



Terzo Digital Health Monitoring Report

Digital Health & Al Tools for Patients and Citizens





The Third Digital Health Monitoring Report is the result of the work of the **Digital Health Policy Lab**, a research project established in 2022 in collaboration between **Indicon Società Benefit** and the **University of Milan**, aimed at promoting the development and access of digital health technologies (DHTs) in the Italian National Health Service.

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Preface

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It is with pleasure and sincere appreciation for the work carried out that I have accepted the invitation to author the foreword to the third edition of the Digital Health Monitoring Report, produced by Indicon Società Benefit in collaboration with the University of Milan – La Statale. This document has become an important reference for understanding the development and prospects of Digital Health in Italy, a sector I consider strategic for the future of our healthcare system and for protecting the health of citizens.

Health is not a cost: it is the first and most valuable investment a community can make for its future. Guided by this principle, I launched and promoted a bill in Parliament, of which I was the first signatory, on Digital Therapeutics (DTx) (C.1208), a commitment I consider a priority to translate the potential of digital innovation into real and measurable clinical benefits for Italian citizens.

Digital Therapeutics (DTx) represent one of the most promising frontiers of contemporary medicine. Their widespread adoption allows patients to be truly placed at the centre of the care pathway, expands access to therapies, promotes continuity of care, and contributes to more sustainable management of resources within the Italian National Health Service (Servizio Sanitario Nazionale, SSN). However, without clear regulations, appropriate assessment frameworks, and structured pathways for integration into clinical practice and reimbursement, there is a risk of losing opportunities and exacerbating inequalities.

This is why my mission, as a physician and as a deputy, is twofold: to promote healthcare innovation that improves treatment outcomes, and to ensure safety, equity, and transparency in evaluation and access processes.

The consolidated act "Provisions on Digital Therapeutics" (C.1208) was created with precisely this aim: to regulate the sector comprehensively, bridging the regulatory gap with other European countries and making Digital Therapeutics effectively accessible to citizens by including them in the Essential Levels of Care (LEA) of the Italian National Health Service. This law is intended to ensure that Digital Therapeutics can be prescribed and reimbursed while safeguarding patients, laying the foundation for an innovative and sustainable healthcare system in which DTx are fully integrated into care pathways.

Parliamentary work, however, does not end with the presentation of an act. It requires listening, dialogue, and collaboration among all stakeholders: institutions, academia, the clinical community, industry, and patient associations. In this perspective, the establishment of the Parliamentary Intergroup "Digital Health and Digital Therapeutics: a Priority for the Country," which I have the honour of chairing, plays a key role in fostering stable and constructive dialogue across expertise, capable of translating knowledge into evidence-based public policies.

The Digital Health Monitoring Report is a valuable tool to support this journey. It is not only an analytical document but also an act of political and scientific responsibility: a platform for shared knowledge that chronicles the evolution of the sector in Italy and Europe, highlights best practices already in place, draws lessons from international experiences, and identifies remaining challenges. Of particular significance is the innovation introduced in this edition, which broadens the analysis to include the impact of Artificial Intelligence (AI) on diagnosis, treatment, and clinical decision support processes. This represents an essential step in fully capturing the transformative potential of digital health and promoting the use of innovation guided by scientific evidence, safety, and a person-centred approach.

Digital Therapeutics are not a distant-future prospect: they are already a reality, requiring political courage, scientific expertise, and a shared vision. Italy has all the resources needed to play a leading role in this transformation, provided it can combine innovation with responsibility, and progress with humanity.



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EXECUTIVE SUMMARY

Digital Health Technologies (DHTs) are digital tools and systems designed to support, enhance, or deliver healthcare services. DHTs certified as Medical Devices (MDs) and intended for patient use to monitor, diagnose, prevent, or treat medical conditions fall under the definition of patient-managed Digital Medical Devices (pDMD). Digital Therapeutics (DTx) represent the subset of DHTs specifically intended for treatment. In Europe, pDMD are regulated under the MD Regulation (MDR) and are defined as Software as a Medical Device (SaMDs), not integrated into a hardware MD, projected to be used by an ordinary user, either alone or with assistance of a healthcare professional.

Global clinical trials on DTx. Clinical trials on DTx increased by 54% in 15 months (n=1.888). Mobile applications are the predominant technology investigated (65.4%), followed by web applications (20.1%), virtual reality systems (6.7%), videogames (5.1%), and applications integrated with wearable devices/sensors (2.8%). Psychiatric disorders are the main therapeutic area (52% of trials), with insomnia, depression, and anxiety as the top three conditions addressed. Most clinical trials are conducted in North America (39.4%) and Europe (33.1%), with Germany leading among EU countries (7% of all trials and 20% of European ones). Italy accounts for only 3% of the total (Submitted to Plos Digital Health).

EU DTx mapping. Germany is the country with the most advanced regulatory framework for Digital Health in Europe. The specific law (DVG) allows clinicians to prescribe certified Digital Health Applications (DiGAs), with a reimbursement by statutory health insurance and a fast-track, evidence-based system. 57 DiGAs are reimbursed in Germany, with 46 on the permanent list and 11 on the temporary list (up to 12 months while gathering evidence). Compared with 2024, when 35 were permanent (+31.4%) and 20 temporary, DiGAs access has increased. Most reimbursed DiGAs target psychiatric disorders.

In the **UK**, Digital Health Technology (DHT) reimbursement depends on local NHS or specific service programs, as there is no specific national law. The Early Value Assessment (EVA), conducted by the National Institute for Health and Care Excellence (NICE) for digital products, provides recommendations to guide local adoption decisions. 27 DTx have been assessed though the EVA process, all targeting psychiatric disorders; 52% received positive recommendations for NHS use during evidence generation, 48% were for research-only use, and none were negatively recommended.

In **France**, the *Prise en Charge Anticipée Numérique* (PECAN) allows temporary reimbursement of DTx up to one year while further evidence is collected. Then, DTx with robust evidence can enter in the List of Products and Services Reimbursable (LPPR). 7 DTx result certified by the Agence du Numérique en Santé (ANS), but none are included in the LPPR.

In **Belgium**, the mHealthBelgium framework regulates digital health applications using a pyramid system: Level 1 (CE marking), Level 2 (reimbursement eligibility), Level 3 light (temporary reimbursement), and Level 3 plus (permanent reimbursement). No DTx are reimbursed; 2 are detected, both at Level 1.

In **Spain**, there is still no dedicated reimbursement pathway for Digital Health Solutions at national level. A preliminary bill for a new Law on Digital Health ("Ley de Salud Digital") is under public consultation.

DiGAs price analysis. The average price of a DiGA is €250.25 (€119.00-618.00) on the permanent and €513.20 (€116.97-2,077.00) on the temporary list. For DiGAs moving from the temporary to the permanent list: 88% had a price reduction, with an average decrease of 48.6% (vs 2024: 91%; average reduction: 47%); 7% had an unchanged price (vs 2024: 3%); and 5% had a price increase (vs 2024: 6%). From 2021 to 2025, DiGAs price reductions when moving from the temporary to permanent list have decreased, peaking at -49% in 2022 and reaching -41% in 2025.

ITA pDMD mapping. 15% of SaMDs commercialised in Italy are pDMDs: 45% with a medical purpose of monitoring (vs 47% in 2024), 41% for therapy (vs 38%), 8% for prevention (vs 9%), and 6% for diagnosis (vs 7%).

ITA DTx mapping. 26 certified DTx are currently commercialized, 11 of which obtained CE marking in 2025. Most are Class I devices (88%), developed by 15 companies, with One Health Vision leading with 10 products (38% of the total).

Budget impact analysis of DTx in Italy. The estimated annual cost of DTx in Italy is approximately €62 million. Musculoskeletal (€15.26 million) and metabolic disorders (€15.51 million) are the areas with the highest potential expenditure.



Italian draft law for DTx and Digital Health Policy Lab proposals. In Italy, DTx are regulated under EU Medical Device Regulation, with a national legislative proposal currently progressing to define their integration into the NHS. A unified bill, combining three previous proposals, outlines definition, evaluation by an ad hoc expert committee, and inclusion in the Essential Levels of Assistance (LEA) based on clinical evidence. Some aspects, such as prescription, dispensing, and measures to ensure equitable access, need to be further defined, as suggested by the Digital Health Policy Lab.

DTx and Artificial Intelligence application in neurodevelopmental disorders. DTx offer personalized, accessible, and continuous support for neurodevelopmental disorders. DTx leverage AI, machine learning algorithms, and real-world data to adapt therapies and monitor progress but require robust clinical validation and standardized methodologies. Challenges include digital inequalities, privacy, ethical concerns, and maintaining the essential human-therapist relationship.

DTx application in mental health. DTx are transforming mental health care by providing accessible, scalable, personalised, and evidence-based interventions for conditions like depression, anxiety, insomnia, and substance use disorders. With around 20,000 mental health apps developed globally and several approved, the mental health sector leads in DTx research, demonstrating significant improvements in symptoms and quality of life. Ensuring privacy, data security, and digital literacy remains essential.

Pharmacological therapy and DHTs combination. The combined use of DHTs and pharmacological treatments improve effectiveness, adherence, personalization, and patient engagement through continuous monitoring, behavioural interventions, and tailored feedback, especially in chronic and mental health conditions. Proper prescription and regulatory alignment are essential to ensure their efficacy and safety.

Data analytics in healthcare: from unsupervised to federated learning. Al-based methods are generally classified into unsupervised and supervised learning: the first explores data structures to reveal patterns and reduce complexity, supporting health data analysis; the second enables classification and regression for prediction tasks. In all cases, data quality, privacy, and the use of federated learning or synthetic data are crucial to ensure reliable and ethical Al applications in healthcare.

Artificial Intelligence as a living component of medical device evolution. Artificial Intelligence (AI) ability to analyse complex clinical data has become a key feature of modern medical devices, especially in Software as a Medical Device (SaMD), which performs medical functions independently of hardware and can learn from real-world data, challenging traditional regulatory models. AI systems demand ethical and clinical accountability. The MDR-AI Act interplay defines Europe new regulatory frontier.

Artificial Intelligence applied to oncology. Al in oncology moves from predictive to foundation models that integrate multimodal clinical, imaging, and genomic data. Generative Al now collaborates with clinicians, supporting complex decision-making. Successful use depends on trust, explainability, and interactive systems. The future lies in continuously learning, agentic Al that enables adaptive, transparent, and patient-centered cancer care.

Economic evaluation of DTx. DTx improve health outcomes and are cost-effective across metabolic, cardiovascular, neurological, rehabilitative, and behavioural conditions. Most evidence comes from the US, Europe, and Asia, with no Italian evaluations identified. Cost-effectiveness is driven by improved adherence, reduced complications, and lower healthcare utilization, with ICERs generally below conventional thresholds.

The Third Digital Health Monitoring Report is the result of the work of the **Digital Health Policy Lab**, a research project established in 2022 in collaboration between **Indicon Società Benefit** and the **University of Milan**, aimed at promoting the development and access of digital health technologies (DHTs) in the Italian National Health Service.



AIM OF THE WORK

Digital Health Technologies (DHTs) are digital tools and systems designed to support, enhance, or deliver healthcare services.

An accurate framing of their definitions and classifications, alongside a comprehensive understanding of the therapeutic areas currently attracting investment, the regulatory and reimbursement frameworks already in place, market dynamics and pricing strategies, as well as the state of the art in Italy and the most advanced fields of application, are essential elements to construct a coherent and informed overview that can effectively support decision-making processes.

The Third Digital Health Monitoring Report is the outcome of the work carried out by the Digital Health Policy Lab, a research project launched in 2022 through a collaboration between Indicon Società Benefit and the University of Milan, with the objective of promote the development and integration of the DHTs within the Italian National Health Service.

The report presents the results of quantitative and qualitative analyses based on public sources, including scientific literature, global clinical trial database, regulatory agency databases, institutional websites, and press releases from manufacturing companies.

The first section of the report outlines a global mapping of clinical studies on Digital Therapeutics (DTx) and the regulatory and reimbursement frameworks, as well as the status of DTx reimbursement in Germany, United Kingdom, France, Belgium, and Spain. A focus is placed on the prices of digital therapies in Germany, the leading country in the reimbursement of these therapies, which systematically publishes detailed information. The report then provides details on the Italian context, including a mapping of certified patient-managed Digital Medical Devices (pDMD) and DTx currently available on the market, a budget impact analysis aimed at estimating the investment required for their access into the National Health Service, and an overview of the draft law currently under parliamentary discussion concerning the reimbursement of these therapies.

The second part of the report reviews clinical practice applications and innovative trends, including the use of DTx in neurodevelopmental disorders and mental health, as well as the combination of DHTs with pharmacological therapies.

The third part addresses Artificial Intelligence (AI) and Health Technology Assessment (HTA), covering data analytics in healthcare (from unsupervised to federated learning), AI as a living component of medical devices evolution, the application of AI in oncology, and finally, economic evaluations of digital therapies, with a focus on cost-effectiveness, cost-utility, and budget impact.



1. DIGITAL HEALTH TECHNOLOGIES (DHTs)

This chapter aims to provide a comprehensive overview of Digital Health Technologies (DHTs), reviewing global clinical trials and the state of the art of their regulatory assessment and reimbursement process in Europe, focusing on Germany, the United Kingdom, France, Belgium, and Spain. For the Italian context, it outlines the current landscape of certified patient-managed Digital Medical Device (pDMDs) and the potential budget impact of Digital Therapeutics (DTx) adoption in the healthcare system.

The chapter also addresses the proposed law on digital therapeutics and related Digital Health Policy Lab proposals, aimed at establishing a clear definition and enabling reimbursement of these therapies in Italy. By integrating clinical, economic, and regulatory perspectives, it offers a structured understanding of the evolving digital health ecosystem.

1.1. GLOBAL CLINICAL TRIALS ON DTx

The data presented in this chapter have been submitted to Plos Digital Health, in 2025, and originated from the analysis conducted by P. Rocco¹, V. Pagella^{1,2}, U. M. Musazzi¹, S. Manellari¹, E. P. Lanati², P. Minghetti¹.

Adaptation for the Digital Health Monitoring Report by Myriam Dilecce². ¹Università degli Studi di Milano; ²Indicon Società Benefit.

The aim of this section is to map the Digital Therapeutics (DTx) undergoing into clinical trials al global level, with a deep dive analysis by type of technology developed, therapeutic area, and Countries leading DTx development. The expected outcome was to have a horizon scanning of the DTx which could soon access to the market.

Data collection and analysis method

The analysis method is the same described in the first DTx monitoring report. We updated our internal excel database with the new data collected from clinicaltrial.gov, which tracks clinical trials worldwide. The last update of the data collection in our database is January 2025.

The following key words were entered into the field "Intervention/Treatment": "Digital Therapeutics", "Digital Therapeutics", "Digital Therapeutics".

As results of literature research showing that most approved DTx have been evaluated through randomized clinical trials (RCTs) [1], the resulting record were then screened for "study type" and "study status", where only the clinical trials with these criteria were selected: "Interventional", "Randomized", or "Not Applicable (NA)". Pilot studies were also included. Trials classified as "Non-randomised", "Observational", "Expanded access", "Terminated", "Withdrawn", "Suspended", or "Unknown" were excluded.

The records retrieved were reviewed in order to check if they investigated devices qualified as DTx respecting the previously defined selection criteria. The review was performed through the technical sheets and manufacturer's website check.

The resulting dataset was analysed by: (I) type of technology developed, (II) therapeutic area, and (III) Countries leading DTx development, grouped by continent (America, Asia, Europe and Oceania).

An analysis by type of technology and Countries leading DTx development stratified by therapeutic area was conducted to assess the prevalence of different technological approaches and geographical distribution across various clinical domains.

Analysis by therapeutic area was performed following macro areas according to Medical Dictionary for Regulatory Activities Terminology (MedDRA), SOC level: Immune system disorders; Cardiac disorders; Ear and labyrinth disorders; Gastrointestinal disorders; General disorders and procedural complications; Metabolism and nutrition disorders;



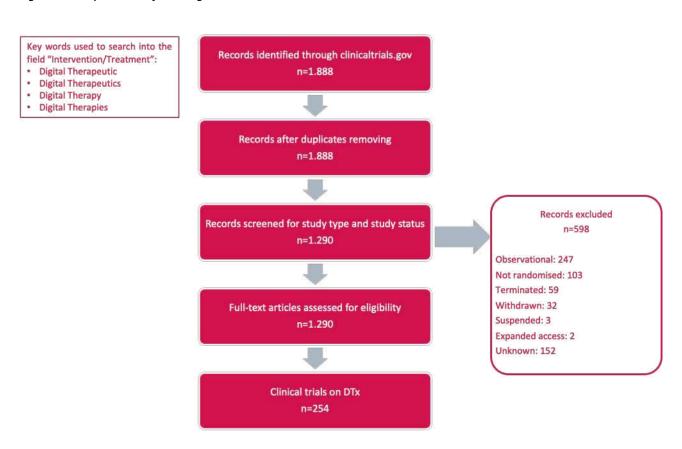
Musculoskeletal and connective tissue disorders; Neoplasms benign, malignant and unspecified; Nervous system disorders; Psychiatric disorders; Renal and urinary disorders; Reproductive system and breast disorders; Respiratory, thoracic and mediastinal disorders.

Results

The number of clinical trials at first identified with "Digital Therapeutics", "Digital Therapeutic", "Digital Therapy", and Digital Therapies" key words was 1,888. No duplicates were found.

Among these, 598 were excluded following exclusion criteria selected (n=247 observational, n=152 unknown, n=103 not randomised, n=59 terminated, n=32 withdrawn, n=3 suspended, n=2 expanded access). A total of 254 clinical trials resulted through the review of technical sheets and manufacturer website.

Figure 1: Study selection flow diagram



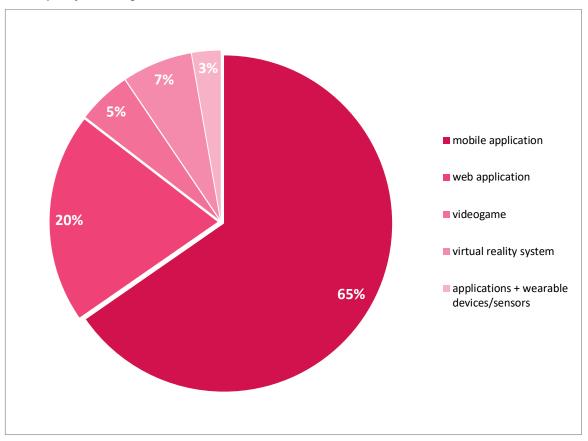
I. Analysis by Type of technology developed

Five categories were identified: mobile application, web application, videogames, virtual reality systems, and applications used in combination with wearable devices or sensors.

Mobile applications emerged as the predominant technology, accounting for 65.4% of the identified trials (n=166). Web applications represented 20.1% (n=51), followed by virtual reality systems at 6.7% (n=17). Videogames were utilized in 5.1% of the trials (n=13), while applications integrated with wearable devices/sensors accounted for 2.8% (n=7).



Figure 2: Analysis of technological devices



II. Analysis by Therapeutic area

The analysis by therapeutic areas addressed by DTx in the clinical trials reviewed revealed a clear predominance of psychiatric disorders as the pathology treated, which accounted for 52% of the total (n=131). Of these, insomnia (22.9%; n=30), depression (19.8%; n=26) and anxiety (10.7%; n=14) represent the most first three pathologies treated.

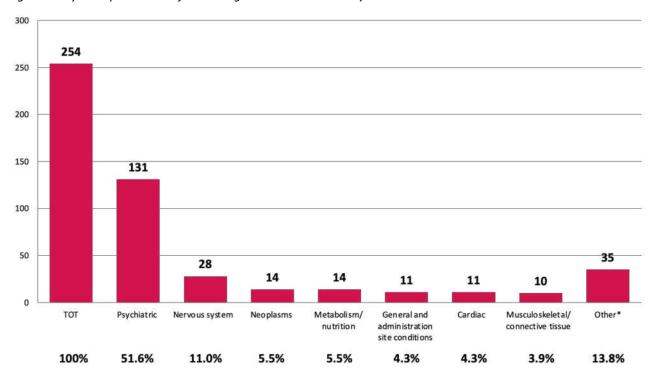
Nervous system disorders, Neoplasms, and Metabolism and nutrition disorders followed, with a prevalence of 11% (n=28), 6% (n = 14), and 6%; (n = 14), respectively.

Other identified categories were present in less proportions, including general disorders and administration site conditions (4%; n=11), cardiac disorders (4%; n=11), musculoskeletal and connective tissue disorders (4%; n=10). Additional categories included respiratory, thoracic, and mediastinal disorders (4%; n=9); renal and urinary disorders (2%; n=6); gastrointestinal disorders (2%; n=6); reproductive system and breast disorders (2%; n=5); injury, poisoning, and procedural complications (2%; n=5).

Finally, categories with very low frequencies were identified: hepatobiliary disorders (1%; n=2), as well as immune system disorders and ear and labyrinth disorders, each represented by a single DTx.



Figure 3: Key therapeutic areas for DTx in global clinical trial analyses



^{*}Respiratory, thoracic and mediastinal disorders; renal and urinary disorders; gastrointestinal disorders; reproductive system and breast disorders; injury, poisoning and procedural complications; hepatobiliary disorders; immune system disorders; ear and labyrinth disorders.

Table 1: Results of analysis by therapeutic areas and pathologies

Therapeutical area	Pathology	Clinical Trials (N)	% of the Total	% within Therapeutic Area
тот		254	100%	-
Psychiatric disorders		131	51.6%	100%
	Insomnia	30	11.8%	22.9%
	Depression	26	10.2%	19.8%
	Anxiety	14	5.5%	10.7%
	Attention-Deficit/Hyperactivity Disorder (ADHD)	12	4.7%	9.2%
	Opioid use disorders	12	4.7%	9.2%
	Schizophrenia	9	3.5%	6.9%
	Behavioural disorders	7	2.8%	5.3%
	Psychosis	5	2.0%	3.8%
	Eating Disorders	4	1.6%	3.1%
	Post-Traumatic Stress Disorder (PTSD)	4	1.6%	3.1%
	Alcohol Abuse	2	0.8%	1.5%
	Cognitive disfunction	2	0.8%	1.5%
	Methamphetamine Abuse	2	0.8%	1.5%
	Hallucinations	1	0.4%	0.8%
	Substance Use Disorders	1	0.4%	0.8%
Nervous system disorders		28	11.0%	100%
	Multiple Sclerosis	6	2.4%	21.4%
	Cognitive disfunction	4	1.6%	14.3%



Thoronoutical area	Dathology	Clinical	% of the	% within
Therapeutical area	Pathology	Trials (N)	Total	Therapeutic Area
	Cognitive Impairment	3	1.2%	10.7%
	Migraine	3	1.2%	10.7%
	Parkinson Disease	3	1.2%	10.7%
	Visual fields Defects	3	1.2%	10.7%
	Dementia	1	0.4%	3.6%
	Developmental Disability	1	0.4%	3.6%
	Dysarthria	1	0.4%	3.6%
	Amyotrophic Lateral Sclerosis	1		
	(ALS)		0.4%	3.6%
	Stuttering	1	0.4%	3.6%
	Tic Disorder	1	0.4%	3.6%
Benign, malignant and unspecific	•	14	5.5%	100%
	Breast cancer	5	2.0%	35.7%
	Other*	4	1.6%	28.6%
	Colorectal cancer	2	0.8%	14.3%
	Lung cancer Head and neck cancer	1	0.4%	7.1% 7.1%
	Melanoma	_	0.4%	7.1%
Metabolism and nutrition disord		1 14	5.5%	100%
Wetabolishi and nutrition disord	Diabetes	7	2.8%	50.0%
	Obesity	6	2.4%	42.9%
	Hypercholesterolemia/		2.470	42.570
	Dyslipidaemias	1	0.4%	7.1%
General disorders and administra		11	4.3%	100%
	Chronic pain	10	3.9%	90.9%
	Back Pain	1	0.4%	9.1%
Cardiac disorders		11	4.3%	100%
	Stroke	6	2.4%	54.5%
	Hypertension	3	1.2%	27.3%
	Acute Myocardial Infarction	1	0.4%	9.1%
	Coronary Artery Disease	1	0.4%	9.1%
Musculoskeletal and connective	tissue disorders	10	3.9%	100%
	Fibromyalgia	4	1.6%	40.0%
	Arthritis	3	1.2%	30.0%
	Patellofemoral Pain Syndrome	2	0.8%	20.0%
	Post Partum Lumbopelvic Pain	1	0.4%	10.0%
Respiratory, thoracic and medias		9	3.5%	100%
	Chronic Obstructive Pulmonary Disease (COPD)	3	1.2%	33.3%
	Asthma	2	0.8%	22.2%
	Long COVID	1	0.4%	11.1%
	Lung Diseases	1	0.470	11.170
	Interstitial/Pulmonary Fibrosis	1	0.4%	11.1%
	Post COVID-19 Condition	1	0.4%	11.1%
	Rhinitis	1	0.4%	11.1%
Renal and urinary disorders		6	2.4%	100%
	Urinary Incontinence	2	0.8%	33.3%
	Chronic Kidney Diseases (CKD)	1	0.4%	16.7%
	Kidney Disease	1	0.4%	16.7%
	Overactive Bladder	1	0.4%	16.7%
	Stress Urinary Incontinence	1	0.4%	16.7%
Gastrointestinal disorders		6	2.4%	100%



Therapeutical area	Pathology	Clinical Trials (N)	% of the Total	% within Therapeutic Area
	Irritable Bowel Syndrome (IBS)	6	2.4%	100%
Reproductive system and breast	disorders	5	2.0%	100%
	Endometriosis	2	0.8%	40.0%
	Dysmenorrhea	1	0.4%	20.0%
	Female Sexual Dysfunction	1	0.4%	20.0%
	Polycystic Ovary Syndrome (PCOS)	1	0.4%	20.0%
Injury, poisoning and procedural	complications	5	2.0%	100%
	Orthopaedic Trauma	5	2.0%	100%
Hepatobiliary disorders		2	0.8%	100%
	Cirrhosis	1	0.4%	50.0%
	Liver Diseases	1	0.4%	50.0%
Immune system disorders		1	0.4%	100%
	Psoriasis		0.4%	100%
Ear and labyrinth disorders		1	0.4%	100%
	Hearing disorders	1	0.4%	100%

^{*}cancer condition investigated broadly, no reference to a specific type

III. Analysis by Countries leading DTx development

The geographical distribution of the analysed clinical trials revealed that the majority were conducted in North America (39.4%, n=100) and Europe (33.1%, n=84). Among European countries, Germany emerged as the leading country, contributing 7% (n=17) of the total number of studies. This was followed by Spain (4%, n=10), Italy (3%, n=8), and the United Kingdom (2%, n=6).

