. However, they can fail to adequately address questions about real-world resource utilization and costs. Hence, scholars may seek to provide “real-world” observational data.<sup>21</sup>

DTx represent a global and interdisciplinary area of research, where scholars from every field (i.e., economics, engineering, law, management, medicine, social and political sciences, etc.) are called to contribute to taking advantage of the numerous opportunities and challenges of this disruptive phenomenon.

In recent years, the scientific literature on DTx has grown tremendously. However, more literature is needed, especially because the community is now looking at how DTx solutions will contribute to creating mixed, or “chimaera,” industries—that is, combinations of transitional industries such as healthcare, pharma, and technology. Moreover, in relation to DTx, there is a need to address the social and political determinants of health, going beyond a mere digital lens.<sup>80,84</sup>

We noticed that further and holistic investigation is required with respect to the technology, economics, and management themes related to DTx. For instance, we found no research on the actors’ ecosystem concerning DTx, although scholars have underscored the importance of involving all key actors (patients, physicians, pharmacists, pharma companies, policy-makers, payors) to deliver effective and profitable DTx.<sup>16,27,31</sup>

**Table 4 - Further research**

| Themes                 | Research Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical effectiveness | <ul style="list-style-type: none"> <li>• Which types of studies (randomized clinical trial, pivotal, retrospective, prospective, etc.) should be pursued to facilitate the introduction of DTx in the market while providing adequate clinical data?</li> <li>• How can studies involve the perspectives of all key actors (patients, physicians, pharmacists, pharma firms, policymakers, payors) in evaluating the clinical effectiveness of DTx?</li> <li>• Which factors drive patients' initial mistrust of DTx (e.g., lack of clinical data), and how can this be overcome?</li> <li>• How can patient engagement impact clinical effectiveness?</li> </ul>                                    |
| Regulatory approval    | <ul style="list-style-type: none"> <li>• How can regulation and the public sector ensure that DTx manufacturers cannot create monopolies or oligopolies in specific industries and contexts and thereby negatively impact deploying markets and patients?</li> <li>• What model should be used to validate, develop, and distribute DTx in ways that patients' outcomes are improved, medical costs are decreased, and all patient demographics can access DTx safely and effectively?</li> <li>• How can patient privacy be ensured and privacy concerns be mitigated given the constant observation of patients (i.e., through biometrics) and the pervasive capturing of patient data?</li> </ul> |
| Economic effectiveness | <ul style="list-style-type: none"> <li>• Which parameters should be analyzed so as to estimate the positive aspects of DTx on public and private expenditure in comparison with TAU?</li> <li>• What is the best payment method (pay for performance, pay for service, bundled payments, etc.) for DTx within health care systems?</li> <li>• How can the improvement or worsening of ecosystem well-being (i.e., patients, physicians, caregivers, etc.) after introducing DTx solutions be measured?</li> </ul>                                                                                                                                                                                    |
| Business model         | <ul style="list-style-type: none"> <li>• Who are the key patients (e.g., ageing people, children, etc.) of DTx, and which types of solutions do they need?</li> <li>• What are the most innovative value propositions related to DTx solutions?</li> <li>• How can the channels to be used to market DTx be investigated?</li> <li>• How can patient engagement be fostered?</li> <li>• How might the adoption of an ecosystem perspective enrich understanding of DTx?</li> </ul>                                                                                                                                                                                                                   |

|            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Technology | <ul style="list-style-type: none"><li>• Which roles might the IoT and sensors/devices in DTx solutions play?</li><li>• Can sensors/devices help monitor adherence to treatment and complement traditional therapeutics approaches?</li><li>• How can the design of DTx solutions (e.g., videogames, apps, devices) enable or constrain patient engagement?</li><li>• What are the implications of tech literacy (especially for ageing populations) for DTx adoption?</li><li>• How can the interaction between human actors (e.g., doctors, caregivers, etc.) and technology (DTx solutions) provide personalized treatments?</li></ul> |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

---

## Conclusions

In conclusion, this research underscored the potential of DTx in improving patient outcomes and fostering innovative business models involving pharmaceutical, technology, and healthcare companies, alongside governments and other key actors, all of which contribute to the creation of a thriving ecosystem. However, realizing this potential necessitates joint action and cultural transformation. At present, the trajectory of DTx appears both promising and uncertain. While these solutions demonstrate remarkable potential and growth, they also entail challenges within certain startups and are not being universally embraced by all stakeholders, with varying levels of skepticism being expressed. The dual narrative underscored the complex landscape DTx providers must navigate.

