Infectious Agents and Cancer

REVIEW

Open Access

Digital health technologies in medicine: evidence, artificial intelligence integration, and ethical challenges

Marco Cascella[1], Cesare Pane[2], Marcello Di Pumpo[3,4], Enrico Sebastiani[5], Martino Bussa[6], Alessio Tagliaferri[7], Barbara Brunetti[8], Pierluigi Meloni[9], Elisa Bianchini[7], Paolo Graziani[7], Federico Faustini[7], Guido D'Onofrio[10], David Manetta[7], Cristina Angela Catania[11], Chiara Jole Fornari[7], Andrea Scarda[12], Federica Smanio[7], Cristina Imbesi[7], Maria Teresa Avella[13], Roberta Fusco[14*] and Vincenza Granata[14]

Abstract

Digital health technologies (DHTs), including digital therapeutics (DTx), are revolutionizing patient care by enabling the prevention, management, and treatment of medical conditions. These tools comprise care delivery mobile applications, wearable devices, and cloud platforms for capturing real-time data and enabling remote monitoring. DTx are regulated, software-based interventions that deliver evidence-supported therapeutic effects; artificial intelligence (AI) and machine learning, including advanced architectures, such as agentic systems and digital twins, may augment DTx workflows but are not defining features of DTx. Growing evidence supports the effectiveness of DHT strategies across different clinical fields. For example, wearable and remote patient monitoring technologies enable continuous assessment and personalized feedback in cardiology and neurology. Additionally, AI-enabled devices are widely implemented for continuous monitoring of glucose levels. However, several key challenges remain. Persistent gender and social biases in datasets and algorithms raise ethical concerns, particularly for underrepresented groups and pediatric populations. Mitigation strategies include regulatory frameworks, explainable AI, and trustworthy AI ecosystems. This work is a narrative, expert-driven review based on illustrative literature curated by domain specialists. It aims to synthesize current evidence, highlight implementation barriers, and propose recommendations to enhance inclusivity, interoperability, and real-world evaluation of digital health technologies. Applications of DHTs in animals within a One Digital Health framework, as well as potential applications in infection-related oncology, are also discussed.

Clinical trial number

Not applicable.

Keywords Artificial intelligence, Digital health, Healthcare, Ethics, Digital therapeutics, Remote patient monitoring, Wearables, Veterinary

*Correspondence:
Roberta Fusco
r.fusco@istitutotumori.na.it

Full list of author information is available at the end of the article

Introduction

Digital health technologies (DHTs) include a wide range of digital tools such as software, connected devices, and data services designed to improve health outcomes across the entire care spectrum, from prevention to diagnosis, monitoring, treatment, and rehabilitation. These tools include telehealth platforms, mobile health apps, wearable sensors, remote patient monitoring (RPM) systems, artificial intelligence (AI), and machine learning (ML) algorithms used for clinical decision-making and predictive analytics. They also encompass AI agents and digital twins that simulate patient physiology. Digital therapeutics (DTx) are a specific, regulated subset of DHTs. They are software-based, evidence-supported interventions designed to deliver direct therapeutic effects to prevent, manage, or treat medical conditions. Unlike general wellness apps, DTx make explicit clinical claims, undergo rigorous evaluation (often as Software as a Medical Device, SaMD), and must meet regulatory, quality, privacy, and cybersecurity standards comparable to other medical technologies [1–3]. A broader overview of the potential of digital healthcare technologies can be found elsewhere [4].

Despite their conceptual appeal, most of these technologies, such as agent-based systems and digital twins, currently remain at an early translational stage. Empirical evidence demonstrating their added value over conventional clinical decision support is still scarce, and substantial challenges persist regarding validation, uncertainty quantification, regulatory qualification, and clinical accountability. As such, these approaches should presently be viewed as complementary research tools rather than mature clinical solutions. However, although these strategies hold great promise for research and clinical care across various medical fields, several major challenges still exist. For instance, a recent study revealed a significant overrepresentation of male figures in generative AI text-to-image outputs [5]. Many of these issues stem from the gender health data gap, which involves two main problems: inadequate research on conditions affecting women and the reliance on male-based data as the medical standard [6]. To avoid perpetuating existing inequalities and ensure data disaggregation, these technologies must be developed and validated with diverse, representative datasets that reduce gender bias and prevent discriminatory outcomes [7].

This narrative review aims to explore the current state of DTx and its potential applications. We also examine how DHTs are applied to animals within the One Digital Health framework, as well as in infection-related oncology. Veterinary applications are included not as a parallel overview, but as a comparative lens to examine how ethical and governance challenges scale across domains within a One Digital Health framework. Moreover, the infection-related oncology domain is presented as a case-study application of the digital health ecosystem. In this context, digital platforms exemplify the opportunities and limitations of AI-enabled DHTs when deployed in settings characterized by constrained diagnostic resources, evolving risk profiles, and the need for scalable triage strategies. Finally, ethics issues and challenges related to data bias are addressed, with a focus on future directions and recommendations as well as the steps necessary to improve inclusivity and minimize health disparities. Accordingly, this review does not follow a formal systematic-search protocol. It adopts a narrative, expert-curated approach in which literature selection was guided by the domain expertise of the contributing authors. For each thematic section, authors identified relevant and high-impact studies based on scientific relevance, methodological quality, and clinical or translational significance within the field addressed. Given the heterogeneity of technologies, examples were selected to be illustrative rather than exhaustive; consequently, study designs and outcomes synthesis were conducted thematically and interpretively, without formal quantitative aggregation. The aim is to shed light on an integrative DTx ecosystem framework that connects clinical evidence, AI architecture, and ethical governance across human and veterinary digital health contexts.

Clinical evidence of digital health technologies

Clinical evidence suggests the potential efficacy of DTx in managing chronic diseases. For instance, in a multicenter randomized trial assessing the HERB digital therapeutic system for hypertension, patients under 65 who were not on antihypertensive medications experienced significant reductions in 24-hour systolic blood pressure using a smartphone app-based intervention compared to lifestyle counselling alone [8]. Another trial (HERB-DH1) showed favorable trends toward improved home blood pressure control when behavioral change content was delivered via a smartphone application [9]. These studies demonstrate the potential of DTx to enhance adherence, improve self-care, and potentially delay the need for pharmacological treatment.

Beyond cardiovascular disease, DTx have demonstrated utility in mental health care, particularly through programs that integrate smartphone-based monitoring with coaching or structured feedback. In a randomized trial comparing web-based coaching versus access to digital resources alone for depression, patients in the coached group achieved superior symptom improvement, highlighting the role of human facilitation in maximizing the effectiveness of digital tools [10]. Furthermore, home-based digital interventions, such as Moving Through Glass, have been shown to improve balance and mobility in individuals with neurodegenerative diseases [11].

The scope of DTx includes vulnerable populations. Among solid organ transplant recipients, who face a high risk of vaccine-preventable infections, digital systems have been proposed to centralize immunization records and send automated vaccine reminders, potentially overcoming barriers like care fragmentation and provider miscommunication [12]. Similarly, in patients with chronic obstructive pulmonary disease (COPD), qualitative research identifies both opportunities and challenges for DHT adoption. Clinicians highlighted patient digital literacy, device data quality, and the lack of integration into clinical workflows as key barriers [13]. Despite promising outcomes, the implementation of DTx remains inconsistent, hindered by structural, regulatory, and behavioral obstacles. However, programs like DOORS (Digital Opportunities for Outcomes in Recovery Services), which offer digital literacy training to patients with severe mental illness, show how targeted interventions can close the "second digital divide" and promote equitable access to digital care tools [14].

Overall, the current evidence base for DTx and related DHTs remains heterogeneous. In addition, many trials rely on intermediate or surrogate endpoints (e.g., behavioral adherence metrics or short-term physiological changes), whereas evidence on long-term clinical outcomes, health-economic impact, and durability of benefit remains limited. This gap complicates comparisons with pharmacological or procedural interventions and partially explains the variability in regulatory and reimbursement decisions across jurisdictions. Randomized trials provide the strongest support in selected indications, such as hypertension [8] and structured mental-health interventions [10]. In contrast, many implementations are supported by smaller feasibility studies or qualitative evaluations that primarily inform acceptability and workflow integration rather than clinical effectiveness. Importantly, effect sizes, follow-up duration, and external validity vary substantially across studies, and the transferability of results is often constrained by population selection, digital literacy, and differences in care pathways. Therefore, clinical conclusions should be interpreted in light of study design and validation maturity, and future work should prioritize reproducible endpoints, longer follow-up periods, and pragmatic evaluation in routine care settings.