A smaller proportion of studies took place in Asia (17.7%, n=45), while only a limited number were conducted in Oceania (2.0%, n=5), all of which were in Australia. South America accounted for 11 studies (4.3%), and 9 studies (3.5%) did not report a specific country of origin, representing a limitation in the geographical traceability of DTx research.

In Asia, notable contributions were made by South Korea (6%, n=15) and China (4%, n=10), with additional studies originating from Hong Kong (2%, n=6) and Taiwan (1%, n=3).



Figure 4: Graphical representation of the geographical distribution of DTx clinical trials



Table 2: Distribution of European DTx clinical trials

European countries	Clinical trials (N)	Percentage (Europe)
Germany	17	20.2%
Spain	10	11.9%
Italy	8	9.5%
France	6	7.1%
UK	6	7.1%
Denmark	5	6.0%
Norway	5	6.0%
Sweden	5	6.0%
Switzerland	4	4.8%
Turkey	4	4.8%
Iceland	3	3.6%
Netherlands	3	3.6%
Finland	2	2.4%
Austria	1	1.2%
Czechia	1	1.2%
Greece	1	1.2%
Ireland	1	1.2%
Poland	1	1.2%
Portugal	1	1.2%
TOT	84	100%

IV. Analysis by Type of technology stratified by Therapeutic area

Mobile applications are the most widely adopted technology across all clinical domains examined, whereas other technologies show a more heterogeneous distribution across therapeutic areas. A notable finding is that Virtual Reality Systems are predominantly applied for nervous system disorders.

Figure 5: Technological devices used for psychiatric disorders

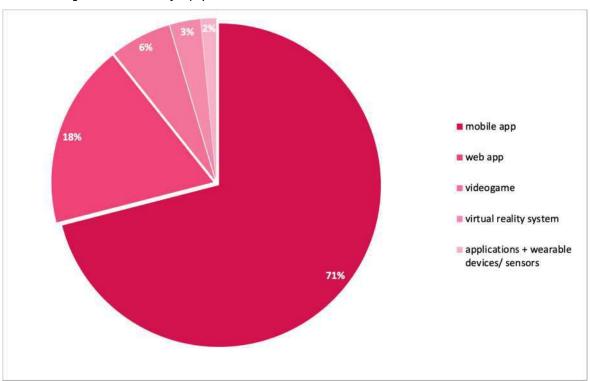




Figure 6: Technological devices used for nervous system disorders

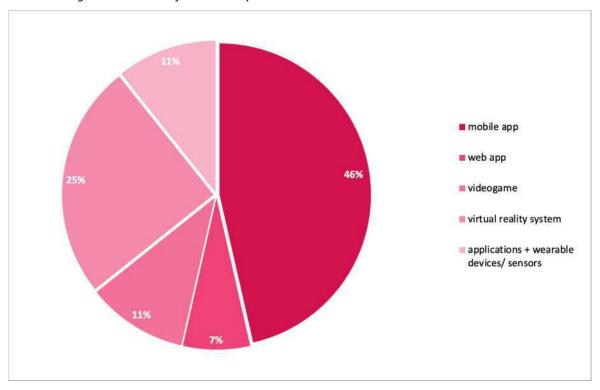


Table 3: Technological devices by therapeutic area

Therapeutic area	Mobile App	Web App	Videogame	Virtual Reality System	App + Wearable Devices/ Sensors	Tot
Psychiatric disorders	93	24	8	4	2	131
Nervous system disorders	13	2	3	7	3	28
Neoplasms benign, malignant and unspecified	9	5	-	-	-	14
Metabolism and nutrition disorders	10	4	-	-	-	14
General disorders and administration site conditions	6	2	-	3	-	11
Cardiac disorders	6	3	-	1	1	11
Musculoskeletal and connective tissue disorders	6	2	-	1	1	10
Respiratory, thoracic and mediastinal disorders	4	3	1	1	-	9
Renal and urinary disorders	6	-	-	-	-	6
Gastrointestinal disorders	5	1	-	-	-	6
Reproductive system and breast disorders	3	2	-	-	-	5
Injury, poisoning and procedural complications	2	2	1	-	-	5
Hepatobiliary disorders	2	-	-	-	-	2
Ear and labyrinth disorders	1	-	-	-	-	1



Immune system disorders	-	1	-	-	-	1
TOTAL	166	51	13	17	7	254

V. Analysis by Countries leading DTx development stratified by Therapeutic area

Most clinical trials originating from America focused on psychiatric disorders, representing 58% (n=76) of all psychiatric therapeutic area. Conversely, Europe showed a greater diversity in therapeutic focus. It was the leading country for studies on nervous system disorders, representing 50% (n=14) of the total in this category and showed a notable presence in research related to neoplasms (n=7) and metabolism and nutrition disorders (n=7).

In Asia, the primary focus was on psychiatric disorders (n=22); however, studies were also conducted in several other therapeutic areas, including nervous system, musculoskeletal, and cardiovascular disorders. Despite this range, Asia overall representation remained lower across most therapeutic domains when compared to Europe and North America.

In Oceania, research activity was almost exclusively concentrated on psychiatric disorders (n=4).

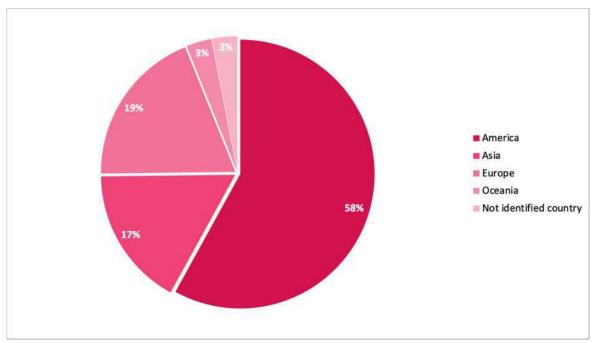


Figure 7: Geographic distribution of DTx clinical trials for psychiatric disorders

Table 4: Countries leading DTx development by Therapeutic area

Therapeutic Areas	America	Asia	Europe	Oceania	Not identified country	Tot
Psychiatric disorders	76	22	25	4	4	131
Nervous system disorders	9	5	14	-	-	28
Neoplasms benign, malignant and unspecified	4	3	7	-	-	14
Metabolism and nutrition disorders	3	2	7	-	2	14
General disorders and administration site conditions	5	1	5	-	-	11



Cardiac disorders	1	4	5	-	1	11
Musculoskeletal and connective tissue disorders	4	3	3	-	÷	10
Respiratory, thoracic and mediastinal disorders	2	2	4	1	-	9
Renal and urinary disorders	1	1	4	-	-	6
Gastrointestinal disorders	4	1	1	-	-	6
Reproductive system and breast disorders	-	1	3	-	1	5
Injury, poisoning and procedural complications	1	-	4	-	-	5
Hepatobiliary disorders	-	-	1	-	1	2
Ear and labyrinth disorders	1	-	-	-	-	1
Immune system disorders	-	-	1	-	-	1
Tot	111	45	84	5	9	254

Discussion vs year 2023 analysis (first DTx monitoring report)

In this paragraph is discussed a comparison respect to results obtained from the same analysis conducted in the year 2023 (data collected as of October 2023), described in the first DTx monitoring report.

The number of clinical trials investigating DTx increased by 54% over 15 months (from n=1.224 in October 2023 to n=1.888 in January 2025). The increase is 41% (from n=180 to n=254) when considering the final number of clinical trials included in the analyses, which excluded Non-randomised, Observational, and Expanded Access studies (non-traditional interventional trials, but regulated programs that allow patients with serious or life-threatening conditions to access not approved therapies or therapies outside standard clinical trials), as well as those classified as Terminated, Withdrawn, Suspended, or Unknown. This trend suggests a growing interest in the development of DTx.

Mobile applications maintain their positions as the predominant type of technology, although their share decreased from 73% to 65%, with a resultant increase in web applications (16% to 20%), virtual reality systems (4% to 7%), and applications combined with wearable devices/sensors (2% to 3%).

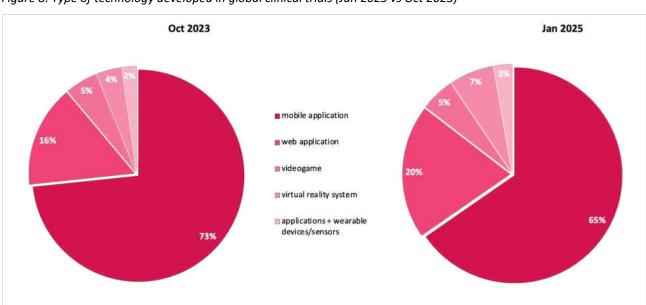


Figure 8: Type of technology developed in global clinical trials (Jan 2025 vs Oct 2023)



Psychiatric disorders continue to represent the leading therapeutic area for DTx development, accounting for 52% of all clinical trials in the January 2025 analysis and 49.4% in October 2023. Within this area, the most frequently targeted conditions are still insomnia, depression, anxiety, ADHD, opioid use disorders, schizophrenia, and behavioural disorders. In contrast, the number of studies focusing on diabetes decreased from 12 to 7 (*Table 5*).

A substantial number of DTx focus on anxiety and depression, likely reflecting the escalating global prevalence of these disorders [2], further amplified by the COVID-19 pandemic [3]. This trend is also supported by the robust evidence base behind the efficacy of Cognitive Behavioural Therapy (CBT) [4], which constitutes a common therapeutic approach employed across numerous DTx. Additionally, CBT is extensively utilized and has proven effective in managing Opioid Use Disorder (OUD), where it plays a critical role in facilitating behavioural modification and preventing relapse [5].

Following psychiatric disorders, nervous system disorders represent the second most frequently targeted category, according to the January 2025 analysis. Indeed, cognitive rehabilitation via digital devices is increasingly recognized as a promising strategy to enhance neuroplasticity in the brain [5].

In oncology, digital tools facilitate care by enabling the collection of electronic patient-reported outcomes (ePROs) and remote monitoring, which have been shown to improve symptom management, reduce symptom burden, decrease unplanned hospitalizations, and ultimately enhance both quality of life and survival [6].

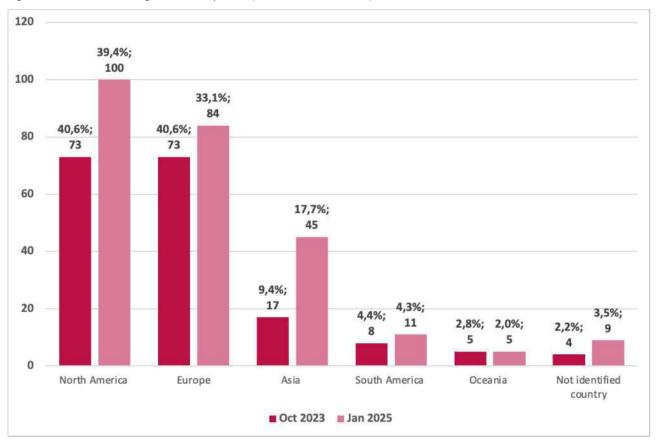
Table 5: Top target pathologies for DTx in global clinical trials (Jan 2025 vs Oct 2023)

Pathology	Clinical Trials (N) Oct 2023	Pathology	Clinical Trials (N) Jan 2025
Depression	27	Insomnia	30
Anxiety	14	Depression	26
Insomnia	14	Anxiety	14
Diabetes	12	ADHD	12
Opioid use disorders	7	Opioid use disorders	12
Behavioural disorders	7	Chronic pain	10
ADHD	7	Schizophrenia	9
Nicotine addiction	5	Behavioural disorders	7
Post-Traumatic Stress Disorder	5	Diabetes	7
Schizophrenia	5	Multiple Sclerosis	6
Stroke	5	Obesity	6
Breast cancer	4	Stroke	6
Panic attacks	4	IBS	6
Multiple Sclerosis	4	Psychosis	5
Eating Disorders	4	Breast cancer	5
Obesity	4	Orthopedic Trauma	5

Compared to the analysis conducted in October 2023, when North America and Europe were leading countries in the development of DTXs (n=73 for both countries), a greater growth trend in the number of clinical trials was observed in North America in January 2025 (n=100 in North America vs n=84 in Europe). The number of studies conducted in Asia increased substantially over the 15-month period (from n=17 in October 2023 to n=45 in January 2025). The number of studies in other countries remained relatively stable.



Figure 9: Countries leading DTx development (Jan 2025 vs Oct 2023)



European countries have shown a growing interest in the development of digital therapeutics (DTx), particularly those with health policies that actively support digital health innovation. The existence of a clear regulatory framework is among the most critical factors facilitating the integration of DTx into healthcare systems and their adoption by healthcare professionals [7]. Germany conducted the highest number of clinical studies on DTx (n=17, accounting for 20% of all European studies) and, since 2020, has introduced a dedicated regulatory framework for so-called Digital Health Applications (DiGA), which enables these technologies to be prescribed and reimbursed through the national health insurance system.



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1.2. STATE OF THE ART OF DTx IN EUROPE

1.2.1.EU DTx Mapping

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The aim of this paragraph is to outline the regulatory pathways for access and reimbursement of DTx in Germany, United Kingdom (UK), France, Belgium, and Spain, providing an update on the access status where data are available.

Germany

Regulatory and Reimbursement Process for Digital Therapeutics (DTx) in Germany

Germany was the first country to introduce a dedicated law for Digital Health – the *Digitale-Versorgung-Gesetz* (DVG, "Digital Healthcare Act"), in the year 2019 – and currently is the country with the most advanced regulatory framework in Europe. DVG include Digital Health Applications (*Digitale Gesundheitsanwendungen*, DiGA) regulatory pathway definition, telemedicine expansion, electronic patient records implementation, telematics infrastructure empowerment. The DVG allows clinicians to prescribe DiGAs, with a reimbursement by statutory health insurance and a fast-track, evidence-based system that integrates digital health into regular care.

For the qualification of an app as a DiGA, it must have the CE marking and be approved by the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM), meeting criteria for safety, data security, and effectiveness. BfArM can temporarily list the app (preliminary approval) for up to 12 months while the developer collects additional evidence. This allows patients to use the DiGA and get reimbursement even before full approval. The DiGA must provide proof of positive healthcare effects, both medical benefits (improvement in health status) and patient-relevant improvements (such as better adherence, improved lifestyle, reduced hospital visits). Evidence can come from clinical studies or real-world data. If BfArM approves the DiGA evidence, it is permanently listed. A DiGA can be evaluated to be directly included in the permanent list. The developer must monitor DiGA use and effectiveness continuously, with updates to the app reviewed by BfArM to ensure ongoing safety and effectiveness.

Table 1: Digital Health Applications (DiGA) reimbursement process

Step	Description
1. DiGA development	The app must be a medical device with a CE mark.
2. Application to BfArM	The manufacturer submits an application for inclusion in the DiGA directory.
3. Initial BfArM assessment	Evaluation of safety, data protection, functionality, and clinical evidence.
4. Temporary approval (up to 12 months)	If basic criteria are met, the app is added to the temporary DiGA list – It can be prescribed and reimbursed while the manufacturer collects additional evidence.
5. Evidence generation	The manufacturer must demonstrate positive healthcare effects and patient-relevant benefits (e.g., better adherence, improved lifestyle, reduced hospital visits) through clinical studies or real-world data.
6. Final BfArM evaluation	BfArM reviews the new evidence. If positive, the DiGA moves to the permanent list.
7. Inclusion in the permanent DiGA list	The app receives full approval, can be prescribed and reimbursed as part of regular care in the German healthcare system.
8. Continuous monitoring	The manufacturer must ensure ongoing safety, data protection, and effectiveness, with updates reviewed by BfArM.



Reimbursement status of DiGAs in Germany

The complete list of reimbursed DiGAs in Germany, classified as temporarily reimbursed, permanently reimbursed, or removed, is published on the BfArM website [1].

As of September 30, 2025, a total of 57 DiGAs were reimbursed in Germany, including 46 permanently listed and 11 temporarily listed. An increasing trend compared with 2024 is evident for DiGAs on the permanent list, as in 2024, 20 were temporary and 35 were permanent listed (+31.4%) (*Table 2*).

In 2025, 9 new DiGAs were added to the reimbursement lists: 5 were added to the temporary list, while 3 were included in the permanent list.

Compared with 2024, 6 DiGAs remained on the temporary list, while 9 transitioned from temporary to permanent list. Additionally, 6 DiGAs temporarily listed in 2024 were removed from the reimbursement status.

Table 2: Evolution of Digital Health Technologies (DIGAs) reimbursement status in Germany

Reimbursement status	2021	2022	2023	2024	2025
Delisted (not reimbursed)	-	5	6	9	6
Permanent List	5	13	29	35	46
Temporary List	22	24	23	20	11
TOT reimbursed	27	37	52	55	57

As in the previous year, in 2025 most reimbursed DiGAs target the therapeutic area of psychiatric disorders, with 20 DiGAs on the permanent list and 4 on the temporary list.

In 2025, two new DiGAs for this area were added to the temporary list, and three were included on the permanent list.

Most of these address social phobia, panic disorder, agoraphobia, and generalized anxiety disorder (n=7, of which 6 are on the permanent list and 1 on the temporary list), and depression (n=7, of which 6 are on the permanent list and 1 on the temporary list); three target Attention Deficit Hyperactivity Disorder (ADHD; n=1 on the permanent list, n=1 on the temporary list); three address insomnia (all on the permanent list); one targets borderline personality disorder (on the permanent list); and two address eating disorders (on the permanent list).

In 2024, no DiGAs for heart diseases were included in the permanent list, whereas this year one was added.

Table 3: Therapeutic areas involved in the use of DiGAs by reimbursement status – 2025 vs 2024

Therapeutic area	Total reimbursed		Permar	ent List	Tempo	emporary List Delisted (no reimbursed		
Year	2024	2025	2024	2025	2024	2025	2024	2025
Psychiatric disorders	20	24	14	20	6	4	1	1
Metabolic disorders	8	6	4	4	4	2	1	2
Oncology	4	3	2	2	2	1	3	1
Musculoskeletal disorders	5	6	4	4	1	2	1	1
Other	2	3	2	3*	-	-	2	-
Heart disease	3	2	-	1	3	1	1	1
Neurological disorders	4	4	1	3	3	1	-	-
Gynaecology/urology	4	4	4	4	-	-	-	-
Addiction	3	3	2	3	1	-	-	-
Otology	2	2	2	2	-	-	-	-
TOTAL	55	57	35	46	20	11	9	6

^{*} Irritable Bowel Syndrome (IBS); chronic pain; aphasia.



7%

42%

Psychiatric disorders

Metabolic disorders

Oncology

Musculoskeletal disorders

Other

Heart disease

Neurological disorders

Gynaecology/urology

Addiction

Otology

Figure 1: Distribution of DiGAs reimbursed in Germany by target therapeutic area as of September 30, 2025

United Kingdom

Regulatory and Reimbursement Process for DTx in UK

In UK, a Digital Health Technology (DHT) must have the UKCA marking as medical device for safety and performance compliance, under the UK Medical Device Regulations (UK MDR 2002).

The NHS encourages DHT manufacturers to demonstrate clinical effectiveness, usability, and safety. The formal evaluation is made by the NHS England through Digital Technology Assessment Criteria (DTAC), which provides a comprehensive framework covering clinical safety, data protection, technical assurance and security, interoperability with NHS systems, and usability and accessibility. This assessment process is not mandatory but allow the DHT to be listed in the NHS Apps Library, which gives NHS patients and clinicians confidence that the DHT is safe and effective.

An independent assessment of clinical effectiveness and cost-effectiveness is conducted by the National Institute for Health and Care Excellence (NICE), which may issue guidance or recommendations to support adoption within the NHS.

Listing in the library and obtaining NICE recommendation do not automatically mean reimbursement through the NHS, like the Germany's DiGA system, but funding usually depends on local NHS trust commissioning or specific service contracts/pilot programs. Examples of these programs are the Accelerated Access Collaborative (AAC) and the NHS Test Beds, which help DHTs scale into the NHS after proving clinical value.

Table 4: DHT assessment process in UK

Step	Responsible Body	Purpose		
1. Development & UKCA	Manufacturer	Legal and regulatory compliance		
2. DTAC Assessment	NHS England	Digital safety and quality assurance		
3. NHS Apps Library	NHS Digital	Public endorsement and visibility		
4. NICE Evaluation NICE		Clinical and cost-effectiveness assessment		
5. NHS Adoption	NHS & AAC	Implementation and scaling		
6. Post-Market Monitoring	Manufacturer & NHS	Ongoing safety and updates		

In 2022, Early Value Assessment (EVA) conducted by the NICE was introduced for digital medical technologies, digital health technologies included, that address national unmet needs. EVA allows for the early evaluation of promising technologies and produces recommendations within the NHS which can influence local adoption decisions. EVA aims to



facilitate earlier patient access to these innovations while concurrently gathering additional evidence to confirm their clinical and cost-effectiveness.

Status of digital medical technologies recommended by NICE though EVA

The NICE website publishes all EVAs [2], divided into "Published," "In consultation," "In development," and "Awaiting development." In the "Published" section, all technologies on which NICE has expressed an opinion are included, providing three types of recommendations for NHS funding:

- Positive recommendation: technologies that can be used in the NHS during the evidence generation period.
- Negative recommendation: More research is needed before technologies can be funded by the NHS.
- Research only: technologies can only be used in research; more research is needed.

Each guidance document reports the recommendation for one or more technologies for the same therapeutic purpose. As of November 2, 2025, 24 guidance documents were listed on the NICE website in the "Published" section: the first was published on March 9, 2023, and the most recent on October 14, 2025.

For each guidance document, a qualitative analysis was conducted to identify all the technologies assessed, the outcome of the recommendation for each, and which of these were DTx.

A total of 130 NICE recommendations were identified from the guidance documents analysed, covering 126 technologies, with 4 technologies appearing in at least 2 guidance documents. Most were positive recommendations (n=81, 62%), 21 (16%) were negative, and 28 (22%) were for research-only.

Out of the 126 technologies analysed, 27 (21%) met the definition of DTx. Of these, 14 (52%) received positive recommendations to be used in the NHS during the evidence generation period, 13 (48%) were recommended for research-only use, and none received a negative recommendation. All of these DTx were for psychiatric disorders.

Table 5: DTx evaluated by NICE for the Early Value Assessment (EVA) that received an NHS reimbursement recommendation ("Published" as of the time of analysis)

Product	Recommendation	Therapeutic area	Practice	Last update
Space from Depression	yes	Psychiatric disorders	Digitally enabled therapies for adults with depression: early value assessment	14/01/2025
Iona Mind	research	Psychiatric disorders	Digitally enabled therapies for adults with depression: early value assessment	14/01/2025
Minddistrict	research	Psychiatric disorders	Digitally enabled therapies for adults with depression: early value assessment	14/01/2025
Wysa	research	Psychiatric disorders	Digitally enabled therapies for adults with depression: early value assessment	14/01/2025
AVATAR for adults	yes	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024
SlowMo for adults	yes	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024
CareLoop for adults	yes	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024



Product	Recommendation	Therapeutic area	Practice	Last update
AVATAR for young people	research	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024
SlowMo for young people	research	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024
CareLoop for young people	research	Psychiatric disorders	Digital health technologies to help manage symptoms of psychosis and prevent relapse in adults and young people: early value assessment	25/03/2024
iCT-PTSD (OxCADAT	yes	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
ict-sad (Oxcadat	yes	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Space from Anxiety (SilverCloud)	yes	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Perspectives (Koa Health)	yes	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Spring (Cardiff University)	yes	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Cerina (NoSuffering)	research	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Iona Mind	research	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Minddistrict	research	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Resony (Rcube Health)	research	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
Wysa	research	Psychiatric disorders	Digitally enabled therapies for adults with anxiety disorders: early value assessment	14/12/2023
gameChangeVR	yes	Psychiatric disorders	Virtual reality technologies for treating agoraphobia or agoraphobic avoidance: early value assessment	15/11/2023
Amelia Virtual Care	research	Psychiatric disorders	Virtual reality technologies for treating agoraphobia or agoraphobic avoidance: early value assessment	15/11/2023
XR Therapeutics	research	Psychiatric disorders	Virtual reality technologies for treating agoraphobia or agoraphobic avoidance: early value assessment	15/11/2023
Lumi Nova	yes	Psychiatric disorders	Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate	05/09/2023



Product	Recommendation	Therapeutic area	Practice	Last update
			symptoms of anxiety or low mood: early value assessment	
Online Social anxiety Cognitive therapy for Adolescents (OSCA)	yes	Psychiatric disorders	Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate symptoms of anxiety or low mood: early value assessment	05/09/2023
Online Support and Intervention for child anxiety (OSI)	yes	Psychiatric disorders	Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate symptoms of anxiety or low mood: early value assessment	05/09/2023
Space from anxiety for teens, space from low mood for teens, space from low mood and anxiety for teens (Silvercloud)	yes	Psychiatric disorders	Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate symptoms of anxiety or low mood: early value assessment	05/09/2023

France

Regulatory and Reimbursement Process for DTx in France

In France, the DTx must obtain a CE marking in accordance with the EU Medical Device Regulation (MDR 2017/745) and comply both privacy/data protection (GDPR) and French data protection laws. The Agence du Numérique en Santé (ANS) – the French digital health agency responsible for technical certification of digital medical devices – must assess DTx following specific standards for interoperability, technical security, and usability.

In 2023, France officially recognized a subset of medical devices as Digital Medical Devices (*Dispositifs Médicaux Numériques*, DMN). A DTx must be categorized as a DMN to access reimbursement pathways.