DTx hold promise as various stakeholders actively engage in their integration and promotion, thereby contributing to a transformative shift in healthcare delivery. Specifically,

- Governments should actively engage in facilitating DTx utilization, incorporating regulatory facilitation, financial support, and public awareness campaigns to maximize the impact of DTx on healthcare delivery.
- Healthcare professionals should prescribe DTx to patients and advocate for their efficacy, seeking to foster patient trust and ensure effective utilization, which will result in enhanced disease management and overall improvements to health.

- Insurers should integrate DTx into policies, providing added value to policyholders by offering them cost-effective solutions, thereby improving health outcomes and reducing expenses.

- Companies should include DTx in benefit packages, thereby enhancing employee well-being and empowering them to proactively manage their health.

Further developments could catalyze a fundamental transformation in the global healthcare landscape, fostering innovation, improving access to care, and optimizing system efficiency to increase value co-creation and well-being for the actors involved.

### **Funding**

This PhD project is supported by a grant from the Italian Minister of Research (PON ricerca 2014-20 Decreto Ministeriale n. 0000153 del 25.01.2017).

### **Ethical approval**

Institutional review board approval was not required, as this article comprises a systematic review of the literature and not original research.

### **Declaration of conflicting interests**

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### **Contributorship**

AR: writing-original draft, resources, methodology, investigation, data curation. MG: writing-review and editing, validation, conceptualization. PL: writing-review and editing, conceptualization. CM: writing-review and editing, investigation. LS: supervision-project administration.

**Patient consent statements:** The authors confirm that the Patient Consent Statement is not required since this study did not involve any patients or subjects as this is a systematic review manuscript based on other published papers.

### **Note**

Guarantor: AR.

| Section and Topic       | Item # | Checklist item                                                                                                                                                                                                                                                                                       | Location where item is reported |
|-------------------------|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| <b>TITLE</b>            |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Title                   | 1      | Identify the report as a systematic review.                                                                                                                                                                                                                                                          | Pag. 1                          |
| <b>ABSTRACT</b>         |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Abstract                | 2      | See the PRISMA 2020 for Abstracts checklist.                                                                                                                                                                                                                                                         | Pag. 1                          |
| <b>INTRODUCTION</b>     |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Rationale               | 3      | Describe the rationale for the review in the context of existing knowledge.                                                                                                                                                                                                                          | Pag. 4-5                        |
| Objectives              | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.                                                                                                                                                                                                               | Pag. 4-5                        |
| <b>METHODS</b>          |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Eligibility criteria    | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.                                                                                                                                                                                          | Pag. 5-6                        |
| Information sources     | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.                                                                                            | Pag. 5-6                        |
| Search strategy         | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.                                                                                                                                                                                 | Pag. 5-6                        |
| Selection process       | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | Pag. 6                          |
| Data collection process | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Pag. 6                          |
| Data items              | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | Pag. 6-7                        |

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                                    | Location where item is reported |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Data items                    | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.                                                      | Pag. 6-7                        |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Pag. 6-7                        |
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.                                                                                                                               | Pag. 6                          |
| Synthesis methods             | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).                                              | Pag. 7                          |
|                               | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.                                                                                                             | Pag. 7-8                        |
|                               | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                                                                            | Pag. 7-8                        |
|                               | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.       | Pag. 7-8                        |
|                               | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).                                                                                                                              | Pag. 7-8                        |
|                               | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                                                                      | Pag. 7-8                        |
| Reporting bias assessment     | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                                                                           | Pag. 6-7                        |

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                                                       | Location where item is reported |
|-------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Certainty assessment          | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                                                                                                | Pag. 6-7                        |
| <b>RESULTS</b>                |        |                                                                                                                                                                                                                                                                                      |                                 |
| Study selection               | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                                                                                         | Pag. 7                          |
|                               | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                                                                                          | Pag. 5-7                        |
| Study characteristics         | 17     | Cite each included study and present its characteristics.                                                                                                                                                                                                                            | Table 2                         |
| Risk of bias in studies       | 18     | Present assessments of risk of bias for each included study.                                                                                                                                                                                                                         | Pag. 7                          |
| Results of individual studies | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.                                                     | Pag. 6                          |
| Results of syntheses          | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.                                                                                                                                                                               | Pag. 6                          |
|                               | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Pag. 7                          |
|                               | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                                                                                       | Pag. 7                          |
|                               | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                                                                                           | Pag. 7                          |
| Reporting biases              | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                                                                                              | Pag. 7                          |
| Certainty of evidence         | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                                                                                                  | Pag. 7                          |