Wearable technologies and remote patient monitoring

Wearables and RPM enable longitudinal capture and real-time tracking of physiological and behavioral data and support scalable follow-up in chronic disease, while enhancing patient engagement. These tools range from photoplethysmography (PPG)-enabled wristbands to smartwatches and implantable devices that transmit continuous data to clinicians (Fig. 1).

In cardiovascular care, wearables have demonstrated clinical utility in various populations. Broers et al. [15] evaluated a lifestyle intervention supported by wearable tracking in patients with cardiovascular disease, showing that personalized feedback led to improved physical activity and behavioral change across multicenter cohorts in Spain and the Netherlands. Similarly, the CHIEF-HF trial utilized Fitbit smartwatches to monitor step counts and correlate them with patient-reported health status using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The study found a significant non-linear association between daily step count and both symptom severity and physical limitation scores, reinforcing the value of wearables in tracking heart failure progression [16].

Furthermore, wearables offer opportunities for early detection of clinical deterioration. Hochstadt et al. [17] demonstrated the feasibility of using smartphone-connected PPG to detect cardiac rhythm abnormalities, including atrial fibrillation, in ambulatory settings with high signal quality and accuracy. In a different context, Wu et al. [18] implemented an RPM system for COPD patients that integrated wearable sensors, air quality metrics, and mobile app data. Their system successfully predicted exacerbations using ML models, exemplifying the integration of environmental and biometric data for remote respiratory care.

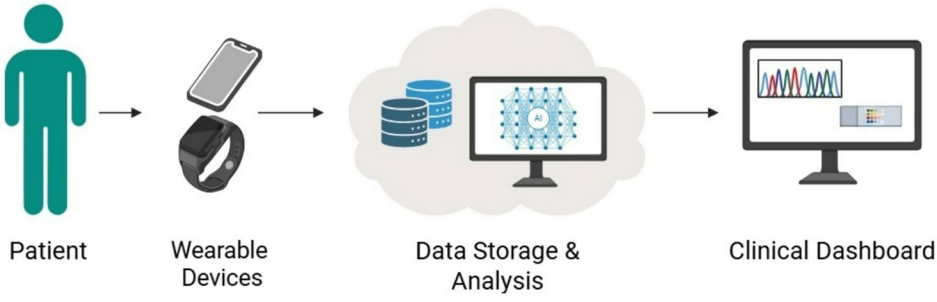

Fig. 1 End-to-end data pipeline for wearable-driven care. Physiological signals collected from a patient via wearable devices (e.g., smartwatch, smartphone) are transmitted to a cloud environment for storage and AI-based analysis. Processed insights are then visualized on a clinical dashboard to support decision-making

The application of wearables in older or frail populations is also advancing. Liu et al. [19] demonstrated that remote follow-up using smartwatches after transcatheter aortic valve replacement (TAVR) in elderly patients was both feasible and clinically valuable, enabling the early detection of complications and reducing unnecessary hospital visits. Complementarily, the REMOTE-CIED trial evaluated RPM in patients with heart failure and implantable defibrillators. The results indicated improved clinical outcomes and reduced burden of in-person follow-ups [20].

Due to their versatility and effectiveness in predicting glucose levels, systems for continuous glucose tracking are among the most widely used wearable medical devices. To avoid or at least reduce the risk of complications in diabetic people, continuous blood glucose monitoring [21] reports to the patient when it is essential to give an insulin injection. Accordingly, predictive algorithms should be capable of acquiring and processing data in real-time (with high sampling rate and fast transitions), producing fast responses with high accuracy for the relationship between both future glucose levels and prediction time. This process should guarantee a low computational weight (Fig. 2).

For this aim, the AutoRegressive Moving Average (ARMA) is one of the most implemented predictive algorithms. It is a mathematical model that utilizes past values of a time series, modulated by specific coefficients, to predict the future level of blood glucose, anticipating hyperglycemia and hypoglycemia events within a specified time window [22]. Investigations have demonstrated the capability of ARMA models to obtain data predictions with time-dependent root mean square errors (RMSEs) at 30, 45, and 60 min, respectively, of ~ 9.04, ~ 11.84, and ~ 14.82 mg/dL. However, these models are not generalizable for every situation and are strictly dependent on the specific subject characteristics; therefore, the hyperparameters should be trained and computed based on the individual patient's history data. This key limitation is particularly evident when a multiple comparison is performed between different ML techniques [23]. For example, a generalized ARMA model performed poorly compared to individual (i.e., patient-centered) ARMA models, especially when the input time series had nonlinear patterns or when a prediction for a timestamp higher than 30 min was required [24].

Despite these limitations, remote monitoring technologies in diabetes care have demonstrated tangible clinical benefits. A retrospective cohort study involving patients with type 1 diabetes revealed that a commercially available remote glucose monitoring platform facilitated more individualized care and helped identify those most in need of intervention [25]. Additionally, in the context of gestational diabetes, RPM was associated with improved maternal glycemic control and better neonatal outcomes compared to standard in-person care [26].

Furthermore, research focused on neurodegenerative diseases. In Parkinson's disease (PD), wearable sensors allow continuous monitoring of key physiological parameters, including movement, tremor, gait, balance, and sleep patterns [27, 28]. The data collected on motor and non-motor symptoms are analyzed using AI algorithms, enabling timely and precise therapeutic adjustments [29]. Moreover, these technologies provide valuable insights into disease progression, treatment efficacy, and quality of life [30].

Clinical utility depends not only on sensor accuracy but also on effective integration into clinical workflows, sustained patient adherence, and post-deployment monitoring to detect performance drift. The evidence supporting wearables and RPM spans proof-of-concept studies, observational cohorts, and pragmatic implementations; however, relatively few large trials have demonstrated a direct impact of device-driven interventions on clinically meaningful outcomes [13]. Moreover, a recurrent limitation is dataset shift related to device heterogeneity, signal quality, and context of use. Combined with missingness in real-world data streams, these issues can substantially degrade model performance outside development cohorts. Beyond these technical challenges,

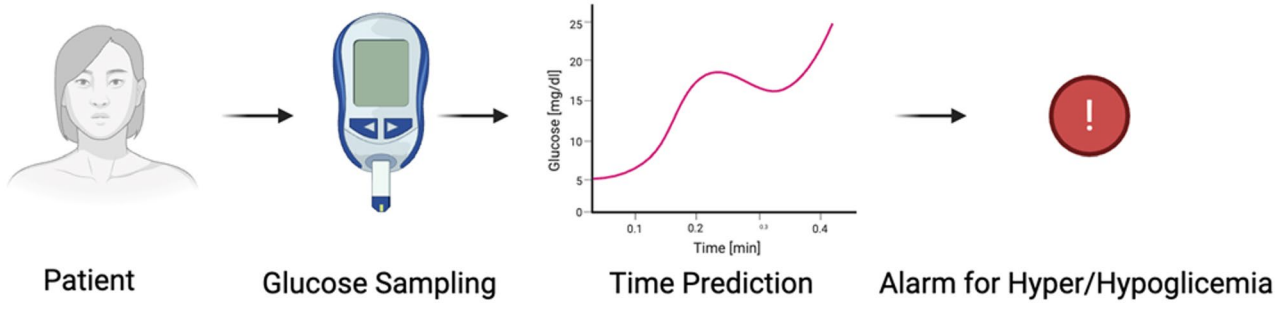

Fig. 2 Workflow of a predictive glucose-monitoring system. A patient performs capillary glucose sampling, and the measured value is used to feed a prediction model that forecasts glucose trends over time. When the model anticipates values crossing hyper- or hypoglycemic thresholds, an alert is triggered to warn the patient/clinician and prompt timely intervention

many wearable-based interventions struggle to translate generated insights into sustained clinical action. In several studies, outputs remain confined to dashboards without clearly defined escalation pathways or accountability mechanisms, increasing the risk of alert fatigue, clinician burden, and ambiguity in responsibility when automated signals are ignored or misinterpreted [13].