A DMN can be classified as Remote Patient Monitoring (RPM) devices or Therapeutic devices/DTx. For the second one, the manufacturer may apply for Prise en Charge Anticipée Numérique (PECAN), which allows a temporary reimbursement, while further evidence is gathered. Once approved via PECAN, the DTx receives reimbursement for up to one year non-renewable at a predetermined compensation/fee. The submission for PECAN includes the initial clinical data supporting therapeutic benefit, the technical certification by ANS for interoperability and security, and the evidence dossier submitted to the commission CNEDIMTS (Commission nationale d'évaluation des dispositifs médicaux et technologies de santé) of the HAS (Haute Autorité de Santé), the French health-technology assessment body. The DMN is assessed by CNEDIMTS for actual medical benefit and added benefit compared with existing solutions.

During or after the PECAN period, when solid evidence of clinical benefit and added value are available, the manufacturer submits for listing on List of Products and Services reimbursable (LPPR) (or List of medical telemonitoring activities, LATM for RPM device) for permanent reimbursement. If approved, the DTx is listed, and the price is negotiated with the Comité économique des produits de santé (CEPS). The reimbursement list LPPR allows multi-year listing renewable.



Table 6: The French reimbursement process for Digital Medical Devices (DMN) classified as DTx

Step	Description	Responsible Body
1. Classification & Regulatory Compliance	DTx must be classified as Digital Medical Device (DMN), obtain CE marking, comply with GDPR and ANS standards for interoperability, security, and usability.	Manufacturer / ANS
2. Early Access (PECAN)	Optional 1-year temporary reimbursement while additional evidence is collected; submission includes clinical data and technical certification.	Manufacturer / HAS- CNEDIMTS
3. Health Technology Assessment (HTA)	Assessment of actual medical benefit and added clinical value compared to existing therapies.	HAS-CNEDIMTS
4. Permanent Reimbursement (LPPR)	Submission for long-term listing on LPPR, negotiation of price with CEPS; evidence of clinical effectiveness required	Manufacturer / CEPS / HAS
5. Post-Market Monitoring	Continuous monitoring for safety, usability, clinical effectiveness, and technical compliance	Manufacturer / ANS

Reimbursement status of DTx in France

A complete list of the solutions certified by the ANS as compliant with the interoperability and safety framework for digital medical devices for the purpose of inclusion on the list of reimbursable products and services (LPPR) or in PECAN from January 2024, is available on the ANS website [3]. As of 22 October 2025, a total of 130 software solutions resulted certified and eligible for reimbursement assessment. Of these, 61% (n=79) were found to be included in the LPPR through web searches (e.g., press releases).

There is no specific list for reimbursed DTx; instead, these are included in the comprehensive LPPR list, which covers all digital medical devices. Thus, a qualitative, individual analysis was conducted by searching the manufacturer or the device website to identify the DTx.

Out of the 130 devices certified by the ANS, 7 (5.4%) resulted DTx (*Table 7*). The remaining devices were hardware-based, or software integrated within hardware, including blood glucose monitoring systems, transcutaneous electrical nerve stimulation devices for pain management, continuous positive airway Pressure systems, stimulation systems, infusion pumps, pacemakers/cardiac monitors, cochlear implants, and bone-conduction sound processors.

Of the 7 DTx certified by the ANS, 0% were included in the LPPR for reimbursement.

Table 7: DTx certified by the ANS as compliant with the interoperability and safety framework for digital medical devices as of 22 October 2025

Software (name, version, model, or reference)	Description	Effective date of the conformity certification	Reimbursement (listed in LPPR)
MyRemedee – Version 1.1.0	Digital therapy application for chronic pain	13/09/2024	No
Kranus Edera, version 1.0.0	Digital therapeutic app for organic erectile dysfunction	07/11/2024	No
Bliss DTx, version 3	Digital therapeutic app for acute procedural pain and anxiety via immersive virtual reality experiences	07/11/2024	No
Oto version 4.3	App for tinnitus relief and therapy	28/03/2025	No
HelloBetter Insomnie version 1.0	Digital therapeutic for insomnia	25/04/2025	No
Poppins Clinical (3.0.0)	Software for children with specific learning disorders	12/06/2025	No
Wellapy version 6.3.0	Digital therapeutic app for obesity	21/10/2025	No



A web search was performed to understand the status of DTx included in PECAN, the exceptional, accelerated, and temporary (1-year) access to reimbursement for presumed innovative digital medical devices (DMN) launched in April 2023.

The search showed that the first case handled in October 2023 and, as of 3 June 2025, a total of 10 evaluations returned in PECAN since 2023, of which 3 were positive, with access to one-year temporary reimbursement:

- 2023: 1 positive, 2 negative

- 2024: 2 positive, 2 negative

2025: 3 negative

Belgium

Regulatory and Reimbursement Process for DTx in Belgium

In Belgium, the official regulatory and validation framework for digital health applications, including DTx is called mHealthBelgium. It is a validation pyramid system based on three-level of assessment:

- Level 1: CE marking
- Level 2: eligibility for the reimbursement request to National Institute for Health and Disability Insurance (NIHDI)
- Level 3 light: in the process of proving social-economic value and temporarily financed by NIHDI
- Level 3 plus: fully proven the social-economic value and definitely financed by NIHDI

Reimbursement status of DTx in Belgium

The mHealthBelgium website publishes all digital health applications categorised according to the mHealth pyramid [4].

As of October 30, 2025, the total number of applications listed was 30, categorized as follow: 19 (63%) level 1, 3 (10%) level 2, 0 (0%) level 3 light, 8 (27%) level 3 plus.

In order to identify the DTx among these technologies, a qualitative analysis of each technology was conducted by examining the individual descriptions provided in the dedicated section of the mHealthBelgium website and by further investigating the manufacturer or the device website.

A total of 2 DTx were detected, both categorised in the level 1 of the pyramid. Thus, no DTx are currently reimbursed in Belgium.

Table 8: DTx detected in Belgium categorised according to the mHealth pyramid

Application	mHealth pyramid level	Pathology	Main purpose
HypnoVR	1	Brain/Nerves, Cancer, Chest/Lung, Dental, Diabetes, Ear/Nose/Throat, Gastrointestinal, Heart/Blood Vessels, Kidney/Genito-urinary, Other, Pain, Pregnancy, Rehabilitation, Skin, Treatment adherence	HypnoVR is a virtual reality (VR) hypnosis solution intended to improve management of patients' pain, stress and anxiety by providing an alternative or complementary solution to chemical treatments.
SelfBack	1	Pain, Rehabilitation, Treatment adherence, Other	SelfBack delivers a brand-new Aldriven digital therapeutics solution with clinical evidence for patients with Low Back Pain (LBP).



Spain

In Spain, there is still no dedicated reimbursement pathway for Digital Health Solutions or DTx at national level.

A preliminary bill for a new Law on Digital Health ("Ley de Salud Digital") is under public consultation (as of Oct 2025). This proposed law is part of Spain broader National Digital Health Strategy, and its goal is to create a legal and procedural framework to integrate digital health technologies – such as apps, connected devices, and DTx – into the public healthcare system (*Sistema Nacional de Salud*, SNS). The law will define clear standards and requirements that a digital health product must meet to be officially recognized as a "digital health product", undergo an HTA, and potentially be included in or financed by the public health system.



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1.2.2. DiGAs price analysis

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The purpose of this paragraph is to provide an update on the DIGA price analysis presented in the Second DTx Monitoring Report [1], which covered data up to September 2024. The same methodology is applied, using data collected as of 30 September 2025. Comparisons with the previous year are based on the data from the second report.

The *Table 1* lists all DiGAs reimbursed in Germany as of 30 September 2025 (n=57), including their therapeutic area, type of technological device, latest price in the permanent listing, and the reimbursement type (temporary or permanent) as of September 2024 and 2025, respectively [1] [2]. For three DiGAs listed as permanent list in 2025, the 2024 data are reported as "not available," since it was not possible to determine whether these DiGAs were directly included in the permanent list or were previously listed as temporary between October 2024 and 29 September 2025 (the period between the 2024 and the current analyses).

The total number of DiGAs analysed was 57, of which 46 were permanently listed and 11 temporarily listed.

The average price of a DiGA on the permanent list was €250.25, ranging from a minimum of €119.00 (Mawendo) to a maximum of €618.00 (Untire).

For DiGAs on the temporary list, the average price was €513.20 (n=54), with prices ranging from €116.97 (Kalmeda) to €2,077.00 (Levidex). Notably, Levidex shows an unusually high price on the temporary list, while the next highest-priced DiGA, Uroletics, is €895.00.

Table 1: DiGAs reimbursed in Germany, with therapeutic area, type of technological device, latest price in the permanent list, and permanent list price

Product	2024	2025	Therapeutic area	Technologic al device	T Price (€)	P Price (€)
Actensio	Т	Т	Heart disease	App	289.17	NA
attexis - digital therapy for ADHD in adulthood	ND	Р	Psychiatric disorders	WA	NA	599.40
Cara Care for irritable bowel syndrome	Р	Р	Other	Арр	718.20	248.00
Companion Patella powered by medi	Р	Р	Musculoskeletal disorders	WA	345.10	223.49
Companion® shoulder	-	т	Musculoskeletal disorders	WA	419.00	NA
Deprexis	Р	P	Psychiatric disorders	WA	297.50	210.00
eCovery - Therapy for low back pain	-	т	Musculoskeletal disorders	Арр	574.00	NA
edupression.com	Р	Р	Psychiatric disorders	WA	357.00	224.80
Elevida	Р	Р	Neurological disorders	WA	743.75	243.00
elona explore - for menthal health	т	т	Psychiatric disorders	Арр	535.49	NA
elona therapy Depression	ND	Р	Psychiatric disorders	WA + App	NA	535.49
Endo-App	Р	Р	Gynaecology/urology	Арр	598.95	235.80
Glucura Diabetes Therapy	Т	T	Metabolic disorders	Арр	499.80	NA
HelloBetter chronic pain	Р	P	Other	WA + App	599.00	235.00
HelloBetter diabetes	Р	P	Metabolic disorders	WA + App	599.00	222.99
HelloBetter panic	Р	P	Psychiatric disorders	WA + App	599.00	230.00
HelloBetter Sleep	Т	P	Psychiatric disorders	WA + App	599.00	241.25
HelloBetter Stress and Burnout	P	P	Psychiatric disorders	WA + App	599.00	235.00
HelloBetter Vaginismus plus	Р	Р	Gynaecology/urology	WA + App	599.00	235.00



Product	2024	2025	Therapeutic area	Technologic al device	T Price (€)	P Price (€)
hiToco®: ADHD parent training	-	Т	Psychiatric disorders	App	599.00	NA
Invirto - the therapy against anxiety	Р	Р	Psychiatric disorders	Арр	428.40	220.00
Kaia back pain - back training at home	Р	Р	Musculoskeletal disorders	Арр	489.39	221.49
Kalmeda	P	P	Otology	Арр	116.97	189.00
Kranus Edera	Р	P	Gynaecology/urology	Арр	552.01	235.00
Kranus Lutera	Р	Р	Gynaecology/urology	Арр	670.49	240.50
Levidex	т	P	Neurological disorders	WA	2.077.00	280.00
Mawendo	Р	Р	Musculoskeletal disorders	WA	119.00	119.00
Meine Tinnitus App	T	Р	Otology	App	250.00	260.00
Mindable: Social Phobia	T	Т	Psychiatric disorders	Арр	765.00	NA
Mindable: Panic & Agoraphobia	Р	Р	Psychiatric disorders	Арр	576.00	245.50
My7steps App	T	P	Psychiatric disorders	WA	470.05	470.05
Neolexon Aphasia	Р	Р	Other	WA + App	487.90	223.01
NeuroNation MED	т	P	Neurological disorders	Арр	499.00	479.70
NichtraucherHelden (Non- smokingHeroes)	Р	P	Addiction	Арр	239.00	211.00
Novego: cope with depression	Р	Р	Psychiatric disorders	WA	249.00	199.00
Novego: Overcoming fears	T	Р	Psychiatric disorders	WA	219.98	189.00
ORIKO ADHD therapy	-	Т	Psychiatric disorders	Арр	479.70	NA
Oviva	Р	Р	Metabolic disorders	Арр	345.00	220.90
Pink! Coach	Р	Р	Oncology	Арр	535.50	234.50
Priovi - digital support for borderline treatment	Р	Р	Psychiatric disorders	WA	855.82	244.00
ProHerz	Т	Р	Heart disease	Арр	550.00	440.00
Selfapy's online course at bulimia nervosa	Р	P	Psychiatric disorders	WA + App	540.00	232.00
Selfapy's online course for binge eating disorder	Р	P	Psychiatric disorders	WA + App	540.00	232.00
Selfapy's online course for depression	Р	Р	Psychiatric disorders	WA + App	540.00	217.18
Selfapy's online course for generalized anxiety disorder	Р	P	Psychiatric disorders	WA + App	540.00	228.50
sinCephalea - migraine prophylaxis	т	Т	Neurological disorders	Арр	690.00	NA
Smoke Free - stop Smoking	Т	P	Addiction	Арр	249.00	231.25
Somnio	Р	Р	Psychiatric disorders	WA + App	464.00	224.99
somnovia	ND	Р	Psychiatric disorders	WA	NA	599.40
Una Health for Diabetes	T	Т	Metabolic disorders	Арр	740.00	NA
Untire	Т	P	Oncology	Арр	618.00	618.00
Uroletics	-	T	Oncology	App	895.00	NA
Velibra	P	P	Psychiatric disorders	WA	476.00	230.00
Vitadio	Р	Р	Metabolic disorders	App	499.80	224.01
Vivira	Р	Р	Musculoskeletal disorders	Арр	239.96	206.79
Vorvida	Р	Р	Addiction	WA	476.00	192.01
Zanadio	Р	Р	Metabolic disorders	Арр	499.80	218.00

 $NA = Not \ Applicable; \ ND = Not \ Available; \ P = permanent \ list; \ T = temporary \ list; \ WA = web \ application. \ 2024 = update \ as \ of \ Sep \ 2024; \ 2025 = update \ as \ of \ Sep \ 2025.$



Of the 57 DiGAs analysed, 43 were those for which it was possible to assess price changes when moving from the temporary to the permanent list. New entries directly added to the permanent or temporary lists, as well as those remaining on the temporary list in 2025, were therefore excluded. Three types of outcomes were observed:

- PRICE REDUCTION for 88% (n=38/43) of the DiGAs, with an average reduction of -48.6% (vs 2024: 91%, n=30, average price reduction -47%). The most significant price reduction occurred for Levidex, a DiGA for the treatment of multiple sclerosis, with a decrease of -86.5%, from €2,077.00 to €280. Last year analysis showed that another multiple sclerosis product, Elevida, had the largest price reduction when it moved from the temporary to the permanent list (-67%).
- UNCHANGED PRICE for 7% (n=3/43) of the DiGAs. Last year, only one DiGA (3%) had the same price when moved from the temporary to the permanent lists.
- PRICE INCREASE for 5% (n=2/43) of the DiGAs (vs 2024: 6%, n=2). The increases reached +61.6% for Kalmeda and +4.0% for Meine Tinnitus App.

Considering all 43 DiGAs, the average price change was a discount of -41.4%.

Table 2: DiGAs reimbursed in Germany on the permanent list, with analysis of the discount in the permanent list compared to the last price on the temporary list

Product	2024	2025	T Price (€)	P Price (€)	Discount
Cara Care for irritable bowel syndrome	Р	Р	718.20	248.00	-65.5%
Companion Patella powered by medi	P	P	345.10	223.49	-35.2%
Deprexis	P	P	297.50	210.00	-29.4%
edupression.com	P	P	357.00	224.80	-37.0%
Elevida	P	P	743.75	243.00	-67.3%
Endo-App	P	P	598.95	235.80	-60.6%
HelloBetter chronic pain	P	P	599.00	235.00	-60.8%
HelloBetter diabetes	Р	Р	599.00	222.99	-62.8%
HelloBetter panic	Р	Р	599.00	230.00	-61.6%
HelloBetter Sleep	T	Р	599.00	241.25	-59.7%
HelloBetter Stress and Burnout	Р	Р	599.00	235.00	-60.8%
HelloBetter Vaginismus plus	Р	Р	599.00	235.00	-60.8%
Invirto - the therapy against anxiety	Р	Р	428.40	220.00	-48.6%
Kaia back pain - back training at home	Р	Р	489.39	221.49	-54.7%
Kalmeda	Р	Р	116.97	189.00	+61.6%
Kranus Edera	Р	Р	552.01	235.00	-57.4%
Kranus Lutera	Р	Р	670.49	240.50	-64.1%
Levidex	T	Р	2.077.00	280.00	-86.5%
Mawendo	Р	Р	119.00	119.00	0%
Meine Tinnitus App	Т	Р	250.00	260.00	+4.0%
Mindable: Panic & Agoraphobia	Р	Р	576.00	245.50	-57.4%
My7steps App	Т	Р	470.05	470.05	0%
Neolexon Aphasia	Р	Р	487.90	223.01	-54.3%
NeuroNation MED	Т	Р	499.00	479.70	-3.9%
NichtraucherHelden (Non- smokingHeroes)	Р	Р	239.00	211.00	-11.7%
Novego: cope with depression	Р	Р	249.00	199.00	-20.1%
Novego: Overcoming fears	Т	Р	219.98	189.00	-14.1%
Oviva	Р	Р	345.00	220.90	-36.0%
Pink! Coach	Р	Р	535.50	234.50	-56.2%
Priovi - digital support for borderline treatment	Р	Р	855.82	244.00	-71.5%
ProHerz	T	Р	550.00	440.00	-20.0%
Selfapy's online course at bulimia nervosa	Р	Р	540.00	232.00	-57.0%



Product	2024	2025	T Price (€)	P Price (€)	Discount
Selfapy's online course for binge eating disorder	Р	Р	540.00	232.00	-57.0%
Selfapy's online course for depression	Р	Р	540.00	217.18	-59.8%
Selfapy's online course for generalized anxiety disorder	Р	Р	540.00	228.50	-57.7%
Smoke Free - stop Smoking	Т	Р	249.00	231.25	-7.1%
Somnio	Р	P	464.00	224.99	-51.5%
Untire	T	P	618.00	618.00	0%
Velibra	Р	P	476.00	230.00	-51.7%
Vitadio	Р	P	499.80	224.01	-55.2%
Vivira	Р	Р	239.96	206.79	-13.8%
Vorvida	Р	Р	476.00	192.01	-59.7%
Zanadio	Р	Р	499.80	218.00	-56.4%

The average discount for DiGAs that moved from the temporary to the permanent list in 2025 was -20.8% (n=9). This value differs substantially from the average discount calculated across all DiGAs – including those that moved to the permanent list last year – of -41.4% (n=43).

Table 3: Price discounts of DiGAs moved from the temporary to the permanent list in 2025

Product	2024	2025	T Price (€)	P Price (€)	Discount
HelloBetter Sleep	Т	Р	599.00	241.25	-59.7%
Levidex	T	Р	2.077.00	280.00	-86.5%
Meine Tinnitus App	T	P	250.00	260.00	+4.0%
My7steps App	T	P	470.05	470.05	0%
NeuroNation MED	T	P	499.00	479.70	-3.9%
Novego: Overcoming fears	т	Р	219.98	189.00	-14.1%
ProHerz	Т	Р	550.00	440.00	-20.0%
Smoke Free - stop Smoking	Т	P	249.00	231.25	-7.1%
Untire	T	P	618.00	618.00	0%

The price evolution of DiGAs from 2021 to September 2025 indicates that the discount applied when a DiGA moves from the temporary to the permanent list has reduced over the years. The average price variation peaked in 2022 at -49% and is at -41% in the 2025.

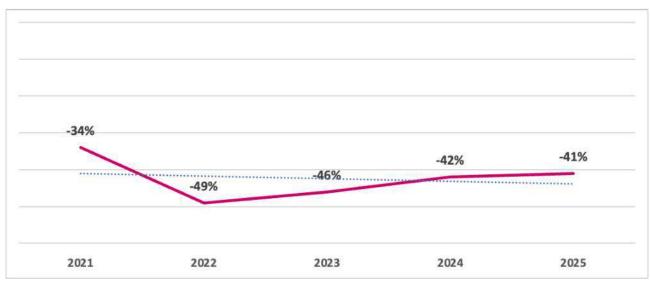
In 2025, the average price was the highest compared with previous years, both for DiGAs on the temporary list and those on the permanent list.



Table 4: Changes in average prices of DiGAs over the years

Year	Number of DiGA entered in the permanent list	Average prices in the temporary list (€)	Average prices in the permanent list (€)	Average price variation
2021	5	468.1	220.8	-34%
2022	8	460.0	216.7	-49%
2023	16	462.6	221.7	-46%
2024	4	459.2	235.7	-42%
2025	9	513.2	250.3	-41%

Figure 1: Discount trend of DIGAs from 2021 to 2025





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1.3. STATE OF THE ART OF pDMD AND DTx IN ITALY

1.3.1.ITA pDMD mapping

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This paragraph presents an analysis based on the Italian Ministry of Health (MoH) medical device registry, aimed at mapping the availability of patient-managed Digital Medical Device (pDMDs) in Italy. A comparison of data from the previous year with the 2025 results is presented to visualize and better understand emerging trends and evolving patterns within the field. Valuable insights into the role of pDMD within the National Healthcare System emerge from the results, allowing for a better understanding of current trends that could guide future policy and research.

A complete list of medical devices with CE marking commercialised in Italy is available on the MoH website [1]. As of September 23, 2025, the list included a total of 2,220,278 certified medical devices.

Subsequently, CND (National Classification for Devices) codes deemed useful for identifying Software as a Medical Devices (SaMDs) were selected [2]. *Table 1* shows the CNDs considered in the analysis.

Table 1: CND codes used to identify SaMDs

CND code	Description of CND code
V92	Software as a device - not included in other classes.
Z129092	Various instrumentation for functional exploration and therapeutic interventions - software medical devices
Z12040182	Instrumentation for monitoring and diagnosis in general medicine - software - accessory components
Z12069082	Instrumentation for monitoring and diagnosis in general medicine - software - accessory components
Z12069092	Various instrumentation for physiotherapy and rehabilitation – software medical devices
Z12100702	Electromyography telemetry transmitter units

Once the devices associated with the relevant CNDs were selected, the data were exported to Excel for easier handling. A database populated with a total of 426 SaMDs was then created, with the following information collected for each: manufacturer, product name, CND code, description of CND code, and medical device class.

Each of SaMDs was analysed by searching the manufacturer website or the device website for information regarding its functionality. Using this methodology, a total of 64 (15%) medical devices corresponding to the definition of pDMDs were identified.

The pDMDs were classified based on their medical purpose and divided into the following categories:

- Therapy Digital Therapeutics (DTx)
- Diagnosis Digital Diagnostics: software and digital tools that offer diagnostic or prognostic insights for a given disease or medical condition
- Monitoring Remote Patient Monitoring (RPM): digital solutions intended to track specific health data, allowing physicians to interpret the information for clinical management
- Prevention Digital Prevention: digital solutions and software designed to support disease prevention by monitoring health indicators and promoting early intervention strategies.



The medical purpose of the 64 identified pDMDs was monitoring for 45% (n=29), therapy for 41% (n=26), prevention for 8% (n=5) and diagnosis for 6% (n=4).

Most of the pDMDs were registered as Class I medical devices (69%, n=44), while 22% (n=14) were registered as Class IIa, 8% (n=5) as Class IIb, and 2% (n=1) as Class III.