| Section and Topic                              | Item # | Checklist item                                                                                                                                                                                                                             | Location where item is reported |
|------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| <b>DISCUSSION</b>                              |        |                                                                                                                                                                                                                                            |                                 |
| Discussion                                     | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                                                          | Pag. 8                          |
|                                                | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                                                            | Pag. 13                         |
|                                                | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                                                      | Pag. 13                         |
|                                                | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                                                             | Pag. 9-14                       |
| <b>OTHER INFORMATION</b>                       |        |                                                                                                                                                                                                                                            |                                 |
| Registration and protocol                      | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.                                                                                             | Pag. 5                          |
|                                                | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.                                                                                                                                             | N/A                             |
|                                                | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.                                                                                                                                            | N/A                             |
| Support                                        | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.                                                                                                              | Pag. 16                         |
| Competing interests                            | 26     | Declare any competing interests of review authors.                                                                                                                                                                                         | Pag. 16                         |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | N/A                             |

*From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71*

---

## Digital therapeutics: a systematic literature review

### Authors

- Andrea Ruggiero is an experienced professional and a researcher with a PhD in Management, Department of Economics, Management and Institutions, University of Naples Federico II, Naples, Italy. E-mail: [andrearug1994@gmail.com](mailto:andrearug1994@gmail.com); Address: Via Cintia, 21. 80126 Napoli; Number: +393663332326. Corresponding author.

- Mauro Gatti is an Architect and Data Scientist, IBM Italy.

- Pietro Leo is an Executive Architect and member of IBM Academy of Technology, IBM Italy.

- Cristina Mele is a Full professor of Management, Department of Economics, Management and Institutions, University of Naples Federico II, Naples.

- Luigi Somaini is a Business Development Manager, IBM Italy.

### Acknowledgments

This research activity is part of the PhD project Andrea Ruggiero has developed which involved IBM Italy, “Università degli Studi di Napoli Federico II” and other institutions. This PhD project is supported also by a grant of the Italian Minister of Research (PON ricerca 2014-20 Decreto Ministeriale n. 0000153 del 25.01.2017). We are thankful to Giovanna Camorali, Vincenzo Saturnino, Francesco Giuliani, Chiara Marchioni, Jaan-Udo Morosov, Thomas Brunschwiller, Roberto Storch, Tullio Fatigati.

### Conflicts of interest

No potential conflict of interest was reported by the authors.

---

## References

1. McKinsey. The health benefits and business potential of digital therapeutics. Available from: <https://www.mckinsey.com/industries/life-sciences/our-insights/the-health-benefits-and-business-potential-of-digital-therapeutics#/>
2. Business Insider. Using video games as medical treatments seemed promising, but a stunning failure raises questions about the future of digital therapeutics. Available from: <https://www.businessinsider.com/how-digital-therapeutics-startups-can-survive-after-pear-bankruptcy-2023-6>
3. Markets and Markets. Digital therapeutics (DTx) market by application (prediabetes, nutrition, care, diabetes, CVD, CNS, CRD, MSD, GI, substance abuse, rehabilitation), sales channel (B2C, patient, caregiver, B2B, providers, payer, employer, pharma)-Global forecasts to 2027. Available from: <https://www.marketsandmarkets.com/Market-Reports/digital-therapeutics-market-51646724.html>
4. Digital Therapeutics Alliance. Comparison guide: Patient-facing digital health technologies (DHTs). Available from: [https://dtxalliance.org/wp-content/uploads/2023/06/DTA\\_FS\\_Patient-Facing-DHT-Comparison-Guide.pdf](https://dtxalliance.org/wp-content/uploads/2023/06/DTA_FS_Patient-Facing-DHT-Comparison-Guide.pdf)
5. ISO. ISO/TR 11147:2023; Health informatics; Personalized digital health: Digital therapeutics health software systems. Available from: <https://www.iso.org/standard/83767.html>
6. Recchia G, Gussoni G. Digital Therapeutics: Scientific, technological, and regulatory challenges. In: Personalized medicine meets artificial intelligence: Beyond “hype”, towards the metaverse. Springer International Publishing; 2023, pp. 37–50.
7. McKinsey. The promise of digital therapeutics. Available from: <https://www.mckinsey.com/industries/life-sciences/our-insights/the-promise-of-digital-therapeutics>
8. Osterwalder A, Pigneur Y. Business model generation: a handbook for visionaries, game changers, and challengers. Vol. 1. John Wiley & Sons; 2010.
9. Wired. Finalmente l’Italia inizia a fare sul serio sulle terapie digitali. Available from: <https://www.wired.it/terapie-digitali-politica-italiana-parlamento/>
10. Deprexix. Digital Therapy That Works. Available from: <https://it.deprexis.com/acquista-un-codice-di-accesso-deprexisr>
11. Recchia G, Capuano DM, Mistri N, Verna R. Digital Therapeutics-What they are, what they will be. Acta Sci Med Sci 2020; 4: 1-9.
12. Torous J, Hsin H. Empowering the digital therapeutic relationship: virtual clinics for digital health interventions. NPJ Digit Med 2018; 1: 16.