Artificial Intelligence-based applications

The integration of AI into wearable and portable medical technologies is reshaping how patient data is interpreted, enabling earlier detection, refined risk stratification, and personalized intervention across diverse clinical domains. These AI-powered devices process high-resolution physiological signals, often collected passively, and translate them into clinically actionable information.

One of the most prominent applications is cardiology. Dhingra et al. [31] developed an AI model capable of predicting new-onset heart failure using single-lead ECGs acquired from portable devices. The model was validated across large and diverse cohorts in the US, UK, and Brazil, demonstrating a 3- to 7-fold increase in heart failure risk among individuals with a positive AI screen, with superior performance compared to traditional clinical scores. Similarly, Lopez-Jimenez et al. [32] validated a cuffless, wearable blood pressure monitor powered by AI, which demonstrated robust accuracy across all hypertension categories.

The capacity of AI to facilitate early detection of critical events was explored by Beqari et al. [33], who applied a machine learning algorithm (NightSignal) to wearable-derived biometrics in patients recovering from cardiothoracic surgery. The algorithm identified 81% of complications up to two days before symptom onset, demonstrating the potential of AI in optimizing perioperative care.

In women's health, Luo et al. [34] validated machine learning models that predict ovulation and menstruation based on wrist skin temperature and heart rate recorded by a wearable device. The study reported an AUC of 0.869 for fertile window prediction, underlining how AI can support reproductive planning in both regular and irregular menstruators.

Moreover, AI is also being deployed in visual diagnostics. The WISDOM AI study by Rochon et al. [35] implemented a computer vision system to triage surgical wound images submitted via smartphones. The algorithm achieved a sensitivity of 89% in identifying wounds that required priority reviews, thereby helping to reduce the clinical burden while maintaining safety standards. Finally, a study by Shah et al. [36] introduced an AI system embedded in a consumer-grade smartwatch to detect pulseless electrical activity, suggesting the feasibility of population-scale arrest detection. Concerning the quality of evidence, AI applications range from internally validated models to early external validation and real-world feasibility demonstrations. Moreover, although some studies report strong discrimination metrics, overall, comparative interpretation requires attention to validation strategy (internal vs. external), calibration, and performance across clinically relevant subgroups. Importantly, high discrimination metrics alone do not guarantee clinical utility. Several AI models demonstrate performance degradation when deployed outside the development environment, particularly in the presence of dataset shift, evolving clinical practices, or differences in device characteristics. Consequently, claims of clinical readiness should be interpreted cautiously unless supported by prospective validation, calibration monitoring, and evidence of benefit within real-world care pathways (Table 1).

Within the proposed DTx ecosystem, these AI-based applications should be interpreted as algorithm-centric layers that act upon data streams generated by wearables and RPM systems, rather than as independent therapeutic interventions.

Artificial intelligence agents and digital twins

Within the DTx ecosystem, AI agents and digital twins represent two complementary but distinct architectural paradigms. AI agents primarily orchestrate decision-making processes, information triage, and task allocation across clinical workflows, whereas digital twins aim to enable near–real-time, individualized simulations of human physiology to support prediction, virtual testing, and personalization. Importantly, both approaches complement, rather than duplicate, earlier AI-enabled monitoring applications by operating at higher levels of abstraction and clinical integration. Additionally, they have distinct validation and governance requirements. Together, they enable personalized medicine by forecasting health outcomes and tailoring treatments based on a patient's unique biological and clinical data.

In artificial agents and multi-agent systems, a specific role is assigned to each agent. Consequently, researchers have utilized these systems to simulate the work dynamics present in medical teams, reproducing the procedures that occur during triage, for example, in the field of emergency medicine and clinical diagnosis. Thus, agents can act at various points in the clinical process, such as the preliminary evaluation of the patient, the establishment of a diagnosis, and the determination of the required treatments, along with the allocation of resources [37].

In this context, digital twins specifically aim to support individualized simulations of human physiology, supporting precision diagnostics, predictive modeling, and personalized treatment strategies. Therefore, they have

Table 1 Selected artificial Intelligence-based applications

AI Model	Aim	Performance	Data Source and Device	Limitations	Ref.
AI model on single-lead ECGs	HF risk prediction	Individuals with a positive AI screen had a 3–7× higher HF risk; outperformed conventional clinical scores	Data from portable devices (large cohorts)	Needs external calibration across devices; potential dataset shift	Dhingra LS et al. [31]
Cuff-less BP AI monitor	Continuous, non-invasive BP estimation	Internal validation showed accuracy across all hypertension classes	Wearable, cuff-less sensor with embedded AI algorithm	Lacked external validation	Lopez-Jimenez F et al. [32]
"NightSignal" ML	Early detection of postoperative complications	81% of complications up to 2 days before symptoms	Wearable biometric data in cardiothoracic surgery patients	Small pilot study (post-stop context)	Beqari J et al. [33]
ML model	Fertile-window prediction	AUC 0.869	Wrist skin temperature and HR (wearable)	Performance may vary in highly irregular cycles	Luo C et al. [34]
WISDOM AI CV tool	Triage of surgical wound images from patients	89% sensitivity for identifying wounds needing priority review	Smartphone photos uploaded by patients to a digital platform	Image quality variability	Rochon M et al. [35]
Smartwatch PEA detector (AI)	Detect pulseless electrical activity (cardiac arrest)	Feasibility demonstrated on a consumer smartwatch	Consumer-grade smartwatch sensors	False alarms are possible	Shah K et al. [36]

Abbreviations: AI, Artificial Intelligence; AUC, Area Under the Curve; BP, Blood Pressure; CV, Computer Vision; ECG, Electrocardiogram; HF, Heart Failure; HR, Heart Rate; ML, Machine Learning; PEA, Pulseless Electrical Activity

the potential to transform medicine into a proactive, data-driven discipline rooted in each patient's unique biological and clinical profile [38]. Another example of this is the Medical Decision-Making Agent (MDAgent). It is a system designed to process multimodal medical data by leveraging large language models (LLMs) to make decisions based on the complexity of a patient's case. MDAgent operates in four stages. First, it assesses the complexities of the clinical case. Second, it brings together an appropriate team, ranging from a single physician to a multidisciplinary group. Third, it conducts an analysis and synthesis of the response using advanced reasoning techniques. Lastly, an MDA consolidates all the inputs to provide a coherent and informed final response. These teams can work independently or in collaboration with each other [37].

A major contributor to this progress is the ongoing growth of comprehensive biochemical resources such as the Virtual Metabolic Human (VMH) in combination with AI-driven technologies. Given each update, these databases enrich DT models by providing deeper biological insights, thereby improving their precision and predictive capabilities.

The expanding VMH platform integrates a range of new biological data, including human metabolic reactions, genes, and enzymes, disease-specific metabolic profiles, host–microbiome metabolic interactions, and pharmacometabolic and drug-response pathways [39].

This influx of data supports high-resolution simulation of individual physiology. For example, a DT enhanced with newly annotated metabolic pathways can offer superior prediction of efficacy and potential side effects compared to static models, based on the following approach:

- A baseline DT is created using a patient's multi-omics data (e.g., genomic and metabolomic profiles) aligned with the VMH framework.
- Computational models predict physiological responses to various conditions such as medications, diets, or diseases.
- Simulation outputs are compared with observed clinical outcomes to assess accuracy.
- Based on discrepancies, the DT is refined, and insights feed back into knowledge bases like VMH, forming a self-improving feedback loop.

Due to robust VMH integration, DTs enable virtual trials to identify which patient subpopulations may benefit from—or be harmed by—specific treatments, facilitating more accurate dosing. Modeling disease trajectories based on individual metabolic maps enhances early detection and risk assessment, particularly for complex conditions such as metabolic syndrome or cancer. Ultimately, predicting personal responses to interventions—ranging from dietary adjustments to probiotics—enables the development of deeply personalized treatment and prevention strategies [40].