Table 2: pDMDs listed in the Italian MoH medical device registry searched for CND code and classified by medical purpose and CE marking class

Product name	Manufacturer	CND code	Medical purpose	Class
ADA ASSESS	ADA HEALTH GMBH	V92	Diagnosis	lla
ALLIMB	JJRENT SAS DI LAWRENCE SPAVIERI & C.	Z12069082	Therapy	I
ANY-DANA-A	SOOIL DEVELOPMENT CO, LTD	Z12040182	Monitoring	lla
ANYTIMEWELL	ZHEJIANG POCTECH CO, LTD	V92	Monitoring	IIb
APP SOCIAL DIABETES	SOCIAL DIABETES SL	Z12040182	Monitoring	IIb
BALBUS	ONE HEALTH VISION SRL	Z12069082	Therapy	I
BALBUS 5.0	DIGITHERAPIX SRL/ONE HEALTH VISION SRL	Z12069092	Therapy	I
BPCOMEDIA	LABORATORI DI INFORMATICA APPLICATA DI CAPASSO GIUSEPPE	Z12040182	Monitoring	lla
CAARING	PERSEI VIVARIUM SRL	Z12040182	Monitoring	1
CARDIOSIGNAL	PRECORDIOR LTD	V92	Diagnosis	lla
CARELINK PERSONAL	MEDTRONIC MINIMED	Z12040182	Monitoring	1
CEREBRUM VR	CEREBRUM VR SRL	V92	Therapy	L
COMESTAI	COME STAI SPA	Z12040182	Prevention	1
COMMUNICATOR AI	DIGITHERAPIX SRL/ONE HEALTH VISION SRL	Z12069092	Therapy	I
CONTINUOUS GLUCOSE MONITORING	MICROTECH MEDICAL (HANGZHOU) CO, LTD	Z12040182	Monitoring	IIb
DEPREXIS	ETHYPHARM DIGITAL THERAPY	V92	Therapy	1
DIAWATCH METEDA	METEDA SRL	Z12040182	Monitoring	1
DID PLUS	METEDA SRL	Z12040182	Monitoring	lla
DOSE CHECK	AMALGAM RX, INC	Z12040182	Monitoring	lla
ENGAGE	VITALHEALTH SOFTWARE BV	Z12040182	Prevention	ı
EULERIA HOME	EULERIA SRL SOCIETA' BENEFIT	Z12069092	Therapy	lla
EUROTOUCH	ME.TE.DA. SRL	Z12040182	Monitoring	I
GLOOKO MOBILE APPLICATION	GLOOKO, INC	V92	Monitoring	lla
GLOOKO WEB APPLICATION	GLOOKO, INC	V92	Monitoring	lla
HEDIA DIABETES ASSISTANT HTN SMART TELEMEDICINE PLATFORM	HEDIA APS HEALTH TELEMATIC NETWORK SRL	Z129092 V92	Monitoring Diagnosis	IIb I
HUMA	HUMA THERAPEUTICS LIMITED	V92	Monitoring	1
IAMHERO	IAMHERO SRL	V92	Therapy	i
ISAGE RX	AMALGAM RX, INC	Z12040182	Monitoring	lla
KAIKU HEALTH	ELEKTA SOLUTIONS AB	Z12040182	Monitoring	lla
KALANIT REHAB	DROP SRLS	V92	Therapy	I
LOGOQUIZ	ONE HEALTH VISION SRL	Z12069092	Therapy	i
MEDICATION DIARY	BRAIN INNOVATIONS SRL	V92	Monitoring	1
MEDICREHAPP	EULERIA S.R.L. SOCIETA' BENEFIT	Z12069092	Therapy	i
MEDOPAD	HUMA THERAPEUTICS LIMITED	V92	Monitoring	1
			_	
METADIETA FOR PREVENTOMICS	METEDA SRL	Z12040182	Prevention	1



Product name	Manufacturer	CND code	Medical purpose	Class
MINDLENSES PROFESSIONAL	RESTORATIVE NEUROTECHNOLOGIES SRL	Z12069092	Therapy	1
MITAG	VOXELMIND SRLS	V92	Monitoring	1
MY DOSE COACH	METEDA SRL	Z12040182	Therapy	lla
MYABBVIECARE	ABBVIE INC	V92	Prevention	1
NUMBERS'ADVENTURES	ONE HEALTH VISION SRL	Z12069092	Therapy	1
PARKINSON REHAB	DROP SRLS Z12069082		Therapy	1
PIC HEALTH STATION	MEDM INC	V92	Monitoring	1
QUICKLYPRO-APP	QUICKLYPRO SRL START-UP	Z12069082	Therapy	1
REALICA	VALIAMO SRL	V92	Prevention	1
REHABILITY	IMAGINARY SRL	Z12069082	Therapy	1
RELAB	TECH4CARE SRL	Z12040182	Therapy	1
REMO	MORECOGNITION SRL	Z12100702	Therapy	1
RITA	ADVICE PHARMA GROUP SRL	V92	Monitoring	1
SCRIVO BENE	ONE HEALTH VISION SRL	Z12069092	Therapy	1
SELECTEAT	DIGITHERAPIX SRL/ ONE HEALTH VISION SRL	Z12069092	Therapy	1
SM@RTEVEN	INFORMATICA E TELECOMUNICAZIONI SRL	Z12040182	Monitoring	I
SOFTWARE PER SISTEMI DI Monitoring CONTINUO DEL GLUCOSIO	ZHEJIANG POCTECH CO., LTD	Z12040182	Monitoring	IIb
SOFTWARE SOLUTIONS CGMS	MEDTRONIC MINIMED	Z12040182	Diagnosis	lla
SURPASS	CINECA CONSORZIO INTERUNIVERSITARIO	V92	Monitoring	I
TANDEM T:SLIM MOBILE APP	TANDEM DIABETES CARE, INC	V92	Therapy	III
TURBOLETTURA	ONE HEALTH VISION SRL	Z12069092	Therapy	I
TUTTASCOLTO	ONE HEALTH VISION SRL	Z12069092	Therapy	1
VINEHEALTH CANCER COMPANION & VINEHEALTHPRO	VINEHEALTH DIGITAL LTD	Z12040182	Monitoring	I
VISITA SMART VERSIONE 1.0.0	MEDICAL CLOUD SRL	V92	Monitoring	1
VOLO BLA BLA	ONE HEALTH VISION SRL	Z12069092	Therapy	I
YOURLOOPS	DIABELOOP	Z12040182	Monitoring	lla
ZULU MERIDIAN	ZULU MEDICAL SRL	V92	Monitoring	ı

Comparative analysis 2025 vs 2024

Respect to 2024, the current landscape of Digital Medical Devices (DMDs) evolved considerably: the total amount of SaMDs increased by 24% (n=344 in 2024), while pDMDs grew by an even more substantial 42% (n=45 in 2024). On the other hand, a limited yet significant ecosystem of pDMDs is available in Italy, with a total of only 64 pDMDs out of 2,220,278 medical devices registered by the MoH as of September 2025.

The pDMD analysis showed that, from a medical purpose perspective, remote patient monitoring remained the leading category, representing 47% (n=21) of devices in 2024 and 45% (n=29) in 2025. DTx followed with 38% (n=17) in 2024 and 41% (n=26) in 2025, confirming the consolidation of these two mature domains. Smaller yet stable segments were digital prevention, accounting for 9% (n=4) in 2024 and 8% (n=5) in 2025, and digital diagnostics, with 7% (n=3) and 6% (n=4), respectively.

In terms of regulatory classification, Class I devices still predominate but slightly decreased from 69% (n=31) in 2024 to 69% (n=44) in 2025. Class IIa devices also declined proportionally from 27% (n=12) to 22% (n=14), whereas Class IIb products increase sharply from 4% (n=2) to 8% (n=5). Notably, Class III devices appeared for the first time, moving from 0% (n=0) in 2024 to 2% (n=1) in 2025.



Model case of DHTs adoption within regional healthcare systems

Among mentioned CE-marked pDMDs commercialised in Italy and listed in the MoH medical device registry is RITA (Remote Intelligence for Therapeutic Adherence).

RITA is a mobile app for oncological therapeutical area developed, by Advice Pharma. It obtained CE marking as a Class I medical device in 2025, and its medical purpose is monitoring; for this reason, it is a pDMD classified as a Remote Patient Monitoring (RPM) device.

RITA has been designed to support the management of the oncology patients, promoting therapeutic adherence, facilitates daily self-management, and strengthens the continuity of care between patients and their clinical teams. From the patient's perspective, it serves as a first-aid tool for addressing the most common problems, while also providing an efficient and "non-invasive" means of communication with healthcare professionals RITA enables users to monitor vital parameters, record symptoms and medications, request drug prescriptions, and complete quality of life questionnaires.

Through integrated telemedicine interface, the app allows to include the caregiver and the clinicians in the communication group. Moreover, RITA continuously collects clinical and patient-reported data, allowing research centres to conduct real-world studies and helping specialists make faster, more informed decisions.

RITA is part of a project that introduced digital technology in the Liguria Region aimed at integrating digital medicine into the regional healthcare system for prevention and treatment [3]. The Liguria Region is, in fact, preparing to create a first-level ecosystem able to sustain the use of digital tools and integrating them into clinical practice. This kind of initiatives provide valuable insight into the ongoing evolution of the Italian digital clinical ecosystem. They demonstrate how digital technologies are progressively being incorporated into traditional care pathways, facilitating future clinical adoption and policy development to support the responsible growth of this emerging field.



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1.3.2.ITA DTx mapping

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The aim of this paragraph is to update the analysis described in the Second DTx Monitoring Report [1], focusing on Digital Therapeutics (DTx) commercialized in Italy and certified with CE marking.

The number of DTx currently commercialized in Italy and listed in the Medical Devices Registry maintained by the Italian Ministry of Health is 26. Of these, 11 are the new ones that obtained CE marking compared to the year 2024. Most of them are Class I medical devices (88%, n=23), while two are Class IIa (8%, n=2), and two are Class III (4%, n=1).

Table 1: Digital Therapeutics (DTx) currently commercialized in Italy and listed in the Ministry of Health Medical Devices Registry

Product	Company	Therapeutic Area	Class	New 2025
Allimb	Jjrent di Lawrence Spavieri & C.	Motor rehabilitation	1	
Balbus	One Health Vision	Stuttering	I	
Balbus 5.0	One Health Vision	Stuttering	1	Х
Cerebrum VR	Cerebrum	Mental health, psychiatric rehabilitation, neuropsychological disorders	I	X
CommunicatorAl	One Health Vision	Aphasia	1	Χ
Deprexis	Ethypharm Digital Therapy	Depression	l	
Euleria Home	Euleria Health	Motor, cardiac and cognitive rehabilitation	lla	
lamHero	lamHero	ADHD, Neurodevelopmental Disorders	I	
Kalanit Rehab	Drop	Musculoskeletal pain	1	
LogoQuiz	One Health Vision	Aphasia	l	Χ
MedicRehApp	Euleria Health	Cardio-respiratory rehabilitation	1	
Mindahead Active App	Mindahead	Mild Cognitive Impairment, Dementia	1	
MindLenses Professional	RESTORATIVE Neurotechnologies	Post-stroke cognitive deficits	1	Х
My Dose Coach	Meteda	Diabetes	lla	
Numbers'adventures	One Health Vision	Dyscalculia and difficulties in the logical-mathematical field	I	
Parkinson Rehab	Drop	Parkinson	I	
QuicklyPro App	QuicklyPro	Motor rehabilitation	1	
REHABILITY	imaginary	Neurological conditions (motor and cognitive rehabilitation)	I	Х
Relab	Tech4Care	Cognitive impairment rehabilitation, Multiple sclerosis, Parkinson	1	
Remo	Morecognition	Rehabilitation of hand and forearm functions	I	Х
Scrivo Bene	One Health Vision	Dysorthography	1	



Product	Company	Therapeutic Area	Class	New 2025
SelectEAT	One Health Vision	Food selectivity	1	Χ
Tandem t:slim mobile app	Tandem Diabetes Care	Diabetes	III	Χ
TurboLettura	One Health Vision	Dyslexia and reading difficulties	I	
TuttAscolto	One Health Vision	Hearing disorders and hearing loss	I	X
Volo Bla Bla	One Health Vision	Phonological disorder	I	Χ

A total 15 companies are involved in the development of these DTx. One Health Vision is the only company that developed more than two DTx, accounting for 10 digital products (38% of the total), all classified as Class I medical devices, 6 of which obtained CE certification in 2025, whereas the others were already certified. Three further DTx developed by One Health Vision are currently awaiting certification: Leggo Facile for acquired dyslexia [2], BuildAttention for attentional and executive functions [3], and Alleniamo la memoria for mnestic abilities [4].

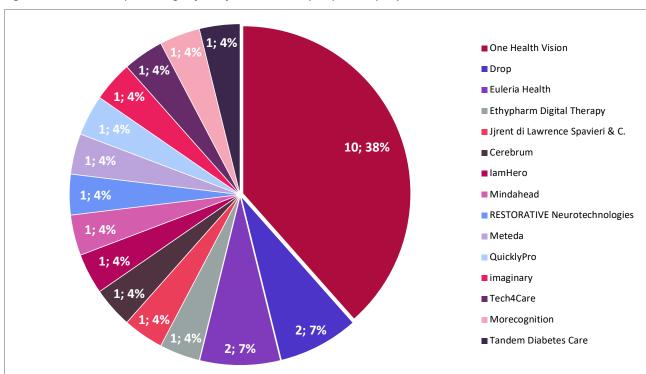


Figure 1: Number and percentage of certified DTx developed per company

The following section provides a detailed description of the new DTx that obtained CE certification, as listed in Table X, including an overview of each intervention, its producer, purpose, and functionality.

Balbus 5.0 [5]

Balbus 5.0 is a mobile app for the treatment of stuttering, developed by One Health Vision Srl.

Balbus 5.0 is the advanced version of Balbus, the first web application produced by One Health Vision for the treatment of stuttering. Balbus consists of five exercises that enable the patient to gain greater control over their speech. Through audio and visual feedback, it helps the patient to achieve greater fluency. There are individual graphs for each exercise for better patient monitoring.



Balbus 5.0 provides immediate and personalized feedback, helping patients improve control over their fluency. Additionally, it encourages the restructuring of irrational thoughts through the application of cognitive-behavioural techniques, offering constant support as if each patient were personally followed by a specialist all day long.

The app is currently available on the market and can be purchased from Play Store and App Store.

Cerebrum VR [6]

Cerebrum VR is Virtual Reality (VR) app for cognitive rehabilitation, developed by CEREBRUM VR Srl, an Italian small start-up focusing on virtual reality solutions.

Through a virtual reality headset, Cerebrum VR allows patients to immerse themselves in experiential situations that simulate everyday reality, helping them work on their cognitive functions. It is divided into 5 Modules containing over 110 exercises of varying levels of difficulty focusing on memory and learning, cognitive estimation, attention and working memory, and planning. It focuses on cognitive stimulation aspects also addressing on metacognitive elements and psychosocial functioning (self-esteem, perceived self-efficacy, agency, empowerment, motivation, initiative).

Cerebrum VR is targeted for Psychotic Spectrum Disorders, Obsessive-Compulsive Disorder, Mood Disorders, Borderline Disorder and Personality, Anxious Symptomatology, and Dementia/Mild Cognitive Impairment.

Communicator AI [7]

Al Communicator is a mobile app for aphasia, developed by One Health Vision Srl, an Italian innovative medium-sized company that creates cutting-edge digital solutions to improve the effectiveness of rehabilitation treatments and promote patient autonomy and well-being.

Using an advanced artificial intelligence algorithm and the convenience of in-home therapy, AI Communicator allows patients to use a gallery of categorized images to express their needs and desires. In situations of severe language impairment, where verbal communication is limited, patients can simply select a category (such as "food" or "comfort") and point to a specific image; the app interprets the selection and helps vocalize the patient's needs.

The app includes a series of exercises aimed at improving various aspects of aphasia: reading comprehension (exercises designed to help patients better interpret spoken and written language), denomination (activities that encourage the recognition and correct naming of objects and concepts), reading and writing (tools to facilitate the reacquisition of reading and writing skills, essential for everyday communication), construction of sentences (exercises that assist patients in forming coherent and understandable sentences).

The app is currently available on the market and can be purchased from Play Store and App Store.

LogoQuiz [8]

LogoQuiz is a mobile app designed for the treatment of aphasia, developed by One Health Vision Srl.

LogoQuiz helps users with aphasia or dysphasia to improve communication skills, facilitate the recovery of impaired linguistic functions, rehabilitate language skills within a playful and engaging scenario for the user, and receive immediate feedback on the accuracy of the answer provided.

LogoQuiz aims to engage users through a serious game set in a television scenario, where users have to answer the questions asked by the presenter, thus winning the quiz and obtaining prizes and rewards. The app features a voice recognition engine that is able to detect what the users say and provide immediate feedback; in this way the users can practice independently and don't need a caregiver to correct what is read.

The app is currently available on the market and can be purchased from Play Store and App Store.

MindLenses Professional [9]

MindLenses Professional is an integrated digital medical device for post-stroke cognitive deficits, developed by RESTORATIVE Neurotechnologies, an Italian start-up focused on developing neurotechnological solutions aimed at neurological recovery.



It consists of medical software and a wearable device (glasses with prismatic lenses) that work together for cognitive rehabilitation and enhancement in patients with cognitive disorders such as memory, language, attention, praxis, and executive function impairments, arising after brain injury caused by ischemic or haemorrhagic stroke.

MindLenses activates brain plasticity and enhances cognitive functions using the combination of non-invasive neuromodulation and serious games.

REHABILITY [10]

REHABILITY is a digital rehabilitation platform for neurological conditions (motor and cognitive rehabilitation), developed by imaginary SrI, an Italian SME active in digital health, serious games, and interactive technology.

REHABILITY consists of a set of interactive medical training games, that enables patients to perform personalized exercises to improve motor, cognitive, and functional abilities. With a hardware kit connected to the TV, patients can continue therapy from home, while specialists remotely monitor progress and adjust treatment parameters. The system is highly scalable, allowing healthcare professionals to manage multiple patients efficiently with tailored therapy plans. Primarily designed for chronic and elderly patients, REHABILITY can easily be integrated in longevity projects and setting to help elderly people realize their potential and promote active ageing, combining physical and mental well-being, social participation and independence in a non-clinical context.

Remo [11]

Remo is a wearable armband for rehabilitation of hand and forearm functions, especially in patients who have suffered a stroke, developed by Morecognition Srl, an innovative Italian start-up.

Remo allows patients to exercise daily, following the guidance of their physiotherapist. It leverages therapeutic motivation, reminding patients when and how to perform their exercises, increasing their engagement and adherence to therapy. It also enables continuous monitoring, allowing physiotherapists to track their patients' exercises, follow their progress, and provide motivation.

SelectEAT [12]

SelectEat is mobile app designed to address food selectivity, developed by by One Health Vision Srl.

The app is a serious game that enables treatment within an engaging and motivational scenario for the user, providing the opportunity for personalized learning. The activities included in the app allow users to simultaneously achieve rehabilitative and educational goals. The app also allows users to view graphs and reports of the exercises performed to monitor performance over time and to track the number of games played with the number of correct responses, in relation to the exercises completed during the week or in a single day.

The app is currently available on the market and can be purchased from Play Store and App Store.

Tandem t:slim mobile app [13]

The Tandem t:slim mobile app is the digital companion for the pomp for insulin t:slim X2, developed by Tandem Diabetes Care, Inc.

The app allows users to deliver a bolus directly from their personal smartphone, serves as a secondary and discreet display for the pump, and enables users to view pump data and receive push notifications directly on their smartphone.

The app is currently available on the market for both Android and IOS and can be purchased from Play Store and App Store.

TuttAscolto [14]

TuttAscolto is a mobile app designed for hearing disorders and hearing loss, developed by One Health Vision Srl.

TuttoAscolto addresses both the auditory and neuropsychological aspects, and is designed for children with language learning difficulties, children with cochlear implants, children whose hearing difficulties affect the correct acquisition of reading and writing skills, children who can consolidate auditory discrimination skills related to the prerequisites of



learning, people with hearing loss, and people who want to prevent the emergence of serious difficulties in the various domains involving neuropsychological functions at the perceptive-auditory level.

The game-based app is designed to maintain attention and stimulate learning through challenges, rewards, and progression. It turns rehabilitation exercises into engaging, playful activities that help the automatic development of targeted skills.

The app is currently available on the market and can be purchased from Play Store and App Store.

Volo Bla Bla [15]

Volo Bla Bla is a mobile app dedicated to children with phonological disorder, developed by One Health Vision Srl.

Volo Bla Bla uses a voice recognition engine developed to evaluate the child pronunciation in real time, transcribing speech, assessing accuracy, and providing immediate feedback. Through engaging 3D gameplay, it enhances engagement and makes therapy sessions fun capturing the child attention and interest.

The system also allows therapists to monitor progress through emailed reports, enabling it to be integrated into broader therapy programs rather than functioning only as a standalone game.

The app is currently available on the market and can be purchased from its dedicated website, downloaded and installed on the personal PC.



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1.3.3. Budget Impact Analysis of DTx in Italy

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Background

In recent years, Digital Therapeutics (DTx) have emerged as clinically validated digital interventions capable of preventing, managing, or treating a wide range of diseases. Despite their growing recognition at the international level, the diffusion of DTx across European countries remains uneven. Germany represents the most mature and regulated DTx market, supported by the Digital Health Applications (DiGA) framework [1], which since 2020 has enabled formal reimbursement of over 50 certified applications through the statutory health insurance system.

In contrast, the Italian market is still at an early stage of development. Only a limited number of technologies are currently registered as patient-managed digital medical devices (pDMDs) with therapeutic purposes, and the absence of a dedicated reimbursement pathway slows down their adoption. This regulatory and economic gap highlights the need for preliminary evaluations of potential expenditure, affordability, and sustainability for the Italian National Health Service (NHS).

The aim of this analysis is therefore to estimate the potential expenditure associated with the adoption of DTx in Italy, stratified by therapeutic area, and to provide a comparison with the German DiGA market, which can serve as a reference benchmark in terms of maturity, therapeutic coverage, and pricing structure.

Methods

A descriptive and comparative analysis was conducted using publicly available data from the Italian Ministry of Health medical device database as of September 2024 [2]. These technologies, primarily software-based and intended for direct use by patients, represent the functional equivalent of the DiGA applications recognized in Germany. Each identified device was subsequently reviewed and manually classified according to its therapeutic area, mirroring that used in the German BfArM DiGA directory as of September 2024.

Because Italy currently lacks official reimbursement tariffs for DTx, the mean price of DiGA applications in Germany was adopted as the reference value. The German pricing model represents the most consolidated European benchmark, being based on transparent negotiations between producers and the Federal Institute for Drugs and Medical Devices (BfArM) following the demonstration of clinical benefit. Prices were grouped by therapeutic class — psychiatric, neurological, musculoskeletal, metabolic, cardiovascular, and others — and the resulting average value was associated with the corresponding Italian area.

Each therapeutic area was weighted according to the epidemiological prevalence of the corresponding diseases within the Italian population.

For every condition, the potential expenditure was obtained by multiplying the average cost of the corresponding DiGA by the estimated number of patients affected in Italy and by a conservative adoption rate set at 1%. This scenario was selected to represent a minimal but realistic penetration level, reflecting early-stage market conditions and the absence of structured reimbursement mechanisms in the country.

Results

The mapping identified 17 therapeutic Digital Therapeutics (DTx) currently available in Italy and 56 approved DiGA applications in Germany. Although the two markets differ considerably in scale, the internal distribution of DTx by therapeutic area allows a proportional comparison of their respective focuses.

In Italy, DTx are predominantly concentrated in neurological disorders and musculoskeletal disorders, which together account for more than three-quarters of the total portfolio. Smaller shares are represented by psychiatric, metabolic, and cardiovascular disorders, each contributing less than one-fifth of the overall offer. In Germany, the internal composition is more diversified: while psychiatric disorders represent the largest group, a consistent presence is also observed across musculoskeletal, metabolic, gynaecological/urological, neurological, and addiction-related indications.



For comparative consistency, DTx addressing multiple therapeutic areas were assigned to their primary clinical indication, identified according to the main functional purpose and the prevalence of the target condition. The detailed distributions for Italy are reported in *Table 1*, where frequencies are expressed as relative proportions within national total.

Table 3: Distribution of Digital Therapeutics (DTx) in Italy by therapeutic area

THERAPEUTIC AREA	NO. OF TECHNOLOGIES	FREQUENCY (%)
NEUROLOGICAL DISORDERS	8	47%
MUSCULOSKELETAL DISORDERS	5	29%
PSYCHIATRIC DISORDERS	2	12%
HEART DISEASE	1	6%
METABOLIC DISORDERS	1	6%
TOTAL	17	100%

Figure 1 presents the distribution of annual prices for DiGA applications in Germany across disease categories. The overall mean cost was €360.88 per user per year, with notable variability between therapeutic areas.

The highest-cost applications were found in neurological and oncological disorders, particularly those addressing complex or chronic conditions such as multiple sclerosis (1,160.20€) and prostate cancer (895.00€). Intermediate price levels characterised psychiatric and musculoskeletal disorders, while the lowest-cost categories included addiction, gynaecological/urological, and otological indications, generally below €250 per year.

These German reference values were subsequently applied to estimate average costs per therapeutic area in the Italian dataset.

1.200 € 1.050€ 900€ 750€ 600€ 450€ 300 € 150€ 0€ Mental disorders. Heart failure. Aphasia. rritable bowel syndrome. ADHD. Endometriosis Diabetes Chronic pain. Breast cancer. **Erectile dysfunction** Vaginismus Cognitive disorders Migraine Multiple sclerosis Eating disorders Urinary tract diseases Obesity Knee disorders Low back pain Spinal osteochondrosis Shoulder disorders Anxiety Depression Stress-related disorders Prostate cancer Personality disorder Phobias Insomnia Panic disorder Addicition Gynaecology/urology Musculoskeletal disorders Oncology Otology (tinnitus) Psychiatric disorders Heart disease Metabolic disorders Neurological disorders Other

Figure 1: Annual cost of DiGA applications in Germany by disease category

For each therapeutic area, the estimated expenditure was obtained by multiplying the average cost of DTx (derived from German reference prices) by the Italian prevalence of the corresponding conditions, assuming a 1% uptake rate as the base scenario. The resulting estimates are reported in *Table 2*.



Table 2: Estimated expenditure of Digital Therapeutics (DTx) in Italy

THERAPEUTIC AREA	AVERAGE DTx COST	PREVALENT PATIENTS	AVERAGE SCENARIO (1%)	TOTAL EXPENDITURE
NEUROLOGICAL DISORDERS	211.42€	2,123,500	21,235	13,552,761€
MUSCULOSKELETAL DISORDERS	368.26€	5,335,212	53,352	15,256,358€
HEART DISEASE	440.00€	1,001,881	10,019	4,408,276€
PSYCHIATRIC DISORDERS	354.28€	4,227,725	42,277	13,204,889€
METABOLIC DISORDERS	285.54€	4,837,775	48,378	15,508,696€
TOTALE COMPLESSIVO	365.19€	17,526,093	175,261	61,930,981 €

The analysis shows that musculoskeletal (€15.26 million) and metabolic disorders (€15.51 million) represent the areas with the highest potential expenditure, reflecting their broad population coverage. They are followed by psychiatric (€13.20 million) and neurological disorders (€13.55 million), while heart disease (€4.41 million) accounts for a smaller share due to a more limited eligible population.

Discussion

The results of this analysis confirm that the Italian market for Digital Therapeutics (DTx) remains underdeveloped and fragmented compared with the more structured experience of Germany. While the German DiGA framework provides a clear regulatory, clinical, and reimbursement pathway for the evaluation and integration of DTx into the public health system, Italy still lacks a coherent national strategy. This absence of a centralized framework has limited the diffusion of digital therapies and slowed their integration into clinical practice, despite growing evidence of their clinical and economic value.

From an economic perspective, the projected expenditure associated with a 1% adoption rate – approximately €62 million annually – appears modest in relation to the potential benefits in terms of efficiency, adherence, and patient outcomes. These findings are consistent with the international evidence reviewed in the previous chapter, which demonstrates that DTx interventions are generally cost-effective and capable of reducing both direct and indirect healthcare costs. Specifically, Davison et al. (2024) found that prescription digital therapeutics for type 2 diabetes improved glycaemic control and reduced diabetes-related complications, achieving favourable cost-effectiveness results [3]. In the cardiovascular field, DTx for essential hypertension enhanced blood-pressure control and patient adherence [4]. DTx lowered healthcare resource utilisation and generated measurable cost savings for the healthcare system even in the mental health field [5].