**13.** Goldsack J, Coder M, Fitzgerald C, Navar-Mattingly N, Corvos A, Atreja A. Digital health, digital medicine, digital therapeutics (DTx): What's the difference. *DiMe* 2019; 10.

**14.** Santoro E, Boscherini L, Lugo A. Terapie digitali: una revisione degli studi clinici. *Ric Pra* 2021; 37: 112-116.

**15.** Ribba B, Peck R, Hutchinson L, Bousnina I, Motti D. Digital therapeutics as a new therapeutic modality: a review from the perspective of clinical pharmacology. *Clin Pharmacol Ther* 2023; 114: 578-590.

**16.** Hong JS, Wasden C, Han DH. Introduction of Digital Therapeutics. *Comput Methods Programs Biomed* 2021; 209: 106319.

**17.** Mantovani A, Leopaldi C, Nighswander CM, Di Bidino R. Access and reimbursement pathways for digital health solutions and in vitro diagnostic devices: Current scenario and challenges. *Front Med Technol* 2023; 5: 1101476.

**18.** An S, Ko J, Yu KS, Kwon H, Kim S, Hong J, Kong HJ. Exploring the category and use cases on digital therapeutic methodologies. *Healthc Inform Res* 2023; 29: 190-198.

**19.** Phan P, Mitragotri S, Zhao Z. Digital therapeutics in the clinic. *Bio-eng Transl Med* 2023; 8: e10536.

**20.** Sapanel Y, Tadeo X, Brenna CT, Remus A, Koerber F, Cloutier LM, et al. Economic evaluation associated with clinical-grade mobile app-based digital therapeutic interventions: Systematic review. *J Med Internet Res* 2023; 25: e47094.

**21.** Wang C, Lee C, Shin H. Digital therapeutics from bench to bedside. *NPJ Digit Med* 2023; 6: 38.

**22.** Thomas J, Harden A, Oakley A, Oliver S, Sutcliffe K, Rees R, et al. Integrating qualitative research with trials in systematic reviews. *Bmj* 2004; 328: 1010-1012.

**23.** Hage E, Roo JP, van Offenbeek MA, Boonstra A. Implementation factors and their effect on e-Health service adoption in rural communities: A systematic literature review. *BMC Health Serv Res* 2013; 13: 1-16.

**24.** Terry G, Hayfield N, Clarke V, Braun V. Thematic analysis. In: *The SAGE handbook of qualitative research in psychology*, 2nd ed. SAGE; 2017, pp. 17-37.

**25.** Dixon-Woods M, Agarwal S, Young B, Jones D, Sutton A. Integrative approaches to qualitative and quantitative evidence. *Health Dev Agency*; 2004.

**26.** Lumbreras AG, Hurwitz JT, Liang X, Schippers S, Phillip K, Bhat-tacharjee S, et al. Insights into insurance coverage for digital therapeutics: A qualitative study of US payer perspectives. *J Manag Care Spec Pharm* 2024;

30: 313-325.

**27.** Denecke K, May R, Gabarron E, Lopez-Campos GH. Assessing the potential risks of digital therapeutics (DTx): The DTx risk assessment canvas. *J Pers Med* 2023; 13: 1523.