Moreover, starting from diagnostic imaging with AI, it is possible to generate DTs that have a wide range of applications. One example is the Lung-DT framework, which combines AI and Internet of Things (IoT) data to classify and monitor lung diseases from real-time chest X-rays [41]. An application in the vascular field is CardioVision. This framework combines diagnostic imaging with a segmentation model to create DTs of the aorta, aortic valve, and associated calcifications, from which morphological measurements can be obtained and

hemodynamic modeling can be supported, thus offering innovative tools to assist in personalized therapeutic decision-making. This approach also enables the simulation of TAVR procedures and the evaluation of devices [42].

Through ongoing feedback between knowledge base expansion and model refinement, DTs are evolving into increasingly sophisticated virtual surrogates. This dynamic interplay is steering medicine toward a future where healthcare is not only personalized but also anticipatory and highly adaptive to individual biology.

Application of DHT in animals: the one digital health framework

Within a One Digital Health perspective, veterinary and human DHT ecosystems should be viewed as interconnected layers of a shared digital infrastructure rather than parallel, unrelated applications. Cross-species data streams (e.g., activity, physiology, geospatial exposure, and environmental context) can inform shared surveillance and risk prediction, particularly for zoonotic threats and climate-sensitive conditions, while also enabling translational insights into behavior, stress, mobility, and chronic disease trajectories. To realize these synergies, interoperable data standards, robust governance, and bias-aware model development are required across both human and veterinary settings.

Digital monitoring technologies have become increasingly accessible, and the global pet wearable market continues to grow. These devices enable owners and veterinarians to monitor their animals' health. Moreover, they can be used for unique identification, tracking, and monitoring their behavior and developmental activities continuously. Pet-specific wearables range from smart harness devices fastened around the pet's body, which are integrated with sensors to monitor body language, posture, sound, body temperature, and heart rate, to smart collars that utilize Global Positioning System (GPS). New technology and products are being created each year [43]. Wearable sensors have countless applications in dairy and beef cattle, with garment-like devices being the most popular among farmers. Neck-mounted accelerometers were used in the studies to monitor feeding and rumination behaviors, and the feeding behavior was accurately assessed [44]. Wearable sensors have significantly enhanced the tracking and analysis of wildlife migration, not only for mammals but also for birds and marine mammals [45].

The advantages of using these technologies are very similar to those of human medicine, including remote monitoring of vital signs. Since pets and owners do not need to travel to send data to a veterinarian, there is improved accessibility of care, facilitating tele-triage, monitoring animal health in real time, collecting data for research, etc. Additionally, dogs and cats may behave differently in a veterinary hospital compared to their at-home settings, and other animals, such as wild ones, are not accustomed to the presence of humans [43]. These devices can be used to monitor pain or movement after surgery, or to track respiratory rate, heart rate, and pulse oximetry in cases of chronic disease. For example, working/police dogs can be constantly monitored to avoid hyperthermia when they are under stress and performing very physically demanding jobs [43].

Other technologies include infrared thermography, which can be used in cattle to detect mastitis or diagnose lameness, in horses to assess musculoskeletal injuries, and in dogs and cats to evaluate osteoarthritis or neoplasia [41].

In veterinary medicine, the problems associated with applying these technologies include species difference, because the research is not equally distributed across animal types, with pets and major farm animals receiving more attention than exotic and wild species; environmental sensitivity; cost and complexities of some devices; ethical considerations for pets, farm animals, and wild animals; and finally training data limitation as veterinary applications often have limited data availability unlike human massive data sets [43]. A key strategic evolution is the transition from One Health to a One Digital Health framework, becoming a real-time, interconnected system capable of integrating data derived from health information of multiple species and environmental areas. In this way, the spread of particular diseases could be more predictable, considering the movements of animals and humans, as well as the habitat preference of the pathogen [43, 44].

Notably, the same barriers emphasized in human digital medicine, such as dataset imbalance, under-representation, interoperability constraints, privacy/ownership concerns, and post-deployment reliability, also apply to veterinary applications, often amplified by smaller datasets and species heterogeneity. For this reason, One Digital Health requires harmonized governance and validation strategies spanning human and animal data.

Data bias and ethical implications

The present topic raises significant concerns about data bias and ethical implications. For example, Yfantidou et al. [46] reported that wearable-based systems disproportionately under-represent individuals with chronic conditions (such as diabetes or hypertension) and women, with such biases further amplified in machine learning models. In a systematic review, Gianfrancesco et al. [47] confirmed that ML algorithms trained on imbalanced datasets routinely underperform for minorities, with downstream effects on the accuracy of digital twin applications as confirmed by Norori et al. [48].

Regarding social and gender bias, Weinberger et al. [49] emphasized that most DTs fail to incorporate gender-sensitive and socioeconomic variables, thereby reinforcing biased clinical predictions and reducing model trust for underserved groups. Furthermore, it has been emphasized that health data systems, including wearables, often default to male-centric models, which can result in poor sensitivity to female-specific symptoms and patterns, ultimately perpetuating clinical misdiagnosis and unequal care [50].

Additionally, pediatric applications face unique challenges, as reported by Drummond et al. [51]. The authors highlighted that limited historical data, difficulties obtaining consent, and the need to preserve children's autonomy all contribute to data quality concerns and ethical complexity in digital twin systems for chronic disease management. Finally, broader socio-ethical assessments, including interviews with industry, policy, and civil society stakeholders, indicate persistent risks related to data ownership, privacy, inequality, and disruption of existing care structures in healthcare DT implementations [52].

To address these issues, mitigation strategies are increasingly being proposed and evaluated. Regulatory frameworks, such as the European Union's General Data Protection Regulation (GDPR) and the FDA's Digital Health Innovation Action Plan, have established standards for transparency, privacy, and user consent, explicitly requiring explainability and audit trails in medical AI systems. Algorithmic transparency is also being promoted, with interpretability methods like SHAP and LIME gaining traction to help clinicians and patients understand model predictions and identify potential biases, as outlined by Amann et al. [53]. Moreover, Herzog et al. [54] proposed that building trustworthy medical AI requires shifting from isolated technical fixes to a holistic, "ecosystem" approach, where adaptive governance structures, embedded ethical principles, and ongoing impact assessments foster justified trust among all stakeholders. Additionally, Boardman [55] argued for the formalization of "ethical analytics" as a new, practically oriented sub-discipline within data science, insisting that ethics must be foundational and interwoven into every stage of AI system development. Finally, Norori et al. [48] call for an "open science" approach focused on inclusivity and transparency, recommending participant-centered development, responsible and privacy-preserving data sharing, and the use of inclusive data standards and interoperable formats. Sharing code and algorithms, generating synthetic data to augment underrepresented groups, and employing participatory science approaches to directly involve vulnerable communities are further proposed.

Importantly, ethical and technical mitigation strategies entail substantial practical trade-offs. Interpretability methods do not necessarily capture underlying causal mechanisms and may be misused as "assurance signals" when models remain poorly calibrated or fragile under dataset shift [53, 55]. Likewise, transparency requirements can be difficult to operationalize in commercial DTx settings, where proprietary models, closed datasets, and contractual constraints limit independent auditing and external scrutiny [54]. Privacy protection represents an additional challenge for high-dimensional multimodal data, as re-identification risks and linkage attacks may persist even after de-identification, particularly when longitudinal and cross-domain data sources are combined [48, 52].

Notably, although ethical and regulatory frameworks provide essential guidance, their real-world effectiveness depends on how they are implemented within deployed systems. Compliance with transparency or explainability requirements does not automatically translate into safer or fairer clinical use. Post-deployment evaluations of AI-enabled diagnostic and monitoring tools have documented performance degradation, subgroup-specific errors, and unanticipated workflow disruptions despite prior regulatory clearance or internal validation [56]. In such cases, explainability techniques such as SHAP or LIME were often insufficient to reveal clinically meaningful failure modes, particularly when models were affected by dataset shift or context-dependent biases [48, 53]. This limitation is consistent with mechanism-level analyses of shortcut learning and spurious correlations in medical AI, where models achieve high apparent performance by exploiting confounders rather than clinically meaningful signals. Recent work on the "Clever Hans" phenomenon highlights how such failure modes may remain undetected without targeted evaluation strategies and stress-testing across contexts [57].