If implemented in Italy, DTx could therefore play a strategic role in the management of chronic and high-prevalence diseases such as depression, diabetes, and cardiovascular conditions. The literature consistently demonstrates that digital interventions support long-term self-management, enhance continuity of care, and promote patient empowerment – dimensions that remain critical weaknesses within the Italian National Health Service (NHS). Their integration into clinical practice could also help to mitigate long-standing disparities in access to specialist services and rehabilitation programs, especially in regions characterised by lower healthcare density or geographical barriers.

Nevertheless, the current Italian context still presents structural and organisational challenges that hinder the systematic adoption of DTx. One of the main barriers is the absence of a dedicated Health Technology Assessment (HTA) pathway specifically tailored to digital interventions. While traditional medical devices and pharmaceuticals follow well-defined evaluation procedures, DTx still fall within a regulatory grey area, where assessment criteria, evidence requirements, and decision-making responsibilities remain unclear. This lack of standardisation, combined with fragmented governance across national and regional levels, often results in heterogeneous and non-replicable local initiatives. As highlighted in several national analyses on healthcare innovation, the difficulties encountered by Italy in integrating digital health solutions are not only regulatory but also cultural and infrastructural, involving issues such as interoperability, training, and the digital divide between regions and age groups.

From a methodological standpoint, some limitations of this analysis must be acknowledged. The use of German DiGA prices as reference values assumes comparable market conditions and reimbursement mechanisms, which are not yet present in Italy. Epidemiological estimates are derived from aggregated national data that may vary across sources, and the 1% adoption rate reflects a conservative static scenario that does not capture future scaling effects. However, these limitations do not alter the core conclusion of the study: that DTx adoption in Italy would be both feasible and economically sustainable.



Overall, the evidence suggests that Digital Therapeutics could represent a transformative and sustainable innovation for the Italian healthcare system. By strengthening patient engagement, adherence, and continuity of care, these technologies have the potential to complement traditional clinical practice and improve efficiency in the management of chronic diseases. Yet, to realise this potential, Italy will need to establish a unified governance and evaluation model, capable of aligning regulatory standards, clinical evidence generation, and reimbursement mechanisms under a national strategy. Only through an integrated approach—anchored to transparent HTA processes and equitable access policies—can Digital Therapeutics evolve from isolated pilot projects into stable and value-driven components of routine healthcare delivery.

Conclusions

This analysis indicates that DTx represent a sustainable and impactful innovation opportunity for the Italian healthcare system. Even with limited initial uptake, the projected expenditure appears proportionate to the potential clinical and organisational gains demonstrated internationally. The main barriers are structural rather than economic, reflecting the lack of a clear evaluation and reimbursement pathway. Establishing a national strategy and dedicated HTA process would enable systematic DTx integration, enhancing efficiency, accessibility, and patient engagement across chronic care pathways.



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1.3.4. Updates on the Italian draft law for DTx and Digital Health Policy Lab proposals

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In Italy, the current regulatory framework for Digital Therapeutics (DTx) is Regulation (EU) 2017/745 on Medical Devices (MDR). A legislative proposal on DTx is currently undergoing the italian parliamentary process, aiming to integrate DTx into the National Health Service (NHS) and reimbursement systems.

The MDR regulates medical devices, defining them in Article 2 as follows: "medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point."

The definition therefore also includes software specifically designed for therapeutic purposes, such as in the case of

Any digital therapeutic that falls under the definition of "medical software" must comply with the MDR to be legally commercialized and used in the EU.

A digital therapeutic must obtain CE marking as a medical device, in accordance with the MDR, in order to be used in Europe (including Italy). This process involves risk classification (Class I, IIa, IIb, III), clinical evaluation, quality management, risk management, and compliance with technical standards.

It must then be validated or qualified as a digital therapeutic if it meets the definition and characteristics outlined in ISO/TR 11147:2023.

The reimbursement of a medical device in Italy requires the inclusion in the Essential Levels of Assistance (*Livelli Essenziali di Assistenza*, LEA). In order to provide a faster way for the reimbursement of medical device qualified as a digital therapeutic is currently under discussion a specific national law on DTx, intended to complement the MDR by defining the reimbursement pathway.

The main legislative proposals on DTx are:

- Chamber of Deputies No. 1208 Members bill by Deputies Loizzo, Molinari, Andreuzza, Davide Bergamini,
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 et al.) of 7 June 2023] [1] [2].
- Chamber of Deputies No. 2095 Members bill by Deputies Quartini, Amato, Di Lauro, Fede, Ferrara, Marianna Ricciardi, Sportiello. Provisions concerning digital therapeutics. Presented on 16 October 2024 [C. 2095 (Quartini et al.) of 16 October 2024] [3].



• Chamber of Deputies No. 2220 - Members bill by Deputies Girelli, Furfaro, Ciani, Malavasi, Stumpo. Provisions concerning digital therapeutics. Presented on 30 January 2025 [C. 2220 (Girelli et al.) of 30 January 2025] [4].

On 2 July 2025, the Chamber's Social Affairs Committee adopted **as the base text a unified bill** (*Table 1*) [5] integrating proposals C. 1208 (Loizzo), C. 2095 (Quartini), and C. 2220 (Girelli), with the aim of providing comprehensive regulation for DTx within the NHS.

The unified text is currently an adopted base text but is not yet law: it must go through the amendment phase, the final committee review, the debate and vote in the Chamber of Deputies, followed by approval in the Senate, and finally promulgation as law.

The Bill C.1208 (Loizzo et al.) of 7 June 2023 initiated the legislative process in Italy to define the role of DTx within the NHS and to regulate their use and reimbursement. Subsequent bills aimed to redefine critical points, while the unified text collected the three bills, which address in the following points:

- 1. **Definition of DTx**: in the unified text of 2 July 2025, "Digital therapeutics are defined as therapeutic interventions mediated by software, with a specific therapeutic indication, designed to prevent, manage, or treat a medical disorder or disease by modifying patient behaviour to improve clinical outcomes."
- 2. **CE Marking as a Medical Device**: each bill, including the unified text of 2 July 2025, refer to the European regulation requiring CE marking as a medical device for commercialization. Bill C. 2095 (Quartini et al.) of 16 October 2024 specifies that a digital therapeutic must be certified as a medical device by a Notified Body designated by the Ministry of Health, which perform conformity assessments of medical devices according to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017; consequently, Class I low-risk devices are excluded, for which a manufacturer's declaration of conformity is sufficient, with the manufacturer assuming full responsibility and no requirement for external body involvement. This specification is reiterated in Article 1, paragraph 3 of the unified text of 2 July 2025.
- 3. **Fields of Application**: while the bill C. 1208 (Loizzo et al.) of 7 June 2023 defines a list of fields of application, the others and the unified text of 2 July 2025 delegate to the MoH the subsequent drafting of a decree to identify the DTx fields of application.
- DTx Evaluation Committee: each bill agrees on the need for an expert evaluation committee to guide decisionmakers in the inclusion of DTx in the LEA. Bill C. 1208 (Loizzo et al.) of 7 June 2023 proposes the establishment of an ad hoc committee by the MoH, composed of ten appointed members (five by the State-Regions Conference, three by AGENAS, one by the MoH, and one by AIFA), chaired by one of the AGENAS-appointed members. Bill C. 2095 (Quartini et al.) of 16 October 2024 integrates at least five DTx experts (not institutional representatives), including at least two patients, into the Medical Devices section of the Technical Health Committee. Bill C. 2220 (Girelli et al.) of 30 January 2025 combines elements of the previous two proposals, submitting the creation of an ad hoc committee composed of seven DTx experts, including at least two expert patients, and adds the presence of a privacy expert. The unified text of 2 July 2025 defines the establishment of an ad hoc committee by the MoH, chaired by a member from the Department of Planning, Medical Devices and Health Professions with experience in medical devices and DTx, composed of fourteen appointed members: three by the State-Regions Conference, two by AGENAS, two by the MoH, one by the National Institute of Health, one by AIFA, one by the Higher Health Council, one by the National Federation of the Orders of Surgeons and Dentists (FNOMCeO), one by the Federation of the Orders of Italian Pharmacists (FOFI), and two by the most nationally representative patient associations with expertise in DTx. Furthermore, the unified text specifies that the committee members shall not receive any remuneration.
- 5. **Inclusion in the LEAs, with request of clinical evidence:** the unified text adopts the proposal of all three bills regarding the inclusion of DTx in the LEA only if supported by at least two clinical trials supporting high-quality evidence. Bill C. 1208 (Loizzo et al.) of 7 June 2023 designates AGENAS as the body responsible for carrying out the tasks to identify DTx to be included in the LEAs, within a dedicated and accelerated pathway specifically for DTx. Bill C. 2095 (Quartini et al.) of 16 October 2024 specifies that, for the purposes of LEAs inclusion, DTx must undergo a Health Technology Assessment (HTA) conducted by AGENAS.

Some topics, however, were addressed differently or not explicitly mentioned in the different bills, while others were excluded from the unified text of 2 July 2025:

Prescription and dispensing within the NHS: medical prescription and the d dispensing of DTx within the NHS were not specifically addressed in any of the bills. Bill C. 2095 (Quartini et al.) of 16 October 2024 states that the MoH will define, through its own act, the procedures and requirements for the prescription and dispensing of DTx within the NHS (Article 1, paragraph 3). The unified text of 2 July 2025 integrates this provision in Article 1, paragraph 4, stating that the MoH shall define these procedures based on the recommendations of the



Evaluation Committee, whereas bill C. 2095 refers instead to an opinion from the Higher Health Council and the National Institute of Health.

- **Observatory for Digital Therapeutics (DTx)**: the first bill C. 1208 (Loizzo et al.) of 7 June 2023 proposes the establishment of a permanent observatory on DTx, aimed at monitoring scientific and technological developments in the field. This measure was not retained by any of the subsequent proposals, nor by the unified text.
- **DTx Registry**: bill C. 2095 (Quartini et al.) of 16 October 2024 proposes the establishment by the MoH of a dedicated registry for DTx, either available or in clinical development in Italy, within the National Database of Medical Devices. This provision was also not included in the unified text.
- **Financial sustainability**: only bill C. 2220 (Girelli et al.) of 30 January 2025 addresses financial provisions, estimating an annual economic impact of €20 million resulting from the implementation of the law on Dtx.

Position and proposals

This section presents a detailed overview of a selection of positions and proposals publicly available from some of the involved stakeholders.

Position and proposals of SIFO - November 19, 2024 [6]

The Italian Society of Hospital Pharmacy and Pharmaceutical Services of Healthcare Organizations (*Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici delle Aziende Sanitarie*, SIFO) clearly expressed a positive position regarding DTx regulation need in Italy, while also highlighting certain conditions and critical issues that need to be addressed in order to be effectively integrated into the NHS. Below the key points:

- Shared definition of DTx
- Requirements to obtain reimbursement and definition of a reference price
- Digital medical devices (pDMDs) as candidates for fast-track reimbursement
- Methods of prescription and dispensing

SIFO highlighted that, following the experimental initiatives launched during the emergency phase of the COVID-19 pandemic, hospital pharmacists and those operating within Territorial Pharmaceutical Services (SFT) are currently structurally involved in various activities related to the digital transition and telemedicine, as well as in the dispensing of DTx (whether stand-alone or add-on therapies), including:

- remote pharmaceutical counselling to support patients and teleconsultation with prescribers for pharmacological therapies review and reconciliation;
- monitoring of adherence and persistence to treatments, therapeutic outcomes, and tolerability;
- active pharmacovigilance on new drugs and management of adverse events (National Pharmacovigilance Network);
- education and information for patients and caregivers on the correct use of medicines and devices; monitoring
 of medical device safety (device-vigilance);
- HTA and evaluations aimed at public procurement processes.

SIFO expressed its position regarding the bill C. 1208 (Loizzo et al.) of 7 June 2023, suggesting the following amendments/integrations:

- Article 1, paragraph 1: the definition, in addition to improving clinical outcomes, should also include diagnosis and monitoring;
- Article 1, paragraph 2 should be removed or modified to state: "For the definition and description of digital therapeutics, refer to the provisions established and regulated by EU Regulations No. 745/2017 and 746/2017.";
- Article 1, paragraph 4, fields of application: it is recommended to expand the fields to include existing or future areas, because of the fast-evolving nature of these therapies;



- Article 2: specify timelines within which the committee must produce the guidelines for manufacturers and healthcare professionals for inclusion of DTx in the LEAs evaluation process. It is suggested that this deadline be set at 2 months from the establishment of the committee. It is also recommended to add that the committee must provide indications regarding the prescription regime and the distribution channel through pharmacies;
- Article 4, paragraph 3: add details on prescription and distribution channel. Proposed wording: "For the purpose of inclusion in the LEAs, it is necessary that digital therapeutics has been subject to at least two clinical studies with high-quality evidence and consequently subject to prescription by a physician and distributed directly by a pharmacist either in hospital and territorial pharmacies, according to the regulations established by the decree for LEAs inclusion."

Position and proposals of AgID - November 19, 2024 [6]

The Agency for Digital Italy (*Agenzia per l'Italia Digitale*, AgID) highlighted that DTx are part of a broader process of healthcare digitalization and digital infrastructure development. In this context, regulatory framework is needed to recognize and enhance the innovative potential of these therapies. It is essential to:

- regulate interoperability, accessibility, and digital identity: DTx must be integrated into existing healthcare
 information systems, ensuring secure and effective data exchange and full compatibility with current
 infrastructures, according to the connected care model;
- enhance the use of artificial intelligence;
- adopt a structured approach to data management, ensuring high standards of security (cybersecurity) and privacy protection;
- promote support measures for equitable and consistent access across the national territory, reducing the risk of disparities between geographical areas.

AgID proposed including AI and machine learning experts in the evaluation committee for DTx and creating collaborations between the observatory and research institutions specializing in emerging technologies.

Finally, for the inclusion of DTx in the LEAs, it is crucial to have solid scientific evidence that considers not only clinical effectiveness but also the validity and complexity of the algorithms used in the integrated application systems.

Position and proposals of FOFI – January 29, 2025 [7]

The Federation of Italian Pharmacists' Orders (*Federazione degli Ordini dei Farmacisti Italiani*, FOFI) endorsed the proposed law on healthcare digitalization, recognizing it as an important step toward improving the quality and sustainability of the NHS. In this context, FOFI highlighted the growing role of the Italian pharmacist, who is no longer limited to only dispensing medications but is an integral part of a broader network of care for citizens health. Community pharmacies, already digitally equipped, are indeed capable of enhancing their activities and offering new NHS services.

The Federation also highlighted that, unlike other European countries, no reimbursed DTx are yet available in Italy. However, interest in this sector is growing, as demonstrated by the 41 DTx currently under development nationwide, of which 17 are already certified as medical devices, 7 are in clinical trial phases, and others are undergoing CE marking. FOFI therefore believes it is necessary to define an access and reimbursement process as soon as possible, providing for a competent authority that, once the HTA process is completed and marketing authorization is obtained, determines the price and reimbursement scheme for DTx.

FOFI pointed out that in this scenario the pharmacist is a central figure. The trust-based relationship the pharmacist maintains with the community can indeed facilitate patient care, strengthening the role of territorial medicine. Proximity to the community and professional expertise allow the pharmacist to actively participate in education, training, and personalized assistance processes. According to FOFI, considering that DTx will increasingly complement traditional therapies, their distribution should take place under the supervision of the pharmacist, who is able to offer a qualified support. In particular, the pharmacist can ensure continuous training and information for the end users of DTx, as well as technical support during the device onboarding phase. This can help reduce waiting lists in clinics and lighten the workload of general practitioners. Moreover, direct contact with the reference pharmacy represents an opportunity to speed up the activation and renewal of digital clinical pathways, also contributing to better control of healthcare spending.



FOFI also underlined the extensive reach of the Italian pharmacy network – 20,000 pharmacies across the country, equivalent to one pharmacy for every 2,938 inhabitants (compared to one for every 3,237 inhabitants on average in Europe) – and suggested entrusting the distribution of DTx to community pharmacies, both public and private, where pharmacists are adequately trained to take charge of the patient, manage the therapeutic plan, and monitor health progress. For this purpose, it is appropriate to define digital Diagnostic-Therapeutic Care Pathways (PDTA), promote awareness of the Electronic Health Record (*Fascicolo Sanitario Elettronico*), and consider possible scenarios for implementing telemedicine, in order to encourage the adoption of innovative organizational models for the delivery of care and assistance within the NHS.

Finally, FOFI suggested to implement the Electronic Health Record, an essential tool to ensure a link among the various professionals involved in patient care. It is crucial to also allow pharmacists, who are already authorized to consult the Record, access to patients risk data to improve patient management, promote therapeutic adherence, and contribute to continuity of care.

Position and proposals of FNOPI – January 29, 2025 [7]

The National Federation of Orders of Nursing Professions (Federazione Nazionale Ordini Professioni Infermieristiche, FNOPI) highlighted the importance of connected care as a new healthcare model in which the citizen plays a central role in their own care journey. Digital transition is not only a technological evolution, but a new vision of the healthcare system, with nursing professionals as key stakeholders of transformation. FNOPI initiated a study on digital healthcare, identifying critical issues and defining guidelines for proper implementation, with particular focus on the training of healthcare personnel.

DTx fit within the broad context of the digitalization of the healthcare system. From a nursing perspective, for example, DTx could be integrated into care pathways with the aim of actively involving both the patient and the caregiver, promoting the maintenance of autonomy or residual capacities and helping to slow cognitive decline in elderly individuals. DTx therefore have the potential to promote models of care close to the community, strengthen the empowerment of the people being cared for, and offer nurses an innovative and proven effective option for care interventions.

The role of the community nurse is not limited to providing care but is central to responding to emerging new healthcare needs: with a proactive approach to health management and an active engagement in the care pathway of both the patient and the caregiver, he works within a multidisciplinary and integrated framework. In a context where healthcare digitalization is advancing rapidly, there is a growing need to overcome digital fragility, particularly among the elderly. In this area, the community nurse plays a fundamental support role by facilitating access to and use of digital tools for patients and their caregivers, thereby contributing to inclusion and equity in healthcare.

FNOPI supported the initiative of a law on DTx, recognizing their innovative potential for the healthcare system. It is essential to regulate the areas of intervention of DTx by developing an organizational model that ensures the active participation of patients and caregivers, following a co-design approach to care pathways. The development of relational and digital skills must become an integral part of healthcare professionals training programs. At the same time, it is essential to educate citizens as well, so that they are empowered to access and use new digital healthcare solutions consciously and effectively.

Position and proposals of the Ministry of Health – February 5, 2025, regarding bill C. 1208 (Loizzo et al.) [8]

With reference to Article 1, paragraph 2, which states: "Digital therapeutics have a digital active ingredient and digital excipients. The digital active ingredient is the main responsible for the clinical outcome and corresponds to a therapeutic algorithm; the digital excipients, such as virtual assistants, reminder services, and reward systems, are value-added services necessary to ensure the best patient experience and to support long-term use of therapy," the MoH noted that no similar provision exists in the context of either medical devices or pharmaceuticals. Furthermore, it warned that such a definition could prove counterproductive, as it may exclude potential technological developments that are currently unforeseeable. The MoH therefore recommended removing this point.

With reference to Article 1, paragraph 3 – which states that digital medical devices, in order to be commercialized, must obtain the CE marking as software-based medical devices at the European level – the MoH pointed out that while the content is accurate, its wording could lead to misunderstandings because medical device marking regulations are not exclusively European but also regulated by national legislation. The MoH therefore suggested rephrasing the provision as follows: "Digital therapeutics are delivered through the use of medical devices placed on the market in accordance with current law.



Article 2, paragraph 1, establishes a DTx evaluation committee composed of ten members: five appointed by the Regions, three by AGENAS, one by the MoH, and one by AIFA. Paragraph 2 states that the committee shall be chaired by one of the members appointed by AGENAS, while paragraph 3 that the committee plays a key role, as it provides preliminary and guiding recommendations on DTx in order to their inclusion in the fast evaluation process for integration into the LEAs. The MoH considered the provisions difficult to reconcile with the following principles: DTx involve the use of medical devices; the competent authority for medical devices is the MoH. The MoH therefore proposed to revise the provision to establish that the committee, still composed of ten members, should include four members appointed by the MoH, three by AGENAS, two by the Regions, and one by AIFA. Moreover, the committee should be chaired by the MoH. Specifically, considering that the bill addresses aspects not only related to the regulatory framework for medical devices, but also concerning the LEA, the committee should be chaired by the Head of the Department for the Planning of Medical Devices and Health Professions, where the management of the LEA Committee is also based.

Article 3, paragraph 1, states that within one month from the date the law enters into force, AGENAS shall establish a permanent observatory on DTx to promptly monitor the scientific and technological developments of these therapies. The MoH suggested establishing the observatory directly through this provision, without deferring it to a subsequent law, in order to reduce timing, by reformulating it as follows: "A permanent observatory on digital therapeutics is established within AGENAS, which provides technical support and secretarial functions, in order to promptly monitor the scientific and technological developments of these therapies."

The MoH also suggested specifying the composition of the observatory and adding a paragraph 3 with the following text: "The observatory referred to in paragraph 1 shall be composed of 15 appointed members: five appointed by the MoH, including one designated as coordinator and one selected from experts in clinical engineering, four appointed by AGENAS, three by AIFA, and three by the Permanent Conference for Relations between the State, the Regions, and the Autonomous Provinces of Trento and Bolzano."

Article 4 outlines that AGENAS shall carry out the tasks within its competence for the identification of DTx to be included in the LEAs, as part of a dedicated and accelerated process for these therapies. It further states that the identified DTx shall be included in the LEAs update process, to be carried out in accordance with the current legislation, and that, for the inclusion in the LEAs, the DTx must be supported by at least two clinical trials supporting high-quality evidence. According to the MoH, this article impacts the responsibilities of the General Directorate for Health Planning of the MoH, and it therefore suggested amending paragraph 1 as follows: "The Ministry of Health, in consultation with AGENAS, shall identify the digital therapeutics that, in accordance with current legislation, may be included in the LEAs."

Position and proposals of Mario Negri Institute for Pharmacological Research IRCCS – February 5, 2025 [8]

The Mario Negri Institute for Pharmacological Research IRCCS addressed the issue of control groups in clinical trials on DTx, arguing that the appropriate comparator is the best available treatment for the specific condition, not a placebo or ineffective intervention. It was pointed out that this specification is missing from the draft laws; although HTA is mentioned, it is based on the evaluation of existing evidence and does not define which control groups should be used.

Position and proposals of FNOMCeO – February 5, 2025 [8]

The National Federation of the Orders of Surgeons and Dentists (Federazione Nazionale degli Ordini dei Medici Chirurghi e degli Odontoiatri, FNOMCeO) highlighted the risk of inequalities and regional fragmentation in the use of DTx if they are regulated only as medical devices. It considered the adoption of a single national approval and reimbursement pathway for DTx to be essential in ensuring equitable access across the country.

Regarding bill C. 1208 (Loizzo et al.), the Federation proposed expanding the fields of application and including a representative appointed by FNOMCeO in the DTx Evaluation Committee.

FNOMCeO also underscored the importance of Article 1, Paragraph 3, of bill C. 2095 (Quartini et al.), which assigns the MoH the responsibility of defining, through a dedicated decree, the procedures and requirements for the prescription, dispensing, and clinical trials of DTx within the NHS.

The Federation called for scientific evidence to be based on randomized clinical trials able to compare the DTx both with the best available therapeutic options and with the absence of treatment. It is equally crucial to ensure dedicated resources to support the reimbursement of DTx.

Finally, FNOMCeO highlighted the need for specific training on DTx for healthcare professionals. This training should address aspects such as efficacy, safety, critical issues related to their use, clinical validation methodology, therapeutic indications, the role of the patient, ethical implications, and data management. FNOMCeO expressed its willingness to



support this educational effort, also through its own platform, by engaging approximately 490,000 physicians and dentists, with the aim of training a new generation of professionals capable of managing and leveraging the opportunities offered by digital healthcare.

Position and proposals of AGENAS – February 12, 2025 [9]

Under the National HTA Programme for Medical Devices – established by Legislative Decrees No. 137, Article 22, and No. 138, Article 18 of 5 August 2022 (Official Gazette No. 214 of 13/09/2022), and adopted for the 2023-2025 period by the Minister of Health's Decree of 9 June 2023 (Official Gazette No. 207 of 05/09/2023), currently being renewed for the 2026-2028 period [10] – AGENAS plays a central and operational role in the inclusion of medical devices within the LEAs. As defined by the programme, the manufacturing companies submit the HTA evaluation requests to AGENAS through the "Digital Technologies Reporting Form" ("scheda per la segnalazione delle tecnologie digitali"). The Digital Technology is then added into a register, prioritised by a steering committee, and then forwarded for HTA evaluation, which is conducted by AGENAS in collaboration with a network of external stakeholders and the regional network. If the evaluation confirms the medical device validity, and scientific evidence on real-world effectiveness is collected concurrently, it may then proceed to assessment by the LEAs Committee and the Regional Tariffs Committee. As of February 2025, two DTx submissions had been received by AGENAS. Within this operational framework, AGENAS proposed to consider the following aspects in the context of drafting a specific law on DTx:

- Fast track: a fast process encompassing all stages, including reimbursement (following the models of Germany and France);
- Defined timelines: clear timeframes for evaluation and market access;
- PNHTA-MD: integration with the existing National HTA Programme for Medical Devices;
- Tariffs: establishment of a simplified process for tariff definition.

Position and proposals of AIFA – February 19, 2025 [11]

AIFA recognized the value of DTx as therapies able to offer numerous benefits, including improvement of access to care, especially for patients in remote and underserved areas, personalization of treatments based on real-time data collection, and long-term healthcare cost reductions through prevention and effective management of chronic diseases. At the same time, AIFA also highlighted the many challenges that need to be addressed:

- a clear and consistent regulatory framework is essential to allow the reimbursement of DTx by the NHS or private health insurers, and to ensure equitable access across the country;
- Regulation (EU) 2017/745 on medical devices does not contain specific provisions for DTx; it is therefore necessary to develop tailored guidelines that consider the unique features of DTx, such as rapid technological evolution, potential vulnerabilities in data protection, and cybersecurity risks;
- it is important to clearly define risk classes for DTx, to ensure their evaluation and approval based on safety and effectiveness;
- the evaluation and approval of DTx must be based on data relating to safety, efficacy, quality, and data protection, prior to their placement on the market;
- physicians and other healthcare professionals must be adequately trained in the use of DTx, and patients must be made aware of their benefits and proper use;
- ensuring cybersecurity and the protection of patients sensitive data is essential the relevant laws in this area include the General Data Protection Regulation (GDPR) and the cybersecurity guidelines for medical devices.