**28.** Strauss G, Flannery JE, Vierra E, Koepsell X, Berglund E, Miller I, et al. Meaningful engagement: A crossfunctional framework for digital therapeutics. *Front Digit Health* 2022; 4: 890081.

**29.** Chung JY. Digital therapeutics and clinical pharmacology. *Transl Clin Pharmacol* 2019; 27: 6-11.

**30.** Carrera A, Zoccarato F, Mazzeo M, Lettieri E, Toletti G, Bertoli S, et al. What drives patients' acceptance of Digital Therapeutics? Establishing a new framework to measure the interplay between rational and institutional factors. *BMC Health Serv Res* 2023; 23: 145.

**31.** Geiger S, Kjellberg H. Market mash ups: The process of combinatorial market innovation. *J Bus Res* 2021; 124: 445-457.

**32.** Biskupiak Z, Ha VV, Rohaj A, Bulaj G. Digital therapeutics for improving effectiveness of pharmaceutical drugs and biological products: Pre-clinical and clinical studies supporting development of drug+digital combination therapies for chronic diseases. *J Clin Med* 2024; 13: 403.

**33.** Lee H, Choi EH, Shin JU, Kim TG, Oh J, Shin B, et al. The impact of intervention design on user engagement in digital therapeutics research: Factorial experiment with a mixed methods study. *JMIR Form Res* 2024; 8: e51225.

**34.** Namgung E, Kwon SU, Han MK, Kim GM, Kim HY, Park KY, et al. Digital therapeutics using virtual reality based visual perceptual learning for visual field defects in stroke: A double blind randomized trial. *Brain Behav* 2024; 14: e3525.

**35.** Nomura A, Takagi Y, Tanigawa T, Takamura M, Node K, Kario K. Blood pressure management in 1,000 patients with CureApp HT digital therapeutics for hypertension. *medRxiv* 2024.

**36.** Oh S, Choi J, Han DH, Kim E. Effects of game-based digital therapeutics on attention deficit hyperactivity disorder in children and adolescents as assessed by parents or teachers: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry* 2024;33:481-493.

**37.** Orsolini L, Longo G, Volpe U. Practical application of digital therapeutics in people with mood disorders. *Curr Opin Psychiatry* 2024;37:9-17.

**38.** Seo YC, Yong SY, Choi WW, Kim SH. Meta-analysis of studies on the effects of digital therapeutics. *J Pers Med* 2024;14:157.

**39.** Monico LB, Eastlick M, Michero D, Pielsticker P, Glasner S. Feasi-

bility and acceptability of a novel digital therapeutic combining behavioral and pharmacological treatment for opioid use disorder. *Digit Health* 2024;10.

**40.** Kario K, Tomitani N, Harada N, Okura A, Hisaki F, Tanigawa T, et al. Home blood pressure-lowering effect of digital therapeutics in hypertension: Impact of body weight and salt intake. *Hypertens Res* 2023;46:1181-1187.

**41.** Li Y, Yip MY, Ting DS, Ang M. Artificial intelligence and digital solutions for myopia. *Taiwan J Ophthalmol* 2023;13:142-150.

**42.** Sun TH, Yeom JW, Choi KY, Kim JL, Lee HJ, Kim HJ, et al. Potential effectiveness of digital therapeutics specialized in executive functions as adjunctive treatment for clinical symptoms of attention-deficit/hyperactivity disorder: A feasibility study. *Front Psychiatry* 2023;14.

**43.** Joshi S, Verma R, Lathia T, Selvan C, Tanna S, Saraf A, et al. Fitterfly diabetes CGM digital therapeutics program for glycemic control and weight management in people with type 2 diabetes mellitus: Real-world effectiveness evaluation. *JMIR Diabetes* 2023;8.

**44.** Xiong X, Braun S, Stitzer M, Luderer H, Shafai G, Hare B, et al. Evaluation of real world outcomes associated with use of a prescription digital therapeutic to treat substance use disorders. *Am J Addict* 2023;32:24-31.

**45.** Maricich YA, Xiong X, Gerwien R, Kuo A, Velez F, Imbert B, et al. Real-world evidence for a prescription digital therapeutic to treat opioid use disorder. *Curr Med Res Opin* 2021;37:175-183.

**46.** Osborn CY, Hirsch A, Sears LE, Heyman M, Raymond J, Huddleston B, et al. One drop app with an activity tracker for adults with type 1 diabetes: Randomised controlled trial. *JMIR Mhealth Uhealth* 2020;8.