These observations highlight the importance of continuous post-market surveillance, explicit accountability pathways, and clinician-in-the-loop oversight to detect bias, manage uncertainty, and recalibrate models over time [54]. From this perspective, ethical governance should not be conceived as a static compliance exercise, but rather as a dynamic, lifecycle-oriented process embedded within routine clinical practice. Collectively, these considerations reinforce the need for ongoing post-deployment evaluation, subgroup auditing, and governance structures capable of defining accountability across developers, providers, and health systems [54].

Future directions and recommendations

Building on the ethical and governance challenges identified across clinical, AI-driven, and One Digital Health applications, the following recommendations aim to strengthen trustworthy and equitable deployment of DTx and DHTs. First, the field must first commit to inclusive,

Fig. 3 Conceptual representation of the digital therapeutics (DTx) ecosystem proposed in this review. The framework illustrates how clinical evidence generation, AI-enabled architectures (including wearables, AI agents, and digital twins), and ethical and governance mechanisms interact across the lifecycle of digital therapeutics. Specifically, six strategic pillars include inclusive datasets, interoperability and privacy, human-centered design, hybrid evaluation, post-market surveillance, and ethical governance. Each element is equally critical and collectively underpins a trustworthy, effective DTx process. The model is applied across human and veterinary contexts within a One Digital Health perspective and serves as a unifying schema linking the clinical, technical, and ethical dimensions discussed throughout the manuscript

representative datasets that encompass gender, life course (including pediatrics), ethnicity, and socioeconomic strata. This process is mandatory for reducing algorithmic bias and improving generalizability [7]. Additionally, robust interoperability and open standards (e.g., FHIR, USCDI) are crucial for privacy-preserving data exchange across institutions and sectors [56]. Sustainable innovation requires human-centered, participatory design that engages patients and clinicians throughout ideation, prototyping, and deployment to optimize usability, adherence, and trust [58]. Fourth, evidence generation should migrate toward hybrid evaluation frameworks that blend randomized controlled trials with real-world evidence, adaptive designs, and formal cost-effectiveness analysis to accelerate iteration while satisfying regulators and payers [59]. Continuous post-market surveillance, combining automated drift detection with clinician-reported outcomes, should become mandatory to assure ongoing safety and effectiveness of AI-driven DTx in diverse real-world settings [60]. Finally, end-to-end transparent governance and "ethical analytics", embedding explainability, accountability, and public oversight from development through decommissioning, are essential for building a trustworthy biomedical-AI ecosystem [61] (Fig. 3).

Integration of digital health and AI in infection-related oncology

Digital health ecosystems, combining DTx-enabled pathways, wearable/RPM data capture, AI-based analytics, and agentic decision support and digital twins, can be operationalized in a clinically complex domain. In this perspective, infection-related malignancies provide a clear scenario in which multimodal data integration (clinical, imaging, molecular/virological, and patient-generated data) and robust governance (privacy, fairness, and cross-site interoperability) are simultaneously required, thereby connecting this oncology focus to the broader themes of the review. Therefore, digital and intelligent technologies can extend their transformative potential beyond general oncology into malignancies driven by infectious agents. Specifically, the analytical and decision-support frameworks can be adapted to the prevention, diagnosis, and clinical management of cancers associated with viral or bacterial infections, such as HPV-related cervical and head-and-neck carcinomas, HBV/HCV-related hepatocellular carcinoma, Epstein–Barr virus-associated lymphomas and nasopharyngeal carcinoma, and Helicobacter pylori-related gastric cancer [62–71]. These neoplasms represent a unique intersection of oncogenic processes and chronic infection, where integrating multimodal data, from histopathology, immunohistochemistry, and molecular profiling to viral load monitoring, immunological status, and patient-generated health information, can offer a deeper understanding of the infection-to-cancer continuum and help to identify actionable biomarkers for early intervention and secondary prevention [65, 66].

Additionally, digital platforms supported by predictive modelling can facilitate longitudinal surveillance of patients at risk, improve triage accuracy within screening programs, and optimize resource allocation in regions with limited laboratory or imaging capacity [65]. In low- and middle-income settings, where infection-associated cancers represent a substantial disease burden, these tools may play a critical role in strengthening early-detection strategies and in supporting decentralized models of care. In parallel, explainable computational models and interoperable health-data infrastructures enable transparent and reproducible assessments of infection-related oncogenic mechanisms, while improving cross-institutional collaboration and real-world data sharing [62, 63].

Moreover, the integration of digital health solutions with molecular pathology and viral genomics holds promise for refining prognostic stratification and treatment personalization. Predictive algorithms can, for instance, correlate viral genomic signatures or integration

patterns with immune-microenvironmental features and patient outcomes, contributing to a more precise delineation of therapeutic pathways. However, such progress must be accompanied by robust ethical and governance frameworks that ensure algorithmic transparency, equitable data representation, and privacy protection [64–66]. Particular attention should be given to mitigating algorithmic bias, safeguarding sensitive virological and genomic data, and validating predictive models in diverse populations before clinical deployment [67, 68].

Ultimately, this convergence of digital innovation, protocol optimization, and infection-related oncology defines a translational paradigm that bridges molecular insight, data-driven reasoning, and clinical decision-making [66–78]. Following the crucial step of embedding fairness, reproducibility, and patient-centric governance within the development cycle of digital and intelligent technologies, it will be possible to accelerate the shift toward a more inclusive and ethically sustainable precision oncology landscape.

Conclusions

Digital health technologies, including regulated DTx, AI-enabled wearables, and emerging agentic and digital-twin paradigms, are reshaping prevention, monitoring, and treatment across clinical domains. However, translation into routine care depends on more than technical performance. This step requires evidence that is both rigorous and representative, interoperability that enables secure data exchange, and governance for ensuring accountability, fairness, and safety over time. Therefore, to fully realize the potential of these technologies, a robust ecosystem should include six pillars that jointly determine clinical trustworthiness: inclusive datasets, interoperable infrastructures, human-centered design, hybrid evaluation strategies combining trials with real-world evidence, continuous post-market surveillance to detect drift and failure modes, and transparent ethical governance. Within this framework, One Digital Health offers an operational rationale to connect human, animal, and environmental data streams in ways that improve surveillance and prediction while demanding harmonized standards and safeguards. Future progress will be determined by the field's ability to align innovation with reproducible evaluation and enforceable governance, ensuring that benefits extend to underrepresented and vulnerable populations rather than amplifying existing disparities.

Abbreviations

DHTs	Digital Health Technologies
DTx	Digital Therapeutics
AI	Artificial Intelligence
ML	Machine Learning
AUC	Area Under the Curve
CAST	Center for Advanced Studies and Technology
CIED	Cardioverter-Implantable Electronic Device
COPD	Chronic Obstructive Pulmonary Disease
DOORS	Digital Opportunities for Outcomes in Recovery Services
DTs	Digital Twins
ECG	Electrocardiogram
ARMA	AutoRegressive Moving Average
RMSE	Root Mean Square Error
MDAgent	Medical Decision-Making Agent
LLMs	Large Language Models
IoT	Internet of Things
TAVR	Transcatheter Aortic Valve Replacement
FDA	US Food and Drug Administration
GPS	Global Positioning System
FHIR	Fast Healthcare Interoperability Resources
GDPR	General Data Protection Regulation
HERB-DH1	Hypertension digital therapeutic trial HERB-DH1
KCCQ	Kansas City Cardiomyopathy Questionnaire
LIME	Local Interpretable Model-agnostic Explanations
PPG	Photoplethysmography
RPM	Remote Patient Monitoring
SaMD	Software as a Medical Device
SHAP	SHapley Additive exPlanations
USCDI	United States Core Data for Interoperability
VMH	Virtual Metabolic Human