AIFA expressed the willingness to provide support by issuing scientific opinions, where appropriate, on the efficacy and safety of DTx, and is initiating a process for their integration, with particular focus on reimbursement and equitable access for patients.



Proposal of Digital Health Policy Lab

The unified text of 2 July 2025, resulting from bills C. 1208 (Loizzo et al.) of 7 June 2023, C. 2095 (Quartini et al.) of 16 October 2024, and C. 2220 (Girelli et al.) of 30 January 2025, as currently defined, includes several challenge points:

- a potential regulatory burden that could slow down an actual application, the reliance on implementing decrees from the MoH, and the potentially symbolic inclusion of "expert patients" in the evaluation committee;
- integration with the European MDR and existing national laws may lead to coordination challenges;
- absence of provisions regarding prescription and dispensing within the NHS, as well as related to financial coverage;
- need to define how to reimburse the DTx during the transitional period before inclusion in the LEAs;
- ensure equitable access for all patients, regardless of their geographic location, socioeconomic status, or other potential barriers;
- clear criteria should be established for the selection of clinical studies to be considered for inclusion in the LEAs;
- clear evaluation timelines should be introduced.

The Digital Health Policy Lab proposes to:

- introduce specific instructions regarding prescription and dispensing within the NHS:
 prescription by General Practitioners (GPs) or by hospital or outpatient specialists, depending on the target pathology, and dispensing by hospital or community pharmacists;
- provide specific training programs for medical doctors and pharmacists to ensure a standardised prescription and dispensing – in term of activation through specific codes, delivery criteria, and firstlevel patient support for technical use – along with continuous education aligned with the system ongoing evolution;
- define an access process with price evaluation for the transitional period waiting for inclusion in the LEAs;
- dedicate a national fund for DTx, divided among the regions, with an evaluation for access to the fund by AGENAS, through the National HTA Program for Medical Devices. The allocation of the national fund should be guided by value-based criteria, prioritizing DTx with proven clinical and economic value, and enabling outcome-based reimbursement models;
- create a regional coordination within the Permanent Conference for Relations between the State, the Regions, and the Autonomous Provinces ("Conferenza Stato-Regioni"), with the aim to ensure equal access;
- delegate to the Digital Therapies Evaluation Committee the task of creating guidelines with details on the target pathologies of DTx for which reimbursement should be allowed, on the HTA evaluation methodology, on the criteria for evaluating clinical evidence, and on the evaluation timelines;
- revise the criterion related to the number of clinical trials conducted on DTx for their inclusion in the LEAs; in particular, it is proposed that DTx should be supported by at least one clinical trial conducted prior to obtaining CE marking, and one Real World Evidence (RWE) study conducted thereafter.
- include a structured economic evaluation framework within the HTA process, ensuring that costeffectiveness, budget impact, and long-term sustainability analyses are systematically performed to support reimbursement and prioritization decisions;
- establish a continuous monitoring system for reimbursed DTx, linking real-world effectiveness and
 economic outcomes to pricing and reimbursement adjustments, in line with value-based healthcare
 principles. Payments should be tied to predefined clinical outcomes, verified after a set period (e.g., 6–
 12 months), through secure and GDPR-compliant data tracking.



Table 1: Unified text of 2 July 2025 - Provisions concerning digital therapeutics (full original text)

Mercoledì 2 luglio 2025 - Commissione XII

ALLEGATO 3

Disposizioni in materia di terapie digitali. C. 1208 Loizzo, C. 2095 Quartini e C. 2220 Girelli.

TESTO UNIFICATO ELABORATO DAL COMITATO RISTRETTO, ADOTTATO COME TESTO BASE DALLA COMMISSIONE

Art. 1.

(Definizione di terapie digitali)

- 1. Per terapie digitali si intendono gli interventi terapeutici mediati da software, con una specifica indicazione terapeutica e progettati per prevenire, gestire o trattare un disturbo medico o una malattia, modificando il comportamento del paziente al fine di migliorarne gli esiti clinici.
- 2. Le terapie digitali sono costituite da un principio attivo digitale e da eccipienti digitali. Il principio attivo digitale è il principale responsabile del risultato clinico ed è riconducibile a un algoritmo terapeutico; gli eccipienti digitali sono servizi a valore aggiunto necessari per garantire la migliore esperienza del paziente e per consentire un uso a lungo termine della terapia.
- 3. I dispositivi medici digitali, ai fini dell'immissione in commercio, sono dotati di marcatura CE come dispositivi medici a base di software a livello europeo, con destinazione d'uso terapeutica e certificazione da parte di un organismo notificato designato dal Ministero della salute e idoneo a svolgere l'attività di valutazione della conformità dei dispositivi medici ai requisiti del regolamento (UE) 2017/745 del Parlamento europeo e del Consiglio, del 5 aprile 2017.
- 4. Con decreto del Ministro della salute, sulla base delle indicazioni fornite dal Comitato di cui all'articolo 2, sono individuati gli ambiti di intervento e le aree specialistiche in cui si applicano le terapie digitali, nonché le modalità e i requisiti per l'erogazione e la prescrivibilità nell'ambito del Servizio sanitario nazionale.

Art. 2.

(Comitato di valutazione delle terapie digitali)

- 1. Entro un mese dalla data di entrata in vigore della presente legge, presso il Ministero della salute è istituito il Comitato di valutazione delle terapie digitali, presieduto da un componente con comprovata esperienza in materia di dispositivi e terapie digitali del Dipartimento della programmazione, dei dispositivi medici e delle professioni sanitarie. Il Comitato è composto da quattordici membri nominati:
 - a) tre, dalla Conferenza permanente per i rapporti tra lo Stato, le regioni e le province autonome di Trento e di Bolzano;
 - b) due, dall'Agenzia nazionale per i servizi sanitari regionali;
 - c) due, dal Ministero della salute;
 - d) uno, dall'Istituto superiore di sanità;
 - e) uno, dall'Agenzia italiana del farmaco;
 - f) uno, dal Consiglio superiore di sanità;
 - g) uno, dalla Federazione nazionale degli Ordini dei medici chirurghi e degli odontoiatri;
 - h) uno, dalla Federazione degli Ordini dei farmacisti italiani;
 - *i)* due, dalle associazioni di pazienti più rappresentative in ambito nazionale, competenti in materia di terapie digitali.
- 2. Il Comitato di valutazione di cui al comma 1 fornisce indicazioni preliminari e orientative sulle terapie digitali, al fine della loro immissione nel percorso di valutazione rapida per l'inserimento nei livelli essenziali di assistenza (LEA).
- 3. Sulla base dell'attività del Comitato, il Ministro della salute presenta alle Camere un rapporto annuale sull'evoluzione delle terapie digitali e sulla disponibilità delle nuove tecnologie.



4. Ai componenti del Comitato non spettano compensi, gettoni di presenza, rimborsi di spese o altri emolumenti comunque denominati.

Art. 3.

(Inserimento delle terapie digitali nei livelli essenziali di assistenza)

- 1. Con la procedura di cui all'articolo 1, comma 554, della legge 28 dicembre 2015, n. 208, nell'ambito del primo aggiornamento utile dei LEA di cui al citato decreto del Presidente del Consiglio dei ministri 12 gennaio 2017 sono effettuate le necessarie valutazioni ai fini dell'inserimento, nel nomenclatore tariffario, delle terapie digitali che presentano i requisiti di cui al comma 2 del presente articolo.
- 2. Ai fini del suo inserimento nei LEA, è necessario che una terapia digitale sia stata oggetto di almeno due studi clinici con evidenze di alta qualità.



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2. CLINICAL PRACTICE APPLICATIONS AND INNOVATIVE TRENDS

2.1. DTx AND ARTIFICIAL INTELLIGENCE APPLICATION IN NEURODEVELOPMENTAL DISORDERS

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Introduction: neurodevelopmental disorders and developmental patterns

Neurodevelopmental disorders – including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders (SLD), intellectual disabilities, fluency disorders, learning disorders, and movement and coordination disorders – generally emerge during childhood development and can affect core aspects such as social interaction, communication, behavior, and learning [1]. The individual developmental trajectory, defined as the evolutionary path a child follows over time, is influenced by neurobiological, genetic, environmental, and therapeutic factors [2]. Early and targeted intervention can positively influence these trajectories, improving cognitive, adaptive, and social outcomes [3]. Over the past few years, the adoption of digital technologies and artificial intelligence (AI) opened new avenues for increasingly personalized management of neurodevelopmental disorders. Digital Therapeutics (DTx) – clinically validated interventions delivered through digital platforms – hold the potential to expand access to treatments, support personalization, enhance therapy effectiveness, and continuously monitor progress [4].

DTx role in the neurodevelopmental disorders management

Accessibility, personalisation, and continuity

DTx can be delivered anytime and anywhere, overcoming geographic or logistical barriers (e.g., rural areas with limited access to specialized services). For instance, rehabilitation services are often located far from where individuals with disabilities live [5]. As previously mentioned, DTx also enable personalization: in many cases, Al algorithms analyse behavioral data to adapt content and difficulty in real time [6]. Furthermore, therapeutic continuity – an essential element for achieving sustained outcomes over time – is supported through reminders, gamification, progress tracking, and automated feedback, thereby enhancing engagement and adherence [7].

Evidence-based: DTx clinical effectiveness

DTx must be grounded in robust clinical evidence in order to not to be merely considered educational or recreational tools [8]. This issue continues to be widely debated in the literature, where it is often emphasized that the evidence-informed is not sufficient, but an evidence-based approach is required. The literature also highlights the need for a more rigorous and inclusive approach, including in terms of prescribing practices [9].

Examining the clinical landscape of digital therapies, Phan et al. summarize FDA-approved products and their clinical applications, analyzing over 300 ongoing clinical trials and discussing the challenges of clinical translation as well as strategies to overcome them [10]. The studies primarily focus on mental and behavioral disorders, neurological disorders, and endocrine, nutritional, and metabolic conditions (e.g., the management of chronic diseases). Despite the growth and proliferation of DTx, the authors highlights that study design and execution remain inconsistent, even though randomized controlled trials (RCTs) constitute most of them. Clearly distinguishing DTx from other health and wellness apps and standardizing regulatory processes at the global level therefore remain the major challenges. Ongoing debate on the optimal integration of digital technologies and the implementation of effective healthcare strategies is essential for progress [11].



Continuous monitoring and data-driven insights

Digital platforms collect longitudinal data (e.g., response times, errors, engagement) that are visible to clinicians and enable timely interventions in cases of plateaus or regressions. These data support predictive analyses and the early identification of emerging needs [12]. Operating though software on devices such as smartphones, PCs, or wearable devices, DTx continuously collect large amounts of real-world data (RWD) in real time. These data concern patient adherence, behavioral status, reported outcomes, and, in some cases, physiological variables.

The continuous data collection, combined with artificial intelligence (AI) and machine learning (ML) algorithms, allows the analysis of information to generate individualized and personalized models, enabling the therapeutic intervention to be adapted dynamically and continuously, thereby maximizing effectiveness. Targeted reminders sent to specialists can provide additional feedback to further optimize care. The ability to deliver adaptive therapy and support clinical decision-making with objective, up-to-date evidence is fundamental to the evolution of the "software as medicine" concept and to demonstrating the health-economic value of DTx [13].

Limitations and challenges of DTx and Artificial Intelligence

Scientific validation and standardisation

As mentioned, many emerging DTx are evaluated in studies with small sample sizes or limited replicability. A key limitation is the lack of large-scale multicentre studies or randomized controlled trials (RCTs) [14]. Clinical testing for DTx is complex and costly, and it is difficult to obtain robust evidence regarding the efficacy and safety of these digital therapies because of the absence of standardized trial methodologies. Furthermore, the use of artificial intelligence does not necessarily address these challenges. While advanced algorithms such as machine learning can analyse a huge amount of data to identify patterns, associations, and correlations, their practical application—particularly in the medical field—still requires further research and scientific development. Prediction errors or misinterpretation by an algorithm could pose significant risks to patient health [15].

Digital device and inequalities

Access to DTx requires the availability of devices (tablets, smartphones), internet connectivity, and the family digital literacy. This can exclude socio-economically disadvantaged groups, thereby exacerbating inequalities [16]. Moreover, certain categories of users may be excluded or may self-exclude due to prejudice and stereotypes. A paradigmatic and harmful bias that widens the generational digital divide is ageism, where discrimination, prejudice, or marginalization of individuals is based solely on their age, affecting both young and older people. A common stereotype, for instance, is that older adults are not able to use digital devices [17]. Furthermore, the literature also highlights the responsibility of developers and those involved in social networks, security systems, and smartphones, since older adults are often excluded due to unacknowledged biases within innovation teams and design practices, resulting in more or less overt ageism embedded in digital platforms [18].

Technology dependence and the balance between human and digital

Digital interaction, although effective, cannot replace the human component of therapy, which is essential in relational contexts such as autism spectrum disorder or attention-deficit/hyperactivity disorder. The literature consistently stresses the need to maintain a balance between technological tools and the therapist–patient relationship [19] [20].

Privacy, data security, and algorithmic transparency

In this context, the collection of sensitive data – Including behavioural and biometric indicators, among others – requires high standards of security and full compliance with the GDPR (General Data Protection Regulation) and all applicable laws and regulations. Furthermore, AI systems must be transparent: clinicians should be able to understand the underlying decision-making processes [21]. Algorithmic transparency, a key concept not only from a legal but also from an ethical point of view, is essential for establishing accountability in the event of error. It supports the individual and/or patient right to information, a prerequisite for accept informed consent regarding the AI use [22].



Ethics of digital solutions and AI in neurodevelopmental disorders

Centrality of the child and informed consent

Since the primary users are children, it is crucial to protect their autonomy and ensure their safety. Parents, caregivers, or legal representatives must receive clear information on the risks and benefits, data management, and duration of the intervention, and consent must be specific, informed, and revocable [23].

Healthcare systems and regulations (such as the GDPR in Europe) recognise minors as vulnerable individuals, making it challenging to balance their decisional capacity with the need for parental protection. Moreover, the study by Cavazos-Rehg highlights that requiring parental consent can sometimes limit adolescents access to mental health apps, due to concerns about privacy and the perceived lack of parental understanding regarding app usage, as well as the handling of personal and health-related data [24].

Autonomy and algorithmic bias

There is a substantial agreement in the referenced literature that AI should support autonomy, not replace it, and that clinical decisions must remain mediated by the human operator. The risk of algorithmic bias, in fact, could lead to choices that are not informed, accurate, or effective; for example, models trained on non-representative data (such as data derived from limited demographic groups). This can generate inequalities in outcomes or exclusions [25].

Equity and universal accessibility

Healthcare policies must promote equity in access to DTx, protecting families with fewer resources, those in rural areas, or from diverse backgrounds [26]. The lack of interoperability among different platforms and technologies represents another significant barrier. DTx should be able to communicate with other healthcare systems, such as electronic health records, medical devices, and remote monitoring systems. The integration of these technologies requires common technical standards, which are not yet fully developed, thereby limiting the overall effectiveness of digital solutions.

Human supervision and responsibility

The introduction of AI does not exempt professional operators from responsibility: they must monitor, evaluate, and correct any errors or inappropriate behaviours of digital platforms [27]. The integration of DTx into the care pathway thus raises important ethical, clinical, and legal considerations regarding human supervision and accountability. The clinician central role in the use of DTx is indispensable and goes beyond mere prescription. Human supervision is necessary and, to date, essential – as included in the definition of "Digital Therapeutic". For example, delivering a "digital active ingredient" based on referenced clinical evidence, ensuring digital literacy among users, and providing continuous feedback on warning signals (e.g., symptom worsening or incorrect use) are all necessary elements to enable timely interventions and preserve the principle of non-maleficence in treatment" [28].

Conclusion

Al-based digital solutions, particularly Digital Therapeutics, represent a promising frontier for the personalized, accessible, and data-driven management of neurodevelopmental disorders. However, their success depends on robust scientific validation, equitable access, ethical safeguards, and sensitive integration with the human clinical experience.



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2.2. DTx APPLICATION IN MENTAL HEALTH

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"The mind is its own place, and in itself can make a heaven of hell, a hell of heaven." — **John Milton, Paradise Lost**

This well-known statement from Paradise Lost provides a fitting epigraph for this chapter, which explores the intersection between Digital Therapeutics (DTx) and mental health. Mental health represents a fundamental dimension of human well-being, yet it remains one of the most persistent and complex challenges across societies and historical epochs. Mental disorders have always been present; however, their **prevalence and visibility** have increased substantially over the past century. Processes such as urbanization, globalization, economic instability, social isolation, and the accelerated pace of modern life have collectively contributed to rising levels of stress, anxiety, depression, and other psychological conditions.

In recent decades, global crises – including armed conflicts, pandemics, and environmental degradation – have further intensified psychological distress worldwide. Despite growing public awareness, **stigma and limited access to high-quality care** continue to impede effective treatment for many individuals. Consequently, a global mental health crisis has emerged that profoundly affects not only individuals but also families, workplaces, and societies, constituting one of the most urgent public health challenges of the contemporary era.

Digital Therapeutics and Mental Health

The growing integration of digital therapeutics (DTx) into healthcare systems represents a significant step toward a more **patient-centered and accessible approach** to mental health care. In the context of mental health, have been developed different DTx since this is an area where it has been proved that there is an added value by providing accessible, personalized, and scalable support for individuals dealing with conditions like depression, anxiety, insomnia, and substance use disorders. DTx enable continuous monitoring, real-time feedback, and adaptive care – helping bridge gaps in access to mental health services while improving patient engagement and outcomes. In addition, digital therapeutics offer a promising solution to several long-standing challenges, including limited access to care, high treatment costs, and the stigma associated with seeking psychological support. Many individuals who experience mental health difficulties face barriers such as long wait times for appointments, geographic isolation, or discomfort with face-to-face therapy.

Digital platforms help bridge these gaps by delivering therapeutic interventions through smartphones, computers, or wearable devices. These platforms can provide real-time monitoring, guided exercises, and personalized feedback, enabling users to receive support anytime and anywhere. Moreover, **DTx allow for continuous and data-driven care**. Through sensors, app usage data, and patient feedback, healthcare providers can monitor progress and adjust treatment plans dynamically. This real-time feedback loop enhances personalization and helps ensure that interventions remain effective over time. Integration with wearable technologies and artificial intelligence further extends these capabilities, offering predictive insights into patient behaviour and potential relapse risks. **One of the key advantages of digital therapeutics in mental health is their ability to offer evidence-based treatments in scalable and cost-effective ways.**

In the field of mental and chronic diseases there are several clinical trials ongoing on DTx making the mental illness the field where have been conducted the most clinical trials in the world over the past five years [1]. In this specific field there are products already available in EU and new DTx are being actively developed for mental disorders such as depression and anxiety disorder, post-traumatic stress disorder, schizophrenia, dementia, and attention-deficit/hyperactivity disorder. There are about 20,000 mental health management applications developed so far [1]. In a recent meta-analysis has been reviews the effectiveness of more than twenty mental health applications suggesting that using applications to relieve symptoms and self-manage illness effectively reduced depressive symptoms [2] When the application was combined with face-to-face or internet-based therapy, the effect was even greater [3].



Evidence Base and Clinical Research

A defining feature of DTx in mental health care is their grounding in **evidence-based therapeutic frameworks**, particularly cognitive behavioural therapy (CBT) and related modalities. The mental health sector currently accounts for the **largest proportion of DTx clinical trials worldwide** over the past five years. In the European Union, several DTx are already approved for use, with ongoing research expanding to conditions such as depression, anxiety disorders, post-traumatic stress disorder (PTSD), schizophrenia, dementia, and attention-deficit/hyperactivity disorder (ADHD). To date, approximately **20,000 mental health management applications** have been developed globally [1].

A recent meta-analysis reviewing over twenty digital mental health applications demonstrated that these interventions significantly reduced depressive symptoms [2]. When used in conjunction with face-to-face or internet-based therapy, the therapeutic effects were further amplified [3].

The space and also the purpose of this chapter is not to review all the DTx available but through some examples explain the frame of application. An important issue is that in this area of application, more than in others, there are contraindications and there is a defined clinical frame in which they can be used.

Case Study: edupression.com®

To pin down these concepts, it is necessary to analyse a DTx used in this context such as the DiGA edupression.com[®]. It is registered in Germany and consists of a medical device system, edupression.com[®] system, with the medical devices edupression.com[®] psychoeducation and edupression.com[®] mood chart. The system is a web-based software that can be accessed using a common browser with an Internet connection (Software-as-a-Service). In the indications it is clearly stated that it can be used in mild depressive episodes, Moderate depressive episodes; Recurrent depressive disorders, present mild episodes, Recurrent depressive disorders, present moderate episodes and its use is suggested in adult (18-65 years).

The application guides patients through the program giving also daily multimedia information and exercises from psychoeducation for self-help. It also contains elements of computer-based cognitive behavioural therapy. The set-up allows patients to set the so-called weekly goals, for which in-depth information and recommendations are displayed during the week. Patients are reminded daily to fill out the mood chart in the form of a short survey with yes/no questions and thus record their mood.

To make the application friendly, Eddy, the therapy avatar, visually accompanies patients on their way in the application. In videos, patients get to know Alice, who suffers from depression, and go through the path to recovery with her. For each chapter there are booklets in portable data format (pdf) for download for reading. Through playful elements, patients are encouraged and "rewarded" (activity points, badges, certificates, sum of time in the program, etc. as gamification) to continue following the health application. This application helps people providing therapy-relevant information (e.g. therapeutic methods, mechanisms of action, opportunities and risks), compensatory competencies in the case of specific, problem-related deficits (e.g. social skills), as well as supporting patients in the development of general self-management and coping skills. This typically also includes elements from cognitive behavioural therapy. In order to ensure the safety of the patients, technical safety precautions are in place: in the case of suicidal thoughts, a warning is sent with a request to seek help. Particularly relevant is the mood chart that gives to patients feedback in form of a graphical representation of their symptoms allowing them to immediately recognize changes in their mood. More important, patients can make an intangible illness visible and tangible for themselves and their social environment.

This DTx is accompanied by a clinical study that is worth to discuss briefly to give to then reader an idea of the quality of the evidence required. Briefly, the study involved patients between the ages of 18 and 65 who had a mild or moderate depressive episode of unipolar depressive disorder at the time of the aptitude interview [4]. The intervention group (IG) received access to standard care and the DiGA edupression.com® and the control group (KG) received access to standard care and an active control condition (mood chart as well as content and exercises without proven influence on depressive symptoms), which corresponded to a sham treatment. The analysis showed a statistically significant and relevant advantage of the IG over the KG in terms of health literacy measured by the D-Lit (adjusted difference to 12 weeks: 0.8; 95% CI: 0.2 - 1.4; p-value: p = 0.016; β-norm: 0.19). With regard to the health-related quality of life measured by WHOQOL-BREF, demonstrate significant effects in the IG compared to the KG. In the two domains of social relationships and environment, on the other hand, there were no effects from the use of the DiGA. With regard to disease perception measured by B-IPQ, small and significant effects were found in the IG compared to the KG. Furthermore, the study was able to demonstrate a statistically significant correlation between usage behaviour and



reduction of depression severity or improvement in depression literacy over the entire study period for the intervention group.

It is important to stress that this **DTx has contraindications e.g it cannot be used** in Schizotypal disorder, Persistent delusional disorder, Bipolar affective disorder, Major depressive episode with psychotic symptoms, recurrent depressive disorder, present severe episode with psychotic symptoms. In addition, **an absolute contraindication** is given in the presence of illnesses that require another form of psychoeducation or treatment or for which the mood diagram developed by edupression.com® is not suitable. For example, the use of edupression.com® is **not indicated in the presence of suicidal thoughts or bipolar disorder or psychotic symptoms in the context of schizophrenia**. This also applies to depressive patients who, for various reasons, are unable to follow the online offer of psychoeducation (e.g. intellectual disability, alcohol, drug intoxication, visual impairment, etc.). Another contraindication that is valid also for other DTx of this class is the **non-suitability for patients who cannot use a digital device** such as a computer/tablet/smartphone or **do not have the necessary language skills**, which may apply to **some geriatric patient groups or patients with a mother tongue that does not exist in the language offered by this DTx or who have a lack of foreign language skills.**

Case Study: somnio® (DTx for Insomnia)

Somnio is a digital application for the treatment of problems falling asleep and staying asleep. In the application, evidence-based and guideline-compliant content from the field of cognitive behavioural therapy for insomnia (CBT-I) is taught. Users learn, for example, how to optimize their sleep times, follow an individually coordinated sleep-wake rhythm, deal with thoughts, or use relaxation techniques to bring themselves into a sleep-promoting state. The efficacy of somnio was investigated in a randomized controlled trial. Patients who used somnio showed a significant reduction in insomnia symptoms compared to a control group. Somnio can be accessed directly from the browser as a web application and is available as an app for smartphones and tablets with the iOS and Android operating system. Also, in this case there was a randomized trial that was necessary to register the DTx [5]. The effectiveness of the digital sleep training somnio was tested in a randomized controlled trial where 56 insomnia patients were randomly assigned to either the intervention group (use of somnio) or the waiting list control group. The primary outcome to measure the effects was the Insomnia Severity Index (ISI). Furthermore, depression and anxiety symptoms as well as sleep-related cognitions, safety behaviour and somatization were recorded. Data collection took place before and after the 6-week treatment period/waiting period and 12 months after completion of treatment. In the intervention group, a sleep diary was also used during the treatment phase to record central parameters of sleep continuity, sleep quality and daytime well-being daily. There was a significant change in the insomnia severity index (ISI). After treatment with somnio, 56% of participants in the treatment group had achieved remission, compared to 11% in the control group indicating a large treatment effect in the intervention group compared to the control group. Furthermore, depression symptoms, sleeprelated cognitions, safety behaviour and somatization decreased all significantly in the treatment group compared to the control group. All parameters of the sleep diary showed significant improvements within the treatment group. The treatment effect could still be demonstrated after 12 months [5].