**47.** Bray L, Sharpe A, Gichuru P, Fortune PM, Blake L, Appleton V. The acceptability and impact of the Xploro digital therapeutic platform to inform and prepare children for planned procedures in a hospital: Before and after evaluation study. *J Med Internet Res* 2020;22.

**48.** Iacoviello BM, Murrough JW, Hoch MM, Huryk KM, Collins KA, Cutter GR, et al. A randomized controlled pilot trial of the Emotional Faces Memory Task: a digital therapeutic for depression. *NPJ Digit Med* 2018;1:1-7.

**49.** Davison NJ, Guthrie NL, Medland S, Lupinacci P, Nordyke RJ, Berman MA. Cost-effectiveness analysis of a prescription digital therapeutic in type 2 diabetes. *Adv Ther* 2024;41:806-825.

**50.** Liu T, Zhan Y, Chen S, Zhang W, Jia J. Cost-effectiveness analysis of digital therapeutics for home-based cardiac rehabilitation for patients with chronic heart failure: Model development and data analysis. *Cost Eff Resour Alloc* 2023;21:82.

51. Kim EJ, Kim JY. The metaverse for healthcare: Trends, applications, and future directions of digital therapeutics for urology. *Int Neurourol J* 2023;27(Suppl 1).
52. Nomura A, Tanigawa T, Kario K, Igarashi A. Cost-effectiveness of digital therapeutics for essential hypertension. *Hypertens Res* 2022;45:1538-1548.
53. Velez FF, Malone DC. Cost-effectiveness analysis of a prescription digital therapeutic for the treatment of opioid use disorder. *J Market Access Health Policy* 2021;9:1966187.
54. Wang W, Gellings Lowe N, Jalali A, Murphy SM. Economic modeling of reSET-O, a prescription digital therapeutic for patients with opioid use disorder. *J Med Econ* 2021;24:61-68.
55. Velez FF, Luderer HF, Gerwien R, Parcher B, Mezzio D, Malone DC. Evaluation of the cost-utility of a prescription digital therapeutic for the treatment of opioid use disorder. *Postgrad Med* 2021;133:421-427.
56. Nordyke RJ, Appelbaum K, Berman MA. Estimating the impact of novel digital therapeutics in type 2 diabetes and hypertension: health economic analysis. *J Med Internet Res* 2019;21.
57. Carrera A, Manetti S, Lettieri E. Rewiring care delivery through digital therapeutics (DTx): a machine learning-enhanced assessment and development (M-LEAD) framework. *BMC Health Serv Res* 2024;24:237.
58. Kendziorra J, Ebers L, Winkler TJ. Unraveling the formation of physicians' decisions to prescribe digital therapeutics. *eLibrary* 2024.
59. Miao BY, Sushil M, Xu A, Wang M, Arneson D, Berkley E, et al. Characterisation of digital therapeutic clinical trials: A systematic review with natural language processing. *Lancet Digit Health* 2024;6:e229.
60. Schmidt L, Pawlitzki M, Renard BY, Meuth SG, Masanneck L. The three-year evolution of Germany's digital therapeutics reimbursement program and its path forward. *NPJ Digit Med* 2024;7:139..
61. Kim M, Patrick K, Nebeker C, et al. The Digital Therapeutics Real-World Evidence Framework: An Approach for Guiding Evidence-Based Digital Therapeutics Design, Development, Testing, and Monitoring. *J Med Internet Res* 2024;26
62. Kumar A, Ross JS, Patel NA, et al. Studies of prescription digital therapeutics often lack rigor and inclusivity: Study examines prescription digital therapeutics standards. *Health Aff* 2023;42:1559-1567.
63. Smits M, Ludden GD, Verbeek PP, et al. How digital therapeutics are urging the need for a paradigm shift: from evidence-based health care to evidence-based well-being. *Interact J Med Res* 2022;11