Author contributions

Conceptualization: Marco Cascella, Maria Teresa Avella; Methodology:Marco Cascella, Cesare Pane, Marcello Di Pumpo, Enrico Sebastiani, Martino Bussa, Alessio Tagliaferri, Barbara Brunetti, Pierluigi Meloni, Elisa Bianchini, Paolo Graziani, Federico Faustini, Guido D'Onofrio, David Manetta, Cristina Angela Catania, Chiara Jole Fornari, Andrea Scarda, Federica Smanio, Cristina Imbesi, Maria Teresa Avella, Roberta Fusco, Vincenza Granata; Formal analysis: Roberta Fusco; Supervision: Marco Cascella, Roberta Fusco, Vincenza Granata; Funding acquisition: Marco Cascella; Resources: Marco Cascella; Writing - original draft Writing - review & editing: Marco Cascella, Cesare Pane, Marcello Di Pumpo, Enrico Sebastiani, Martino Bussa, Alessio Tagliaferri, Barbara Brunetti, Pierluigi Meloni, Elisa Bianchini, Paolo Graziani, Federico Faustini, Guido D'Onofrio, David Manetta, Cristina Angela Catania, Chiara Jole Fornari, Andrea Scarda, Federica Smanio, Cristina Imbesi, Maria Teresa Avella, Roberta Fusco, Vincenza Granata

Clinical trial number : not applicable.

Funding

This research received no external funding.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval

Not applicable.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, 84081 Baronissi, Salerno, Italy
[2]Department of Medicine and Ageing Sciences, Center for Advanced Studies and Technology CAST. "G. d'Annunzio" University of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy
[3]Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, 20123 Rome, Italy
[4]Italian Society for Artificial Intelligence in Medicine (SIIAM), Rome, Italy

[5]Neuromuscular and Rare Disorders Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU, via Commenda 12, 20122 Milan, Italy
[6]School of Medicine and Surgery, University of Milano-Bicocca, 20126 Milan, Italy
[7]Independent Researcher, Naples, Italy
[8]Department of Veterinary Medical Sciences, University of Bologna, 40064 Bologna, Italy
[9]Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy
[10]Azienda Sanitaria Locale di Pescara, Via Renato Paolini 47, 65124 Pescara, Italy
[11]SynbrAIn., Milan , Italy
[12]Independent Researcher, Rome, Italy
[13]Istituto Nazionale Previdenza Sociale, Centro Medico Legale di Lucca, Via Barsanti e Matteucci 173, 55100 Lucca, Italy
[14]Radiology Division, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Via Semmola, 80131 Naples, Italy

Received: 7 November 2025 / Accepted: 5 February 2026
Published online: 19 February 2026

References

1. von Huben A, Howell M, Howard K, Carrello J, Norris S. Health technology assessment for digital technologies that manage chronic disease: a systematic review. Int J Technol Assess Health Care. 2021;37(1):e66. https://doi.org/10.1017/S0266462321000362.
2. Yan K, Balijepalli C, Druyts E. The impact of digital therapeutics on current health technology assessment frameworks. Front Digit Health. 2021;3:667016. https://doi.org/10.3389/fdgth.2021.667016.
3. Hong JS, Wasden C, Han DH. Introduction of digital therapeutics. Comput Methods Programs Biomed. 2021;209:106319. https://doi.org/10.1016/j.cmpb.2021.106319.
4. Yeung AWK, Torkamani A, Butte AJ, et al. The promise of digital healthcare technologies. Front Public Health. 2023;11:1196596. https://doi.org/10.3389/fpubh.2023.1196596.
5. Currie G, Hewis J, Hawk E, Rohren E. Gender and ethnicity bias of Text-to-Image generative artificial intelligence in medical Imaging, part 2: analysis of DALL-E 3. J Nucl Med Technol. 2025;53(2):162–8. https://doi.org/10.2967/jnmt.124.268359.
6. Lego VD. Uncovering the gender health data gap. Cad Saude Publica. 2023;39(7):e00065423. https://doi.org/10.1590/0102-311XEN065423.
7. Cirllo D, Catuara-Solarz S, Morey C, et al. Sex and gender differences and biases in artificial intelligence for biomedicine and healthcare. NPJ Digit Med. 2020;3:81. https://doi.org/10.1038/s41746-020-0288-5.
8. Kario K, Nomura A, Kato A, et al. Digital therapeutics for essential hypertension using a smartphone application: A randomized, open-label, multicenter pilot study. J Clin Hypertens (Greenwich). 2021;23(5):923–34. https://doi.org/10.1111/jch.14191.
9. Kario K, Nomura A, Harada N, et al. A multicenter clinical trial to assess the efficacy of the digital therapeutics for essential hypertension: rationale and design of the HERB-DH1 trial. J Clin Hypertens (Greenwich). 2020;22(9):1713–22. https://doi.org/10.1111/jch.13993.
10. MacLean S, Corsi DJ, Litchfield S, et al. Coach-Facilitated Web-Based therapy compared with information about Web-Based resources in patients referred to secondary mental health care for depression: randomized controlled trial. J Med Internet Res. 2020;22(6):e15001. https://doi.org/10.2196/15001.
11. Tunur T, DeBlois A, Yates-Horton E, Rickford K, Columna LA. Augmented reality-based dance intervention for individuals with parkinson's disease: A pilot study. Disabil Health J. 2020;13(2):100848. https://doi.org/10.1016/j.dhjo.2019.100848.
12. Feldman AG, Atkinson K, Wilson K, Kumar D. Under immunization of the solid organ transplant population: an urgent problem with potential digital health solutions. Am J Transpl. 2020;20(1):34–9. https://doi.org/10.1111/ajt.15605.
13. Slevin P, Kessie T, Cullen J, Butler MW, Donnelly SC, Caulfield B. Exploring the barriers and facilitators for the use of digital health technologies for the management of COPD: a qualitative study of clinician perceptions. QJM. 2020;113(3):163–72. https://doi.org/10.1093/qjmed/hcz241.
14. Hoffman L, Wisniewski H, Hays R, et al. Digital opportunities for outcomes in recovery services (DOORS): A pragmatic Hands-On group approach toward increasing digital health and smartphone Competencies, Autonomy, Relatedness, and alliance for those with serious mental illness. J Psychiatr Pract. 2020;26(2):80–8. https://doi.org/10.1097/PRA.0000000000000450.
15. Broers ER, Gavidia G, Wetzels M, et al. Usefulness of a lifestyle intervention in patients with cardiovascular disease. Am J Cardiol. 2020;125(3):370–5. https://doi.org/10.1016/j.amjcard.2019.10.041.
16. Golbus JR, Gosch K, Birmingham MC, et al. Association between wearable device measured activity and Patient-Reported outcomes for heart failure. JACC Heart Fail. 2023;11(11):1521–30. https://doi.org/10.1016/j.jchf.2023.05.033.
17. Hochstadt A, Havakuk O, Chorin E, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. J Electrocardiol. 2020;60:138–41. https://doi.org/10.1016/j.jelectrocard.2020.04.017.
18. Wu CT, Li GH, Huang CT, et al. Acute exacerbation of a chronic obstructive pulmonary disease prediction system using wearable device Data, machine Learning, and deep learning: development and cohort study. JMIR Mhealth Uhealth. 2021;9(5):e22591. https://doi.org/10.2196/22591.
19. Liu X, Fan J, Guo Y, et al. Wearable smartwatch facilitated remote health management for patients undergoing transcatheter aortic valve replacement. J Am Heart Assoc. 2022;11(7):e023219. https://doi.org/10.1161/JAHA.121.023219.
20. Chiu CSL, Timmermans I, Versteeg H, et al. Effect of remote monitoring on clinical outcomes in European heart failure patients with an implantable cardioverter-defibrillator: secondary results of the REMOTE-CIED randomized trial. Europace. 2022;24(2):256–67. https://doi.org/10.1093/europace/euab221.
21. Jancev M, Vissers TACM, Visseren FLJ, van Bon AC, Serné EH, DeVries JH, de Valk HW, van Sloten TT. Continuous glucose monitoring in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetologia. 2024;67(5):798–810. https://doi.org/10.1007/s00125-024-06107-6.
22. Reifman J, Rajaraman S, Gribok A, Ward WK. Predictive monitoring for improved management of glucose levels. J Diabetes Sci Technol. 2007;1(4):478–86. https://doi.org/10.1177/193229680700100405.
23. Eren-Oruklu M, Ci-nar A, Quinn L, Smith D. Estimation of future glucose concentrations with subject-specific recursive linear models. Diabetes Technol Ther. 2009;11(4):243–53. https://doi.org/10.1089/dia.2008.0065.
24. Goel S, Sharma S. A comparative study of time series models for blood glucose prediction. In: Proceedings of the Third International Conference on Information Management and Machine Intelligence: ICIMMI 2021. Singapore: Springer Nature Singapore; 2021. p. 81–91.
25. Crossen SS, Romero CC, Lewis C, Glaser NS. Remote glucose monitoring is feasible for patients and providers using a commercially available population health platform. Front Endocrinol (Lausanne). 2023;14:1063290. https://doi.org/10.3389/fendo.2023.1063290.
26. Kantorowska A, Cohen K, Oberlander M, et al. Remote patient monitoring for management of diabetes mellitus in pregnancy is associated with improved maternal and neonatal outcomes. Am J Obstet Gynecol. 2023;228(6):726. https://doi.org/10.1016/j.ajog.2023.02.015.
27. Lukšys D, Jonaitis G, Griškevičius J. Quantitative analysis of parkinsonian tremor in a clinical setting using inertial measurement units. Parkinsons Dis. 2018;2018:1683831. https://doi.org/10.1155/2018/1683831.
28. Bougea A. Application of wearable sensors in parkinson's disease: state of the Art. J Sens Actuator Networks. 2025;14(2):23. https://doi.org/10.3390/jsan14020023.
29. Kehnemouyi YM, Coleman TP, Tass PA. Emerging wearable technologies for multisystem monitoring and treatment of parkinson's disease: a narrative review. Front Netw Physiol. 2024;4:1354211. https://doi.org/10.3389/fnetp.2024.1354211.
30. Bougea A, Angelopoulou E. Non-Motor disorders in Parkinson disease and other parkinsonian syndromes. Med (Kaunas). 2024;60(2):309. https://doi.org/10.3390/medicina60020309.
31. Dhingra LS, Aminorroaya A, Pedroso AF, et al. Artificial Intelligence-Enabled prediction of heart failure risk from Single-Lead electrocardiograms. JAMA Cardiol. 2025;10(6):574–84. https://doi.org/10.1001/jamacardio.2025.0492.
32. Lopez-Jimenez F, Deshmukh A, Bisognano J, et al. Development and internal validation of an AI-Enabled Cuff-less, Non-invasive continuous blood pressure monitor across all classes of hypertension. J Cardiovasc Transl Res. 2025;18(2):280–90. https://doi.org/10.1007/s12265-024-10589-5.
33. Beqari J, Powell JR, Hurd J, et al. A pilot study using Machine-learning algorithms and wearable technology for the early detection of postoperative complications after cardiothoracic surgery. Ann Surg. 2025;281(3):514–21. https://doi.org/10.1097/SLA.0000000000006263.