Regulatory and Ethical Considerations

As stated above there are several DTx registered worldwide. At the present stage the majority of DTx in EU are registered in Germany [6]. One important consideration for this field of application is that the widespread and increasing adoption of digital therapeutics in mental health also raises important ethical considerations. Indeed, it is necessary to ensure patient privacy, maintaining data security, and addressing the digital literacy disparities are critical to building trust and inclusivity. In addition, it is necessary to continue the research and reinforce the regulatory oversight to validate new interventions and ensure that they meet rigorous clinical standards.

Conclusion

Digital therapeutics are reshaping the landscape of mental health care by extending access to **evidence-based**, **scalable**, **and patient-cantered interventions**. As technological innovation continues, DTx hold significant promise to complement traditional psychotherapy, reduce barriers to care, and empower individuals to take an active role in managing their mental health. The responsible integration of DTx into mainstream healthcare thus represents a **critical milestone toward an equitable**, **data-driven**, **and responsive mental health ecosystem** for the future.



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2.3. PHARMACOLOGICAL THERAPY AND DHTS COMBINATION

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Digital Health Technologies (DHTs) can be used either as standalone interventions or in combination with pharmacological therapies to enhance treatment effectiveness, patient engagement, and disease management.

The combined use is not an alternative, but rather a true synergy that can be achieved through different approaches, depending on the disease and the therapeutic objective:

- 1. Add-on Therapy: The DHT is used in combination with an ongoing pharmacological treatment to enhance its overall effectiveness. For example, a digital Cognitive Behavioural Therapy (CBT) app can support drug treatment for depression, anxiety, or insomnia by addressing the behavioural and cognitive components of the disorder.
- **2.** Optimization of Therapeutic Adherence: DHTs act as "digital excipients" to the pharmacological therapy, supporting patients with medication and DHTs reminders, while facilitating the management of clinical diaries. This significantly improves the consistency and accuracy with which patients follow their treatment plan.
- **3.** Monitoring and Personalization: DHTs allow real-time monitoring of vital parameters (e.g., blood glucose in diabetes, through integration with sensors) or symptoms. This data enables the physician to personalize drug dosage or intervene promptly, thereby optimizing pharmacological therapy. This combination is mainly promising in chronic diseases and mental disorders, where behavioural, cognitive, and adherence factors are crucial:
 - **Type 1 and Type 2 Diabetes:** DHTs that analyse glycemic trends and suggest dietary or physical activity adjustments, supporting insulin or oral therapy.
 - **Anxiety and Depression Disorders:** apps based on digital CBT, in combination with antidepressant or anxiolytic medications.
 - Addictions: DHTs for craving management and psychological support, in combination with pharmacological treatments for addiction cessation.
- **4.** Combined Pharmacological-Digital Therapy: in some cases, the DHT is developed and clinically studied together with a specific drug. The efficacy results refer exclusively to that combination. An example from the United States is the use of a DHT for the treatment of substance use disorders in combination with pharmacological therapy or as part of a broader treatment program.

In Italy, the regulatory framework for DHTs reimbursement is still evolving. In contrast, both the United States and Germany (DiGA) already have specific, authorised DHTs that are used in combination with pharmacological treatments. The key concept is that these DHTs are prescribed as "digital medicines," with clinical trials demonstrating their efficacy either as an add-on or in combination with standard therapies. The *Table 1* lists selected examples.



Table 1: Examples of DHTs used in combination with pharmacological treatments

Therapeutic Area	DHT/platform	Type of combination	Application details		
Opioid/substance addiction	reSET-O® (Pear Therapeutics - USA)	Add-on	Prescribed in combination with pharmacological treatment (e.g. buprenorphine, methadone) to enhance abstinence. It is a contingency management—based Cognitive Behavioural Therapy (CBT).		
Substance addiction	reSET® (Pear Therapeutics - USA)	Add-on	For the treatment of alcohol, cocaine, marijuana, and stimulant substances use. Used in combination with outpatient care and clinical monitoring.		
Major depression	DTx for depression (e.g. in development phase)	Add-on/Replacement	Delivery of a digital form of Cognitive Behavioural Therapy (CBT), in which the DTx are designed to be used either as an add-on to pharmacological treatment (antidepressants) or as a replacement.		
Atopic Dermatitis (Eczema)	Sidekick Health (in collaboration with Pfizer)	Support and Management	Solutions that help patients to manage their condition and adherence, often in combination with topical or systemic medications.		
Digital Diabetes (General) Management Platforms		Monitoring and Optimisation	Many validated platforms integrate data from glucometers or sensors to help patients personalize diet and physical activity, supporting pharmacological therapy (e.g. insulin or oral medications).		

In summary, the use of DHTs in combination with pharmacological therapy is not only aimed at treating the condition, but also at improving patient quality of life by enhancing the medication effect through behavioural support, personalization, and increased adherence.

The prescription should therefore be evaluated for its appropriateness, considering the authorised combination, to ensure the efficacy and safety of the DHTs.



3. ARTIFICIAL INTELLIGENCE, HTA E POLICY

3.1. DATA ANALYTICS IN HEALTHCARE: FROM UNSUPERVISED TO FEDERATED LEARNING

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In this introductive section on Al-based methods, a very general classification will be adopted, which subdivide the algorithms based on two key approaches: supervised and unsupervised learning. Such a classification, which focuses on learning objectives rather than on the involved algorithms, allows a comprehensive and clear-cut subdivision of most methods exploited in data science including also approaches which are not necessarily comprised in the Al field. As detailed below, the key difference between supervised and unsupervised learning is the use of labelled data in the former.

Stated differently, supervised learning methods aim to predict a target label and require a training set, which includes a significant number of instances, each of which is associated with a set of features including the target value. The involved methods exploit the training set to train a model able to predict the label for new (external) instances. The unsupervised learning involves methods which do not require a target label since they analyse the input datasets to reveal patterns, trends and outliers. Basically, the unsupervised learning aims to reduce the complexity of the input data by revealing the most important features as well as the relations between them.

Remarkably, the two classes of approaches can act synergistically. For example, unsupervised learning methods can be used to extract the most informative features to be utilized to develop predictive models by supervised learning.

Unsupervised analysis

As mentioned above, unsupervised analysis explores relations and patterns within unlabelled data. This means that unsupervised approaches are not utilized to generate predictive models but to explore how the data are structured to reveal clusters, outliers and trends. The algorithms for unsupervised analyses can be subdivided into three main groups: clustering, dimensionality reduction and autoencoders. For brevity, attention is here focused on the last two groups.

Dimensionality reduction enhances interpretability by reducing data complexity while retaining key information and variability. This can be obtained by either feature selection or feature extraction. The former selects a subset of relevant features from the original input data (the selection is based on statistical analyses), while the latter generates new sets of features by processing the initial input data and is particularly useful when many features appear to be equally relevant. In this context, the principal component analysis (PCA) is the most well-known and widely applied algorithm for data reduction and is commonly utilized in health data analysis to explore complex datasets such as patient health records, genetic data, and in medical imaging. In detail, PCA transforms the original dataset in a new set of features, called principal components (PCs), which are prioritized based on the encoded variance. In this way, the first PCs capture the maximum information from the original data, while the successive PCs are progressively less relevant and can be ignored.

As examples of PCA applied to health data, recent studies involved PCA analyses to correlate physical and mental exercise to risk of stroke [1], to better investigate the unclear relations between brain injuries and neurodegenerative diseases [2] or to analyse cardiac imaging for accurate classification of hearth diseases [3]. These few case studies emphasize how PCA can have enhancing roles in disease diagnosis, treatment optimization, and in the identification of relevant biomarkers. A more recent algorithms is the t-distributed stochastic neighbour embedding (t-SNE) [4]. The algorithm reduces the data complexity, while conserving the degree of similarity among the analysed datasets, and is particularly useful to graphically visualize highly complex data. Such a method finds relevant application to explore health data as well as genomics outputs (such as single-cell RNA-seq datasets) [5].

The recent progress in artificial intelligence techniques and in neural network architectures also influenced unsupervised learning by the development of the autoencoder approach. Autoencoders are specific neural networks able to analyse and condense unlabelled data to an encoded latent representation which must be informative enough



to allow the initial data to be recreated. In this way, the neural network discriminates between relevant features and noise. Autoencoders find fruitful applications in image analysis and are particularly effective in abnormality detection [6]. As an example, autoencoders were recently utilized to distinguish benign and malignant breast tumours [7]. Similarly, autoencoders can be utilized to compare health records to find similar patients or missing data [8] [9].

To better evaluate the role of unsupervised analyses on health data a literature analysis based on PubMed was carried out (accessed on 20th October 2025) by submitting the following term "health" plus the name of the unsupervised method. PCA provide about 16,500 references starting from the 1960s, Autoencoders and t-SNE show a limited number of citations (1200 and 250, respectively) but are markedly younger methods since the first papers dates to 2013 and 2014.

Supervised learning

As mentioned above, supervised learning approaches exploit labelled datasets to train models able to predict the label of new instances. Supervised learning usually requires two curated datasets: the training set by which the model is trained and the test set by which the predictive power of the resulting model is assessed. The predictions can be subdivided into classification and regression. In the former, the models classify the data into categories and predict which category a new instance belongs to. In the latter, the target label is a continuous value, and the models aim to predict such a value by exploiting the relationships between dependent and independent variables within the training set.

Classification requires balanced training sets in which the categories are equally populated. Many machine learning algorithms are well suited for classifications such as support vector machine, decision tree and random forest. For example, decision tree is an algorithm which generates models based on rules and relations extracted from the input data and organized into a tree-like flowchart. Decision tree algorithms are commonly used in operational research to suggest which strategy should be most productive to reach a defined objective but also find countless applications as machine learning tool to develop predictive models.

Predictive models based on tree algorithms are relatively easy to be generated and are highly explainable since each included rule is easily understandable and the overall tree flowchart somewhat mimics the human reasoning approach; nevertheless, predictive models based on a single tree rarely show satisfactory performances. Thus, random forest (RF) method combines sets of tree models involving different features and different parts of the training data to reach a final prediction usually by a majority consensus. Even though slightly more computationally expensive and less understandable, the RF predictive models show markedly enhanced predictive power.

The recent development of deep learning methods based on various neural network architectures played a key role also in the development of novel classification approaches. As recently reviewed [10], deep learning methods offer some relevant advantages compared to machine learning techniques such as the capacity to handle larger and more complex datasets while requiring reduced efforts in data curation and preparation and, more in general, in human guidance. In return, deep learning methods are computationally more expensive and require longer training time for the models and tailored hardware infrastructures (mostly based on GPUs). Furthermore, the complexity of the neural networks renders the generated models markedly less explainable and thus deep learning tools works as black boxes hampering an easy understanding of the rationale behind the obtained predictions.

While avoiding a detailed description of their architecture, it is sufficient to recall that neural network are composed by interconnected nodes; each node receives an input, applies a mathematical function and generates an output which can be passed to the next nodes depending on an activation function which allows nonlinearity to be introduced in the resulting models thus becoming able to learn complex relationships between data. On these grounds, deep learning approaches prove extremely successful in generating classification models even when managing huge, complex and untreated resources.

All binary classification models are evaluated by various metrics derived from the confusion matrix which classifies the corrected predictions in true positives and true negatives, while the wrong outputs are subdivided into false positives and false negatives. The utilized metrics can have either a general meaning, such as the accuracy which evaluates the percentage of correct predictions, or a class-specific relevance such as sensitivity and specificity, which encodes for the capacity to recognize the positive and the negative instances, respectively. Among the used metrics, Matthews Correlation Coefficient (MCC) is a very popular parameter since it is robust and informative condensing in a single balanced score all the values of the confusion matrix.

All classification algorithms are incessantly utilized to analyse health data and to get an idea about how much (and how long) they are utilized in the field, a literature analysis was performed based on PubMed (accessed on 20th October



2025) by interrogating the resource with the following terms: "health", "classification" plus the name of the considered algorithm. The first analysis involves the two major classes of methods: machine learning counts 15,000 papers starting from 1985, while deep learning is mentioned in 7000 papers and the first citation dates to 1995. Focusing on specific algorithms, Random Forest and Support Vector Machine (a method based on optimal function which maximizes the distance between each class) show a similar occurrence with about 3,700 references even though the latter is more recent (2001 vs 1988). Similarly, Naïve Bayes (a probabilistic method) and KNN clustering (a method based on data similarity) techniques count about 800 citations, the former being more recent (1998 vs 1989). Papers involving Neural networks substantially coincide with deep learning with 7,700 citations even though they appeared a few years earlier (1990). Lastly, logistic regression (a type of regression algorithm targeted for binary responses) reports 15,000 occurrences although it should be noted that this methos is the oldest one (dates to 1980) and is often used as baseline to appreciate the enhancements offered by more sophisticated approaches.

As mentioned above, regression handles datasets in which the label is a continuous value and the models attempt to predict this value by exploiting relationships among data extracted by the training set. Although there is an extended arsenal of algorithms specially devoted for regression analyses (linear, multivariate, nonlinear, polynomial methods), most Al-based approaches already described for classifications can be also exploited for regression. Even though methods based on decision trees are more suited for classification they can be also used in regression, and their weak predictions can be reinforced by using specific techniques such as the already mentioned random forest or the gradient boosting method which combines multiple predictors to yield a single consensus model able to improve the prediction accuracy. Finally, neural networks are also well suited for regression maintaining all the advantages already discussed for classification.

When repeating the same literature analysis on PubMed by replacing the terms "classification" by "regression", the occurrence of machine learning methods is markedly higher than that of deep learning (12,000 vs 2,000). Methods based on decision trees are quite popular with random forest which shows 6,000 references starting from 1997. Such an analysis also confirms the potential of other consensus methods, such as gradient boosting which counts 2500 citations while being a very recent technique (the first paper dates to 2013). The various regression methods reveal an incredibly huge number of citations (about 475,000), which date back to the 1940s long before the advent of Al-based approaches.

Data quality: concerns and perspectives

Regardless of the applied algorithms or the pursued objectives, the resulting performances of any analysis strongly depend on the quality of the processed data. There are several aspects that are considered when focusing on data quality (such as accuracy, completeness, validity, consistency, uniqueness or timeliness). For brevity, here attention is focused on the first two factors which are of paramount relevance when handling health data [11]. The former evaluates the correctness of the utilized data and answers to the following question: "how close data values are to the true or correct value?". In detail, data accuracy can be assessed in terms of error-free precision, integrity and believability. The first factor mostly depends on how much datasets are curated. Integrity and believability refer to data trustworthiness and mainly depend on user's perception. Overall, data accuracy principally depends on how data are collected and prepared for further analyses.

There are different tools for treating health data, which can be collected from diverse sources. In general, and besides an initial cleaning and validation to minimize the wrong data, these programs integrate and convert various sources of data (such as medical records, clinical trials, and research studies) into an only one structured and standardized format which supports further analyses and a constant updating. A still debated question is whether a completely automatized interrogation of disparate sources and collection of the retrieved data can reach the desired level of data accuracy, and which can be the still required manual curation by professional experts.

Even though data completeness is mostly referred to the lack of missing data and to the approaches which can used to fill these gaps, here attention is focused on the role of data size to have datasets large enough for the planned analyses. Even though there are obvious limitations, the performances of a model tend to increase with the size of the training set, and this is particularly true for deep learning algorithms since they tend to easily give overfitting when analysing small datasets [12].

Although the last years have seen a sharp and continuous increase of the available scientific data (resulting in the so-called big data) collecting very large health datasets still raises some concerns mostly related to privacy aspects and intellectual property issues. Even though the analysis of these relevant concerns goes beyond the objectives of this section, here attention is focused on two strategies which can be applied to bypass the resulting problems: federated learning and synthetic data.



The former is a collaborative approach in which different organizations (called clients) contribute to the development of a global model without sharing the own training data. Stated differently, each client develops its predictive model by exploiting its data and the so generated models from the participating organizations are integrated by a central server in a global centralized model by exploiting various consensus techniques. The integrated model is then shared to the clients which can iteratively optimize it by constantly updating the local training set and the resulting local model. The advantages of such an approach are mainly related to the privacy of data which always remain on the local client. In return, such a decentralized approach can induce communication overhead since the constant communications between clients and server can result in substantial bottlenecks. The multifaceted applications of federated learning for health data range from network of hospitals which collaborate in developing optimized predictive models to medical devices which can locally process the patient's data and communicate to the server the resulting models without sharing personal data. As a rule, one may conclude that a federated model is worse than the model attainable by sharing all the training sets but is markedly better than all local models.

Synthetic data is generated by an algorithm (usually deep learning or generative AI) to be as similar as possible to real data by retaining the same patterns and relationships characterizing them. This means that synthetic and real data should produce the same results when utilized in a statistical analysis. As such, synthetic data can replace real-world data in generating models, performing statistical analyses or testing hypotheses and can be used alone or in combination with real data to enlarge the training datasets in the so-called data augmentation. As recently reviewed [13] synthetic data can be used in healthcare for different applications such as to enhance clinical data and the resulting predictive models especially for rare diseases and conditions as well as in personalized medicine, to extend fair treatment recommendations across diverse patient populations or to provide to researchers extended and high-quality health datasets without exposing sensitive patient information. Concerning the last applications, it should be noted that synthetic data are not intrinsically anonymous. Nevertheless, the absence of sensible data can be finely governed during the generation of synthetic data which thus acts as a sort of data anonymized process.



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3.2. ARTIFICIAL INTELLIGENCE AS A LIVING COMPONENT OF MEDICAL DEVICE EVOLUTION

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Artificial Intelligence (AI) and Machine Learning (ML) have become pivotal forces in the evolution of modern medical technologies, reshaping how diagnostic, monitoring, and therapeutic devices are conceived, validated, and deployed. Over the past decade, AI's capacity to extract meaningful patterns from complex clinical data, ranging from imaging to physiological signals, has transformed it into a defining feature of next-generation medical devices. This transformation has been particularly evident in the domain of Software as a Medical Device (SaMD), a regulatory concept first articulated by the International Medical Device Regulators Forum (IMDRF) to describe software that performs medical functions independently of any specific hardware component [1].

Unlike embedded software that controls hardware functions, SaMD operates autonomously to analyse patient data, support diagnosis, or recommend therapeutic actions. Its impact lies in its ability to evolve: adaptive algorithms can learn from real-world data, refining predictions or recommendations over time. Such dynamism, however, challenges the traditional regulatory paradigm that assumes medical devices remain stable once approved. The U.S. Food and Drug Administration (FDA) has acknowledged this shift through a series of guidance documents formalising a lifecycle approach to AI device oversight, emphasising transparency, change control, and continuous monitoring rather than static premarket evaluation [2].

At the heart of this movement is the recognition that Al-driven devices blur the boundaries between research and clinical application. Their development lifecycle extends beyond design and validation to include deployment, monitoring, retraining, and decommissioning, phases traditionally underemphasised in device regulation. All systems embedded in medical devices or implemented as software products demand not only technical excellence but also ethical and clinical accountability. They must integrate clinical reasoning, data governance, and usability considerations into the core of their architecture. Consequently, medical device manufacturers have had to rethink their innovation strategies, embracing multidisciplinary teams that unite engineers, clinicians, and regulatory experts around the concept of "total lifecycle management."

This convergence is also giving rise to a new form of collaboration between "complementary intelligences." Traditional predictive AI (ML/DL) provides validated, domain-specific accuracy, while foundation and agentic AI, represented by large language models (LLMs) and autonomous agents, extend adaptability, contextual understanding, and reasoning across heterogeneous data sources. Rather than competing paradigms, these systems function as interoperable layers: ML offers precision; LLMs offer interpretability and workflow integration. Together they create a symbiotic intelligence, bridging structured and unstructured data, clinical logic and linguistic reasoning, to advance patient-centered care [3].

The scale of adoption is already substantial. By the end of 2024, the FDA had authorised over one thousand AI/ML-enabled medical devices, the majority related to diagnostic imaging. These devices illustrate both the maturity of AI methods in certain domains and the persisting regulatory uncertainties in others. While image-based diagnostics lend themselves naturally to data-rich supervised learning, emerging applications in decision support, remote monitoring, and interventional robotics introduce far greater complexity. Here, the algorithm is no longer a passive analytic engine but an active component of the clinical decision pathway. This shift carries profound implications for safety, liability, and public trust [4].

The conceptual boundary between software and device is dissolving. All now operates across a continuum that spans standalone software tools, clinical decision support systems (CDSS), and All modules embedded directly within hardware devices. This continuum challenges both engineering practice and legal interpretation, demanding a nuanced understanding of intent, functionality, and risk.

At one end lie Al-based software applications designed to process clinical data, such as radiological images, electrocardiograms, or electronic health records, to deliver diagnostic insights or treatment recommendations. These tools, when intended for clinical use, are regulated as SaMD and as Medical Device Software (MDSW) under the



European Union's Medical Device Regulation (MDR, Regulation (EU) 2017/745). The MDR's Rule 11 explicitly recognises software that provides information used for diagnosis or therapy as potentially high-risk, often requiring Class IIa or higher classification. This marks a significant departure from the earlier regulatory leniency applied to digital health applications, acknowledging the direct clinical consequences of algorithmic outputs [5].

Yet beyond software-only solutions, AI has increasingly been integrated into the operational cores of hardware devices. Modern imaging systems, surgical robots, and smart sensors embed ML algorithms to guide acquisition parameters, assist with intraoperative navigation, or deliver real-time prognostic alerts. In these systems, the distinction between "device" and "intelligence" collapses: AI becomes a native component of the device's function rather than an external analytical layer.

The rise of CDSS occupies a pivotal middle ground between these two extremes. CDSS represents algorithmic tools designed to aid clinicians by synthesising patient-specific data with established medical knowledge, providing recommendations or alerts within the clinical workflow. Traditional CDSS relied on rule-based reasoning, but modern systems increasingly employ deep-learning models and LLMs that learn from large-scale data. While these systems can enhance decision-making accuracy, they introduce new epistemological questions about explainability and control. The clinician's ability to "independently review" the basis for a recommendation becomes critical, not merely for safety but for preserving professional agency.

Here, agentic AI introduces a new operational paradigm: systems capable of reasoning through multiple steps, querying medical databases, or even autonomously triggering actions under clinician supervision. This evolution transforms CDSS from static rule-based tools into dynamic collaborators. Multiagent frameworks already execute structured tasks, information retrieval, report summarization, treatment recommendation, within FHIR-compliant environments, while maintaining traceable audit trails. Their strength lies not only in automation but in their capacity for continuous alignment with human reasoning, thereby preserving the clinician's centrality in care [6].

The convergence between the MDR and the Artificial Intelligence Act (AI Act) marks a decisive step in shaping the governance of AI-enabled medical devices. Both frameworks pursue the same overarching goals—safety, performance, and accountability—but they approach them through different lenses. The MDR is product-centred, rooted in clinical validation and patient safety, while the AI Act introduces a system-level governance model, embedding ethical, data, and lifecycle management requirements into law. These regimes apply simultaneously and complementarily: AI systems qualifying as medical devices must comply fully with both sets of rules [7]. In essence, the MDR—AI Act interplay defines Europe's new regulatory frontier: a move from static product compliance to dynamic, ethical lifecycle governance for medical AI. This mirrors a deeper cultural transition, from validating static devices to cultivating trustworthy digital ecosystems. In this setting, clinical safety depends as much on algorithmic performance as on the behavior of the sociotechnical system: how humans, software, and workflows interact over time. Transparency, therefore, must evolve from documentation to design, embedding traceability, uncertainty quantification, and adaptive oversight as intrinsic device features rather than external audits.

Where earlier debates focused on explainability as a mechanism for compliance, a more nuanced understanding is now emerging. The real challenge is not merely to make AI systems explainable in a formal sense, but to make them usefully interpretable within clinical reasoning. Traditional approaches to eXplainable AI (XAI) often produce static, post-hoc visualizations of model logic. What physicians require is not an abstract narrative of "why" the algorithm produced a given output, but contextual indicators that convey when and how much a recommendation can be trusted.

This reconceptualization shifts XAI from an exercise in retrospective justification to one of prospective trust calibration. Clinicians operate in uncertain, time-sensitive environments; they benefit more from actionable cues than from static feature attributions. In this sense, explainability evolves into what has been termed eXtended and eXplorable AI, where systems are designed for interaction, transparency of uncertainty, and adaptive reliance rather than passive interpretation [8].

In practice, this means that the frontier of medical AI is no longer only about "explainability," but about explorability: the clinician's ability to interrogate, test, and co-reason with the model. Explorable AI allows the user to ask "what if?" questions, simulate alternative scenarios, and visualize uncertainty in meaningful clinical terms. These interactions help clinicians calibrate trust dynamically, transforming algorithms from static advisors into participatory cognitive partners.

Such systems embody the concept of "multimodal cognition", an approach that integrates numerical prediction, linguistic reasoning, and contextual awareness within a single decision loop. This multidimensional intelligence is inherently multidisciplinary: it thrives only when engineers, data scientists, regulatory authorities, and clinicians codesign interpretability and oversight mechanisms from the outset. As a result, the success of medical AI is no longer judged solely by its predictive accuracy but by its usability, interpretability, and alignment with human cognitive processes.

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Looking ahead, the regulatory and clinical integration of AI will depend on this fusion of complementary intelligences. Traditional AI ensures precision, generative models ensure adaptability, and agentic AI ensures reasoning continuity across complex workflows. Together they create a new generation of medical devices: dynamic, interactive, and self-reflective, that can adapt to real-world variability without compromising safety or human oversight. In this sense, the trajectory first envisioned by Pauker, Gorry, Kassirer, and Schwartz in 1976, simulating clinical cognition through hypothesis generation, is finally materializing as a living collaboration between human and machine cognition. The physician is not replaced but amplified: their reasoning extended across modalities, their decisions supported by a new ecosystem of intelligent tools.