- 64.** Carl JR, Jones DJ, Lindhiem OJ, et al. Regulating digital therapeutics for mental health: Opportunities, challenges, and the essential role of psychologists. *Br J Clin Psychol* 2022;61:130-135.
- 65.** Bolpagni M, Pardini S, Gabrielli S. Human centered design of AI-powered digital therapeutics for stress prevention: Perspectives from multi-stakeholders' workshops about the Shiva Solution. SSRN 2024.
- 66.** Rheinberger D, Baffsky R, McGillivray L, et al. Digital therapeutics in the hospital for suicide crisis-content and design recommendations from young people and hospital staff. *Digit Health* 2024;10.
- 67.** Weimann TG, Gißke C. Unleashing the potential of reinforcement learning for personalizing behavioral transformations with digital therapeutics: A systematic literature review. *BIOSTEC* 2024;2:230-245.
- 68.** Fougère M, Greco-Vuilloud J, Arnous C, et al. Sensory stimulations potentializing digital therapeutics pain control. *Front Pain Res* 2023;4.
- 69.** Stanojevic C, Bennett CC, Sabanovic S, et al. Conceptualizing socially-assistive robots as a digital therapeutic tool in healthcare. *Front Digit Health* 2023;5:1208350.
- 70.** Yoo JH, Jeong H, Chung TM. Cutting-edge technologies for digital therapeutics: A review and architecture proposals for future directions. *Appl Sci* 2023;13:6929.
- 71.** Adler DA, Wang F, Mohr DC, et al. A call for open data to develop mental health digital biomarkers. *BJPsych Open* 2022;8.
- 72.** Watson A, Chapman R, Shafai G, et al. FDA regulations and prescription digital therapeutics: Evolving with the technologies they regulate. *Front Digit Health* 2023;5:1086219.
- 73.** Akili announces business transformation, focusing on non-prescription model. *Business Wire*. <https://www.businesswire.com/news/home/20230913220525/en/Akili-Announces-Business-Transformation-Focusing-on-Non-prescription-Model> (2023, accessed 12 July 2023).
- 74.** Yan K, Balijepalli C, Druyts E. The impact of digital therapeutics on current health technology assessment frameworks. *Front Digit Health* 2021;3.
- 75.** Recchia G, Barbanti P, Cottini L, et al. Digital Therapeutics, prerequisites for development of the technological and economic ecosystem in Italy and Europe. *Tendenze* 2021;127.
- 76.** Belluck P. First digital pill approved to worries about biomedical “big brother.” *New York Times* 2017;13.
- 77.** Odekerken-Schröder G, Mele C, Russo-Spena T, et al. Mitigating loneliness with companion robots in the COVID-19 pandemic and beyond: an inte-

grative framework and research agenda. *J Serv Manag* 2020;31:1149-1162.

**78.** Mele C, Russo-Spena T, Marzullo M, et al. Boundary work in value co-creation practices: the mediating role of cognitive assistants. *J Serv Manag* 2022;33:342-362.

**79.** Ruggiero A, Mahr D, Odekerken-Schröder G, et al. Companion robots for well-being: A review and relational framework. In: *Research handbook on services management*. Cheltenham: Edward Elgar Publishing, 2022, pp. 309-330.

**80.** Conrad P, Potter D. From hyperactive children to ADHD adults: Observations on the expansion of medical categories. *Soc Probl* 2000;47:559-582.

**81.** Hacking I. *The social construction of what?*. Cambridge: Harvard University Press, 1999.

**82.** Floridi L. *The ethics of information*. Oxford: Oxford University Press, 2013.

**83.** Cornet VP, Holden RJ. Systematic review of smartphone-based passive sensing for health and wellbeing. *J Biomed Inform* 2018;77:120-132.

**84.** Read J, Moncrieff J. Depression: Why drugs and electricity are not the answer. *Psychol Med* 2022;52:1401-1410.





**Tendenze Salute e Sanità**

*Fondazione Tendenze Salute e Sanità*, già *Fondazione Smith Kline*, è iscritta al Registro Unico Nazionale del Terzo Settore dall'agosto 2023. Nella sua veste di aggregatore di competenze, esperienze e conoscenze, la Fondazione da sempre si pone come punto di riferimento e incubatore di progettualità per Operatori sanitari, Pazienti e Istituzioni, allo scopo di offrire contributi originali nel complesso panorama della sanità. Dall'inizio degli anni Duemila ha avviato le iniziative nell'area della Prevenzione, riconosciuta essere un imprescindibile pilastro del "sistema salute" italiano. La Fondazione ha più recentemente intrapreso ulteriori nuovi progetti per stimolare la ricerca e la sanità del nostro Paese lungo un percorso di trasformazione digitale, destinato a rappresentare un profondo cambiamento organizzativo, tecnologico e culturale con importanti implicazioni etiche e sociali.