34. Luo C, Su YF, Ren YY, et al. Prediction of the fertile window and menstruation with a wearable device via machine-learning algorithms. Reprod Biomed Online. 2025;51(1):104795. https://doi.org/10.1016/j.rbmo.2025.104795.
35. Rochon M, Tanner J, Jurkiewicz J, et al. Wound imaging software and digital platform to assist review of surgical wounds using patient smartphones: the development and evaluation of artificial intelligence (WISDOM AI study). PLoS ONE. 2024;19(12):e0315384. https://doi.org/10.1371/journal.pone.0315384.
36. Shah K, Wang A, Chen Y, et al. Automated loss of pulse detection on a consumer smartwatch. Nature. 2025;642(8066):174–81. https://doi.org/10.1038/s41586-025-08810-9.
37. Kim Y, Park C, Jeong H, Grau-Vilchez C, Chan Y, Xu X, McDuff D, Lee H, Ghassemi M, Breazeal C, Park HW. A demonstration of adaptive collaboration of large language models for medical decision-making. arXiv. 2024 Nov 1;arXiv:2411.00248. https://doi.org/10.48550/arXiv.2411.00248.
38. Böttcher L, Fonseca LL, Laubenbacher RC. Control of medical digital twins with artificial neural networks. Philos Trans Math Phys Eng Sci. 2025;383(2292):20240228. https://doi.org/10.1098/rsta.2024.0228.
39. Kimpton LM, Paun LM, Colebank MJ, Volodina V. Challenges and opportunities in uncertainty quantification for healthcare and biological systems. Philos Trans Math Phys Eng Sci. 2025;383(2292):20240232. https://doi.org/10.1098/rsta.2024.0232.
40. Ginsburg GS, Phillips KA. Precision medicine: from science to value. Health Aff (Millwood). 2018;37(5):694–701. https://doi.org/10.1377/hlthaff.2017.1624.
41. Avanzato R, Beritelli F, Lombardo A, Ricci C. Lung-DT: an AI-based digital twin framework for monitoring and diagnosing chest health. Sens (Basel) Febr 1. 2024;24(3):958. https://doi.org/10.3390/s24030958.
42. Rouhollahi A, Willi JN, Haltmeier S, Mehrtash A, Straughan R, Javadikasgari H, Brown J, Itoh A, de la Cruz KI, Aikawa E, Edelman ER, Nezami FR. CardioVision: A fully automated deep learning package for medical image segmentation and reconstruction generating digital twins for patients with aortic stenosis. Comput Med Imaging Graph. 2023;109:102289. https://doi.org/10.1016/j.compmedimag.2023.102289. Epub 2023 Aug 19.
43. Mitek A, Jones D, Newell A, Vitale S. Wearable devices in veterinary health care. Vet Clin North Am Small Anim Pract. 2022;52(5):1087–98. https://doi.org/10.1016/j.cvsm.2022.05.001.
44. Zhao X, Tanaka R, Mandour AS, Shimada K, Hamabe L. Remote vital sensing in clinical veterinary medicine: A comprehensive review of recent Advances, Accomplishments, Challenges, and future perspectives. Anim (Basel). 2025;15(7):1033. https://doi.org/10.3390/ani15071033.
45. Kays R, Crofoot MC, Jetz W, Wikelski M. ECOLOGY. Terrestrial animal track-ing as an eye on life and planet. Science. 2015;348(6240):aaa2478. https://doi.org/10.1126/science.aaa2478].
46. Yfantidou S, Sermpezis P, Vakali A, Baeza-Yates R. Uncovering bias in personal informatics. Proc ACM Interact Mob Wearable Ubiquitous Technol. 2023;7(3):1–30.
47. Gianfrancesco MA, Tamang S, Yazdany J, Schmajuk G. Potential biases in machine learning algorithms using electronic health record data. JAMA Intern Med. 2018;178(11):1544–7. https://doi.org/10.1001/jamainternmed.2018.3763.
48. Norori N, Hu Q, Aellen FM, Faraci FD, Tzovara A. Addressing bias in big data and AI for health care: A call for open science. Patterns (N Y). 2021;2(10):100347. https://doi.org/10.1016/j.patter.2021.100347.
49. Weinberger N, Hery D, Mahr D, et al. Beyond the gender data gap: co-creating equitable digital patient twins. Front Digit Health. 2025;7:1584415. https://doi.org/10.3389/fdgth.2025.1584415.
50. Baskett F, Books. Invisible women: exposing data bias in a world designed for men: Mind the gap. Br J Gen Pract. 2020;70(694):250. https://doi.org/10.3399/bjgp20X709745.
51. Drummond D, Coulet A, Technical. Ethical, Legal, and societal challenges with digital twin systems for the management of chronic diseases in children and young people. J Med Internet Res. 2022;24(10):e39698. https://doi.org/10.2196/39698.
52. Popa EO, van Hilten M, Oosterkamp E, et al. The use of digital twins in healthcare: socio-ethical benefits and socio-ethical risks. Life Sci Soc Policy. 2021;17:6. https://doi.org/10.1186/s40504-021-00113-x.
53. Amann J, Vetter D, Blomberg SN, et al. To explain or not to explain?-Artificial intelligence explainability in clinical decision support systems. PLOS Digit Health. 2022;1(2):e0000016. https://doi.org/10.1371/journal.pdig.0000016.
54. Herzog C, Wagner B, Lütge C, Jongsma KR. Towards trustworthy medical AI ecosystems – a proposal for supporting responsible innovation practices in AI-based medical innovation. AI Soc. 2025;40:2119–39. https://doi.org/10.1007/s00146-024-02082-z.
55. Boardman J. A new kind of data science: the need for ethical analytics. 2022. Published and grey literature from PhD candidates. 33. https://digitalcommons.kennesaw.edu/dataphdgreylit/33.
56. Canali S, Schiaffonati V, Aliverti A. Challenges and recommendations for wearable devices in digital health: data quality, interoperability, health equity, fairness. PLOS Digit Health. 2022;1(10):e0000104. https://doi.org/10.1371/journal.pdig.0000104.
57. Vásquez-Venegas C, Wu C, Sundar S, Prôa R, Beloy FJ, Medina JR, McNichol M, Parvataneni K, Kurtzman N, Mirshawka F, Aguirre-Jerez M, Ebner DK, Celi LA. Detecting and mitigating the Clever Hans effect in medical imaging: A scoping review. J Imaging Inf Med. 2025;38(4):2563–79. https://doi.org/10.1007/s10278-024-01335-z.
58. Velez FF, Luderer HF, Gerwien R, Parcher B, Mezzio D, Malone DC. Evaluation of the cost-utility of a prescription digital therapeutic for the treatment of opioid use disorder. Postgrad Med. 2021;133(4):421–7. https://doi.org/10.1080/00325481.2021.1884471.
59. Huh KY, Oh J, Lee S, Yu KS. Clinical evaluation of digital therapeutics: present and future. Healthc Inf Res. 2022;28(3):188–97. https://doi.org/10.4258/hir.2022.28.3.188.
60. Thomas L, Hyde C, Mullarkey D, Greenhalgh J, Kalsi D, Ko J. Real-world post-deployment performance of a novel machine learning-based digital health technology for skin lesion assessment and suggestions for post-market surveillance. Front Med (Lausanne). 2023;10:1264846. https://doi.org/10.3389/fmed.2023.1264846.
61. Sankar BS, Gilliland D, Rincon J, et al. Building an ethical and trustworthy biomedical AI ecosystem for the translational and clinical integration of foundation models. Bioeng (Basel). 2024;11(10):984. https://doi.org/10.3390/bioengineering11100984.
62. Hindocha S, Zucker K, Jena R, Banfill K, Mackay K, Price G, Pudney D, Wang J, Taylor A. Artificial intelligence for radiotherapy Auto-Contouring: current Use, perceptions of and barriers to implementation. Clin Oncol (R Coll Radiol). 2023;35(4):219–26. https://doi.org/10.1016/j.clon.2023.01.014.
63. Jain S, Jain PK, Puranik AK. Digital health technology & cancer care: conceptual framework leading comprehensive fruitfulness. J Healthc Leadersh. 2024;16:525–35. https://doi.org/10.2147/JHL.S486263.
64. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. Nat Rev Cancer. 2018;18(8):500–10. https://doi.org/10.1038/s41568-018-0016-5.
65. Lipkova J, Chen RJ, Chen B, Lu MY, Barbieri M, Shao D, Vaidya AJ, Chen C, Zhuang L, Williamson DFK, Shaban M, Chen TY, Mahmood F. Artificial intelligence for multimodal data integration in oncology. Cancer Cell. 2022;40(10):1095–110. https://doi.org/10.1016/j.ccell.2022.09.012.
66. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542(7639):115–8. https://doi.org/10.1038/nature21056.
67. Montomoli J, Bitondo MM, Cascella M, Rezoagli E, Romeo L, Bellini V, Semeraro F, Gamberini E, Frontoni E, Agnoletti V, Altini M, Benanti P, Bignami EG. Algor-ethics: charting the ethical path for AI in critical care. J Clin Monit Comput. 2024;38(4):931–9. https://doi.org/10.1007/s10877-024-01157-y.
68. Cascella M, Shariff MN, Viswanath O, Leoni MLG, Varrassi G. Ethical considerations in the use of artificial intelligence in pain medicine. Curr Pain Headache Rep. 2025;29(1):10. https://doi.org/10.1007/s11916-024-01330-7.
69. Bellini V, Semeraro F, Montomoli J, Cascella M, Bignami E. Between human and AI: assessing the reliability of AI text detection tools. Curr Med Res Opin. 2024;40(3):353–8. https://doi.org/10.1080/03007995.2024.2310086.
70. Grassi R, Belfiore MP, Montanelli A, Patelli G, Urraro F, Giacobbe G, Fusco R, Granata V, Petrillo A, Sacco P, Mazzei MA, Feragalli B, Reginelli A, Cappabianca S. COVID-19 pneumonia: computer-aided quantification of healthy lung parenchyma, emphysema, ground glass and consolidation on chest computed tomography (CT). Radiol Med. 2021;126(4):553–60. https://doi.org/10.1007/s11547-020-01305-9.
71. Granata V, Fusco R, Catalano O, Avallone A, Palaia R, Botti G, Tatangelo F, Granata F, Cascella M, Izzo F, Petrillo A. Diagnostic accuracy of magnetic resonance, computed tomography and contrast enhanced ultrasound in radiological multimodality assessment of peribiliary liver metastases. PLoS ONE. 2017;12(6):e0179951. https://doi.org/10.1371/journal.pone.0179951.
72. Fusco R, Petrillo M, Granata V, Filice S, Sansone M, Catalano O, Petrillo A. Magnetic resonance imaging evaluation in neoadjuvant therapy of locally advanced rectal cancer: A systematic review. Radiol Oncol. 2017;51(3):252–62. https://doi.org/10.1515/raon-2017-0032.