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3.3. ARTIFICIAL INTELLIGENCE APPLIED TO ONCOLOGY

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The three worlds of cancer AI

Artificial Intelligence (AI) has already redefined the landscape of oncology, it has now entered the clinical mainstream, influencing how cancers are detected, classified, monitored, and treated. The transition has been very fast: in less than a decade, oncology has moved from experimenting with diagnostic algorithms to designing complex, intelligent systems that can reason, communicate, and collaborate with clinicians and patients. This evolution can be understood through three conceptual stages ("worlds"): predictive AI, foundation AI, and generative or agentic AI, each being a progressive expansion in scale, adaptability, and impact.

The earliest wave of clinical AI in oncology consisted of **predictive algorithms**: models made for a singular task and that link one type of input (data) to one type of output. These include deep-learning systems that detect nodules on CT scans, classify pathology slides, or identify suspicious lesions in mammography, for instance.

Each of these systems was trained on large, labelled datasets to answer a very specific clinical question: "Is this lesion malignant?" or "Does this slide indicate a high-grade tumor?". Their reliability and narrow focus made them ideal candidates for regulatory approval under SaMD framework. By the end of 2024, the FDA had authorized more than one thousand Al-enabled medical devices) and the European Medicines Agency is following suit. The majority of these tools address diagnostic imaging tasks in oncology. However, this first generation of Al is powerful but remains limited. Each system operated in isolation, transfer of its knowledge to new domains is difficult, for technical and regulatory aspects, and combining information across modalities such as imaging, genomics, and clinical text is also very complicated.

The second wave of innovation introduced **foundation models**, different from the first as they are trained on vast collections of multimodal data to develop generalized representations of human biology and disease. Once trained, they can be fine-tuned for many specialized clinical tasks. In oncology, foundation models are beginning to link what were once separate analytical domains. There are many types of foundation models, especially ones in pathology and -omics data, able to predict response to therapy, identify molecular alterations, etc. Similarly, multimodal LLMs have been implemented and can interpret radiological images alongside clinical notes and laboratory data, connecting disparate information streams that oncologists previously had to synthesize manually. This approach is transformative for cancer medicine, where the complexity of patient data has exceeded the capacity of individual clinicians or traditional statistical tools.

The third stage in this progression introduces **generative and agentic AI**, systems that can not only recognize patterns but also reason, summarize, and communicate with the end users. Built on large language model architectures, these systems are able to generate coherent clinical narratives, draft reports, synthesize literature, and even suggest treatment options supported by evidence. These agents are also linked with specialized analytic modules such as molecular classifiers or radiomics predictors and are then upscaled in generative AI that acts as agentic orchestrator, named as such as they are able to direct, like an orchestra conductor, multiple specific agents: a full clinical assistant that retrieves information, evaluates possible actions, cites its sources, and explains its reasoning in natural language.

In oncology, early demonstrations of these multi-agent frameworks are already underway. AgentClinic, developed at Stanford, simulates interactions between clinicians, patients, and AI tools to train and test decision strategies in realistic virtual environments [1]. These prototypes illustrate how generative agents can coordinate tasks, manage uncertainty, and enhance multidisciplinary communication in complex cancer care settings. Such systems signal a profound change in how AI interacts with the clinical environment. The model is no longer a silent diagnostic engine; it becomes a cognitive collaborator capable of contributing to reasoning, education, and communication.



Fields of application

This evolution now well established, we can focus on the main fields of application (hallmarks) of AI in the oncological setting.

Screening and Early Detection

The first (and earliest) field of application has been the capacity to optimize population screening through precision triage and workload redistribution while maintaining or enhancing diagnostic accuracy. All systems have matured from "pattern detectors" into "clinical actors," influencing not only diagnostic output but workflow efficiency and health system equity. Al-based triage in imaging has now reached Level 1 clinical evidence, demonstrating the feasibility of deploying autonomous systems under regulatory oversight without compromising safety or trust [2] [3].

Growing evidence from large-scale perspective randomized control trials is beginning to establish the clinical value of AI in oncological screening, particularly in mammography. The Mammography Screening with Artificial Intelligence (MASAI) randomized controlled trial, conducted in Sweden and enrolling over 100,000 women, demonstrated that AI-assisted screening increased the detection of clinically significant breast cancers by 29% without raising recall or false-positive rates, while halving radiologists workload [4] [5].

Complementary findings emerged from the ScreenTrustCAD trial, a population-based, paired-reader, non-inferiority study evaluating AI as an independent reader rather than a support tool. The trial confirmed that single reading with AI was non-inferior, and slightly superior, to standard double reading by two radiologists, achieving comparable recall rates with substantially reduced workload [6].

Building on these results, a secondary analysis of ScreenTrustCAD investigated how radiologists' recall decisions varied depending on whether an abnormality was flagged by AI or by a human reader. Importantly, radiologists knew the origin of each flag during consensus discussions, creating a non-blinded setting that revealed systematic bias in the radiologists, who were less likely to recall women whose mammograms were flagged solely by AI than those identified by human peers, despite the AI-flagged cases exhibiting a markedly higher positive predictive value for cancer (22% vs. 3.4%) [7]. These findings underscore that even when AI systems demonstrate equivalent or superior diagnostic accuracy, their clinical impact ultimately depends on the degree of trust and acceptance within human—AI decision-making processes.

From Detection to Prognostication

For a few years now, AI tools have switched from detecting disease to predicting its trajectory, combining radiologic, genomic, and clinical features into prognostic signatures of evolution and response. Deep learning architectures have shown promise in non-invasive tumor characterization by setting up "virtual biopsies" [8] [9] and in predicting molecular features such as PD-L1 expression, EGFR mutations, or microsatellite instability directly from imaging [10].

These approaches are now being validated in the real world, towards full disease modelling. For instance, multimodal AI systems that integrate CT or PET/CT radiomics with clinical and laboratory parameters can identify high-risk lung cancer phenotypes and predict treatment outcomes with increasing accuracy, but also in breast and gynecological cancers [11] [12].

Al in treatment decision support, and optimization

The integration of AI into clinical research is transforming how trials are designed, monitored, and interpreted. Adaptive designs leveraging real-time AI analytics are enabling earlier detection of treatment benefit or futility, optimizing enrolment and stratification based on evolving biomarker signals.

In oncology, the promise of AI extends far beyond detection and moves to personalized therapeutic guidance, as a decision support tool for medical oncologists. The integration of molecular and immune features with clinical and imaging data has enabled predictive models capable of informing immunotherapy response, patient selection, and resistance mechanisms. One such example is the I3LUNG project [13], which analyses multimodal data to develop a decision-support model integrating clinical, radiomic, genomic, and biological data to predict individual responses to immunotherapy in non-small cell lung cancer (NSCLC). Using explainable AI techniques, I3LUNG harmonizes data across multiple centres, internationally, addressing GDPR-compliant privacy constraints while training models on real-world, high-dimensional datasets. This initiative is one example that shows how AI can either discover new biomarkers and



patterns or increase the efficacy of known ones. The project includes a full-fledged clinical validation phase to bridge the gap between computational prediction and clinical decision support.

In parallel, national initiatives have started to establish Al-driven biodata systems. In Italy, APOLLO 11 [14] integrates data analysis (clinical, genomic, and imaging) with virtual biobanks to model treatment. Integrating multi-omic and longitudinal data for patient stratification, AI has become a longitudinal solution across the whole spectrum of cancer research and care. The next step is digital twin–based oncology, where patient-specific models simulate therapeutic scenarios in silico before clinical implementation.

Clinical trial design and matching

For patients who do not respond to or are ineligible for standard-of-care therapies, clinical trials have always represented a crucial opportunity to access innovative treatments. Designing and matching patients to clinical trials involves defining appropriate inclusion and exclusion criteria and ensuring that each participant is directed toward the most suitable study. This process is fundamental for translating novel discoveries from the laboratory to clinical practice but is riddled with many bottlenecks and complications. The complexity of eligibility criteria and the labor-intensive nature of patient screening make the process inefficient: only about 7% of patients with cancer ultimately enroll in clinical trials [15], while approximately 20% of trials are terminated early due to insufficient accrual. Persistent disparities in participation by race, sex, age, and socioeconomic status further limit the representativeness of trial populations [16] [17].

Al-driven systems can accelerate patient identification, reduce manual screening workloads, and refine trial protocols by analyzing real-world clinical and molecular data. For example, Trial Pathfinder, an Al model trained on data from 61,094 patients with advanced NSCLC, was able to simulate trial eligibility and identify exclusion criteria that could be safely removed without altering survival outcomes. Commercial applications are also emerging. Platforms like IBM Watson for Clinical Trial Matching use machine learning to align oncology patients with suitable studies, improving both the efficiency and accuracy of trial enrolment across cancer types and institutions.

Most recently, LLMs have introduced new capabilities for interpreting the often complex and unstructured eligibility criteria found in clinical notes and trial protocols. Early research suggests that LLMs can substantially enhance the accuracy and speed of patient—trial matching, paving the way for a more adaptive and equitable clinical research ecosystem.

Human-AI Collaboration and the Trust Gap

These developments highlight a recurring paradox in clinical AI: the gap between technical performance and human trust. Even when AI systems achieve parity or superiority in accuracy, their clinical impact depends on human acceptance, interpretability, and workflow integration.

As artificial intelligence becomes increasingly embedded in healthcare decision-making, one of the most pressing challenges is ensuring that its reasoning can be understood and trusted by clinicians, patients, and regulators. This need has given rise to the concept of Explainable AI (XAI), a field focused on making models transparent, interpretable, and aligned with human understanding.

Beyond explainability lies a deeper goal: **explorability**. While traditional XAI techniques offer static, retrospective insights, next-generation systems aim to support dynamic interaction between clinician and algorithm. Explorability allows users to modify variables, simulate alternative scenarios, and visualize model uncertainty in real time. In oncology, such interactive transparency can help multidisciplinary tumor boards compare treatment options, assess likely outcomes, and calibrate confidence in the model's suggestions before making final decisions.

Practical experience supports the value of this approach. In the I3LUNG project, adding explainable visualizations to lung cancer predictive models improved diagnostic accuracy and consistency, particularly among less experienced clinicians. The intervention not only raised overall performance but also demonstrated that clear, interpretable feedback enhances shared understanding and team confidence.

In the long term, we foresee that explainability will evolve: Al systems will not only justify their conclusions but also document their reasoning, uncertainty, and data provenance. This transparency will strengthen both clinical reliability and public trust. In cancer care, where the consequences of error are profound and the demand for individualized treatment is growing, explainable and interpretable Al is not simply desirable; it is indispensable for the responsible integration of intelligent systems into everyday practice.

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The next frontier of artificial intelligence in oncology will be shaped by the rise of agentic and explorable AI systems: platforms capable of continuous learning, transparency, and collaboration with clinicians. Unlike earlier generations of predictive models that operated as static diagnostic tools, these new systems will engage actively in clinical reasoning, integrating multimodal data, medical guidelines, and real-time feedback from healthcare teams. Their design will emphasize not only accuracy but also interpretability, auditability, and adaptability within evolving clinical and regulatory environments.

In this paradigm, AI will no longer function as a passive source of predictions but as an active participant in the delivery of care, supporting clinicians in planning, monitoring, and adapting treatment strategies in response to each patient's unique trajectory. Such systems will learn continuously while maintaining compliance through embedded safeguards and transparent documentation of their processes. By coupling cognitive collaboration with human oversight, agentic and explorable AI will lay the groundwork for a new generation of precision oncology that is adaptive, interpretable, equitable, and deeply patient-centered.



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3.4. ECONOMIC EVALUATION OF DIGITAL THERAPEUTICS: A SYSTEMATIC REVIEW

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Introduction

Digital Therapeutics (DTx) represent a rapidly expanding category of evidence-based software interventions designed to prevent, manage, or treat medical disorders through clinically validated mechanisms of action. Unlike wellness or fitness applications, DTx undergo regulatory evaluation, often requiring evidence of efficacy and safety comparable to that of pharmacological or device-based interventions. Their integration into healthcare systems has generated increasing interest from policymakers, payers, and HTA bodies, driven by the promise of improving outcomes while optimizing resource utilization.

This literature review aimed to systematically identify and synthesize the available economic evaluations of Digital Therapeutics, focusing on their cost-effectiveness, cost-utility, and budget impact. The goal was to map current evidence, compare methodological approaches, and identify data gaps relevant to HTA and reimbursement policy development.

Methods

We conducted a targeted literature review to identify and classify published evidence on the cost-effectiveness of Digital Therapeutics (DTx). The aim was to explore how DTx have been evaluated in terms of their economic value, modelling approaches, and implications for Health Technology Assessment (HTA) and access models across different healthcare systems. The analysis focused on studies reporting cost-effectiveness, cost-utility, or budget impact evaluations of DTx, defined as evidence-based digital interventions designed to deliver therapeutic benefits to patients.

1. Identification

The search strategy was developed in accordance with the PRISMA 2020 guidelines [1]. The following search string was applied:

(("digital therapeutics"[Title/Abstract] OR "digital therapeutic"[Title/Abstract] OR "DTx"[Title/Abstract]) AND ("cost-effectiveness"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract] OR "cost-utility"[Title/Abstract] OR "economic evaluation"[Title/Abstract] OR "cost-benefit"[Title/Abstract] OR "budget impact"[Title/Abstract] OR "health economic"[Title/Abstract]))

The initial search retrieved 44 records.

2. Screening

In the second phase, titles and abstracts of the 44 unique records were reviewed to exclude studies that did not meet the predefined scope of the review. The main reasons for exclusion were:

- The study did not concern a Digital Therapeutic (e.g., mobile health, telemedicine, or wellness app).
- The article did not include any economic or cost-effectiveness evaluation.
- The paper represented an editorial, commentary, or study protocol without economic results.
- The population or intervention was not healthcare-related (e.g., non-human or preventive behavioural app).

Records meeting at least one of the above exclusion criteria were removed. Following this phase, 28 articles were excluded, and 16 were retained for full-text evaluation.



3. Eligibility

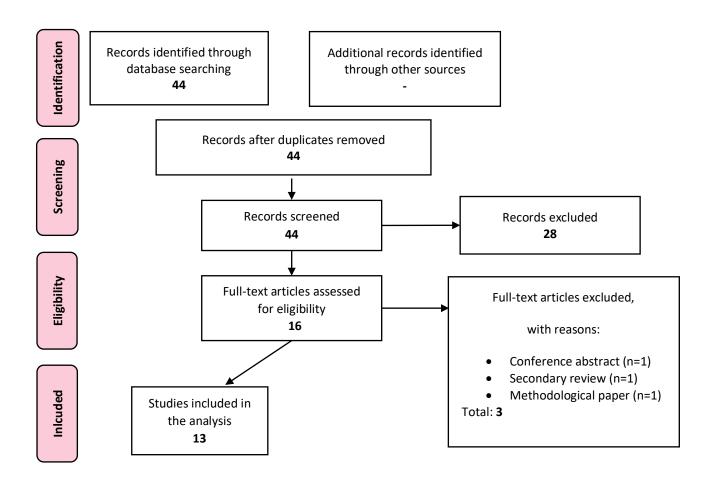
Full-text articles were retrieved and assessed to ensure compliance with methodological and thematic inclusion criteria.

Out of 16 full-text articles assessed for eligibility, three were excluded: one conference abstract lacking peer-reviewed data, one secondary review without original economic results, and one methodological paper without quantitative outcomes.

4. Inclusion

Ultimately, 13 studies met all inclusion criteria and were incorporated into the qualitative synthesis. The flow of information generated throughout the different stages of the systematic review process is presented in *Figure 1*.

Figure 1: Flow Chart



Results

A total of thirteen studies published between 2019 and 2025 met the inclusion criteria and were analyzed. Most of the evidence originated from the United States (n=8), followed by Europe (n=3) and Asia (n=2). Notably, no Italian economic evaluations were identified, confirming the absence of national data on the cost-effectiveness of Digital Therapeutics (DTx) and revealing a significant research gap in the Italian context.

The reviewed studies covered a broad range of conditions, including metabolic and cardiovascular diseases, substanceuse disorders, chronic pain, neurological and rehabilitative conditions, and ophthalmologic impairments. Across these diverse contexts, Digital Therapeutics consistently improved health outcomes and demonstrated favorable cost-



effectiveness profiles compared with standard care. A summary of the included studies, detailing their comparators, analytical methods, perspectives, and main economic results, is presented in *Table 1*.

In metabolic and cardiovascular conditions, digital interventions achieved meaningful health gains while generating cost savings or remaining highly cost-effective. For example, lifetime simulations in diabetes management reported savings of approximately \$7,000 per patient [2], while a Japanese Markov model in hypertension [3] estimated an Incremental Cost-Effectiveness Ratio (ICER) of \$10,434 per QALY gained, below national thresholds. The ICER represents the additional cost required to gain one unit of health benefit – typically measured as a Quality-Adjusted Life Year (QALY) – when comparing an intervention with standard care. ICER values below a country's willingness-to-pay threshold are generally considered economically acceptable.

For rehabilitative and musculoskeletal applications, reported ICERs ranged from €5,000 to €35,000 per QALY, with models suggesting potential cost savings under higher adherence or optimized pricing conditions [4] [5]. Finally, studies in neurological and ophthalmologic disorders reported ICERs below \$15,000 per QALY, mainly due to improved monitoring and adherence [6] [7].

Overall, cost-utility analyses (CUA) represented the most common approach (n=9), followed by cost-effectiveness analyses (CEA) (n=3) and one budget impact analysis (BIA). Models most frequently relied on Markov or Monte Carlo structures, with time horizons ranging from 12 weeks to lifetime, with the majority of models extending over two to five years.

Most studies adopted a payer perspective (n=10), while three included a societal perspective, accounting for productivity losses and informal care.

In summary, Digital Therapeutics were cost-effective in all thirteen studies and cost-saving in five, with results consistently robust in sensitivity analyses. Their economic value primarily derived from improved adherence, reduced relapse and complication rates, and lower healthcare utilization. These findings suggest that, when properly integrated into chronic care pathways, Digital Therapeutics can deliver both clinical and economic benefits with high potential for long-term sustainability.

Table 4: Economic evaluations of Digital Therapeutics: evidence synthesis from the literature

DTx	Comparator	Type of Analysis	Method	Results	Perspective	Study Reference
BT-001 (AspyreRx) — Type 2 Diabetes	Standard of care: standard medical management and counseling	Cost- Effectiveness Analysis	Microsimulation (UKPDS OM2)	The DTx was dominant, improving glycemic control and preventing complications, resulting in cost savings (~\$7,300 per patient) and QALY gains.	Payer	Davison et al., 2024 [2]
HERB DTx – Essential Hypertension	Standard of care: lifestyle counseling and physician follow-up	Cost- Effectiveness Analysis	Markov model (lifetime)	The DTx achieved costeffectiveness (ICER ≈ \$10,434/QALY) through better blood pressure control and fewer cardiovascular events.	Payer	Nomura et al., 2022 [3]
Luminopia / CureSight – Amblyopia	Standard of care: patching, glasses, or atropine therapy	Cost- Effectiveness Analysis	Trial + model	The DTx was cost-effective, improving adherence and visual outcomes without increasing total costs.	Payer	Koc et al., 2024 [7]
reSET-O – Opioid Use Disorder	Standard of care: medication-assisted treatment with buprenorphine + counseling	Budget Impact Analysis (5 years)	Budget model	Integrating the DTx generated cumulative savings (-\$0.01 to -0.04 PMPM) by reducing relapses and hospitalizations.	Payer	Velez et al., 2022 [8]
reSET-O – Opioid Use Disorder	Standard of care: buprenorphine + standard counseling	Cost- Effectiveness Analysis	Decision model (12 weeks)	The DTx was dominant, improving outcomes and reducing costs compared to standard therapy.	Payer	Velez & Malone, 2021 [9]
reSET-O – Opioid Use Disorder	Standard of care: medication- assisted therapy and counseling	Cost-Utility Analysis	Decision model (12 weeks)	The DTx was cost-effective, providing marginally higher QALYs at modestly higher cost, driven by improved retention and reduced relapses.	Payer	Velez et al., 2021 [10]



DTx	Comparator	Type of Analysis	Method	Results	Perspective	Study Reference
ViViRA – Low Back Pain	Standard of care: physiotherapy and unsupervised exercises	Cost-Utility Analysis	Monte Carlo simulation (3 years)	The DTx was cost-effective (ICER €34,315/QALY) and became cost-saving when priced ≤ €165 or with higher adherence.	Societal	Lewkowicz et al., 2023 [4]
Cardiac Rehab DTx – Atrial Fibrillation Post- Ablation	Standard of care: conventional home-based rehabilitation	Cost- Effectiveness Analysis	Trial-based model (12 weeks)	The DTx enhanced exercise capacity and QoL, achieving cost-effectiveness within national thresholds but without net savings.	Payer	Liu et al., 2023 [11]
reSET-O – Opioid Use Disorder	Standard of care: medication-assisted therapy	Cost- Effectiveness / Cost-Utility	Decision model (12 weeks)	The DTx achieved slightly higher QALYs at small additional cost, being cost-effective overall.	Payer	Wang et al., 2021 [12]
Cardiac Rehab DTx – Chronic Heart Failure	Standard of care: home-based cardiac rehabilitation	Cost- Effectiveness Analysis	Markov model (10 years)	The DTx improved adherence and outcomes, remaining cost-effective but not cost-saving compared to standard rehab.	Payer	Liu et al., 2023 [13]
Decision- Support DTx – Low Back Pain	Standard of care: physiotherapy ± medical supervision	Cost-Utility Analysis	Markov model	The DTx was cost-effective (ICER €5,486/QALY) and potentially cost-saving when priced lower or with strong adherence.	Societal	Lewkowicz et al., 2022 [5]
Better Therapeutics (BT) – Type 2 Diabetes / Hypertension	Standard of care: conventional pharmacologic management without digital behavioral support	Cost- Effectiveness Analysis	Simulation model (3 years)	The DTx reduced medical costs by \$97–145 per patient per month, improving adherence and preventing acute events.	Payer	Nordyke et al., 2019 [14]
MS Sherpa – Multiple Sclerosis	Standard of care: routine neurological monitoring and follow-up visits	Early HTA (Scenario- based)	Decision model (lifetime)	The DTx became cost-saving when efficacy improved relapse detection ≥15%, due to earlier treatment adaptation and reduced progression costs.	Societal	Cloosterman et al., 2021 [6]

Discussion

The findings of this review show that Digital Therapeutics (DTx) consistently demonstrate favorable cost-effectiveness across multiple chronic and behaviorally mediated conditions. Despite differences in context and modelling assumptions, all thirteen studies reported ICERs below conventional thresholds, and several showed net cost savings. These results underline the potential of DTx to improve both clinical outcomes and the efficiency of healthcare systems.

A key mechanism behind these outcomes is the ability of DTx to enhance adherence and self-management, leading to measurable clinical gains and reduced healthcare utilization. Interventions for metabolic, cardiovascular, and behavioral disorders achieved the most substantial economic impact, while rehabilitative and neurological applications showed cost-effectiveness under specific adherence or pricing conditions.

From a methodological standpoint, most evaluations relied on model-based analyses, typically Markov or Monte Carlo simulations. Although these frameworks allow long-term extrapolation, they depend on assumptions about sustained adherence and engagement that may not fully reflect real-world conditions. Furthermore, the predominance of the payer perspective (10 out of 13 studies) – focused on direct medical costs – tends to underestimate the broader societal value of DTx. The few studies adopting a societal perspective suggest that accounting for productivity and caregiver time would further improve cost-effectiveness results [4, 6].

The complete absence of Italian studies highlights a major research gap at the national level. Despite the strategic emphasis on digital health within the *Piano Nazionale di Ripresa e Resilienza* (PNRR), Italy lacks peer-reviewed analyses assessing the cost-effectiveness or budget impact of Digital Therapeutics in its specific organizational and economic



context. To address this gap, future research should prioritize the development of standardized HTA frameworks for Digital Therapeutics.

Overall, the reviewed literature provides compelling evidence that Digital Therapeutics can enhance clinical outcomes while optimizing healthcare resource allocation. Their cost-effectiveness is particularly evident in chronic, high-burden conditions where adherence and behavioral change are critical. However, the current evidence base remains limited by methodological variability, short follow-up horizons, and insufficient representation of public healthcare systems. Addressing these limitations—especially through coordinated national HTA efforts—will be essential to fully realize the clinical and economic potential of Digital Therapeutics in Italy and beyond.

Conclusion

This review confirms that Digital Therapeutics (DTx) consistently demonstrate cost-effectiveness – and in several cases, cost savings – across a range of chronic and behaviorally mediated conditions. Their value derives primarily from improved adherence, enhanced self-management, and reduced healthcare utilization. However, existing evidence remains geographically concentrated and often industry-sponsored. The absence of Italian studies underscores an urgent need for independent, locally contextualized research and for the establishment of a national HTA framework to guide the evaluation, pricing, and sustainable integration of Digital Therapeutics within the Italian National Health Service (SSN).



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GLOSSARY

Al – *Artificial Intelligence*: a broad field of computer science focused on creating systems capable of performing tasks that normally require human intelligence.

API – *Application Programming Interface*: a set of tools and protocols that allows different software applications to communicate with each other, enabling programmatic interaction with AI models.

DHT – Digital Health Technology: digital tools and systems designed to support, enhance, or deliver healthcare services.

DiGA – *Digitale Gesundheitsanwendungen*: Digital Health Applications in Germany regulated by a dedicated law for Digital Health – the *Digitale-Versorqung-Gesetz* (DVG, "Digital Healthcare Act").

DTx – Digital Therapeutics: the subset of DHTs and pDMD specifically intended for treatment.

DL – *Deep Learning*: a subset of ML based on artificial neural networks with multiple layers, particularly effective for processing complex data such as images, audio, or text.

LLM – *Large Language Model*: a type of generative AI trained on vast amounts of data, designed to understand and generate human-like language, images, or other content.

ML – *Machine Learning*: a subset of AI that uses algorithms to identify patterns in data and make predictions or decisions without being explicitly programmed for each task.

pDMD – *patient-managed Digital Medical Devices*: DHTs certified as Medical Devices and intended for patient use to monitor, diagnose, prevent, or treat medical conditions.

RPM – *Remote Patient Monitoring*: products intended to monitor patient data to inform management of a specific disease, treatment regiment, medical condition, or health outcome.

SaMDs - Software as a Medical Device: software intended to be used for a specific medical purpose