73. Verma H, Mistry S, Jayam KV, Shrestha P, Adkins L, Liang M, Fares A, Zarrinpar A, Braithwaite D, Karanth SD. Artificial intelligence in oncology: A 10-Year ClinicalTrials.gov-Based analysis across the cancer control continuum. Cancers. 2025;17(21):3537. https://doi.org/10.3390/cancers17213537.
74. Fusco R, Sansone M, Filice S, Granata V, Catalano O, Amato DM, et al. Integration of DCE-MRI and DW-MRI quantitative parameters for breast lesion classification. Biomed Res Int. 2015;2015:237863. Epub 2015 Aug 3. PMID: 26339597; PMCID: PMC4538369. https://doi.org/10.1155/2015/237863.
75. Granata V, Fusco R, Setola SV, De Muzio F, Dell'Aversana F, Cutolo C, et al. CT-based radiomics analysis to predict histopathological outcomes following liver resection in colorectal liver metastases. Cancers (Basel). 2022;14(7):1648. https://doi.org/10.3390/cancers14071648
76. Salvatore C, Roberta F, Angela L, Cesare P, Alfredo C, Giuliano G, et al. Clinical and laboratory data, radiological structured report findings and quantitative evaluation of lung involvement on baseline chest CT in COVID-19 patients to predict prognosis. Radiol Med. 2021;126(1):29–39. Epub 2020 Oct 12. Erratum in: Radiol Med. 2021;126(4):643. https://doi.org/10.1007/s11547-020-01322-8
77. Granata V, Fusco R, Catalano O, Piccirillo M, De Bellis M, Izzo F, Petrillo A. Percutaneous ablation therapy of hepatocellular carcinoma with irreversible electroporation: MRI findings. AJR Am J Roentgenol. 2015;204(5):1000–1007. https://doi.org/10.2214/AJR.14.12509
78. Cappabianca S, Granata V, Di Grezia G, Mandato Y, Reginelli A, Di Mizio V, et al. The role of nasoenteric intubation in the MR study of patients with Crohn's disease: our experience and literature review. Radiol Med. 2011;116(3):389–406. https://doi.org/10.1007/s11547-010-0605-1

Publisher's note