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Innovative Diagnostic and Therapeutic Methods in Clinical Medicine: A Systematic Review

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Abstract

Aims: Clinical medicine has evolved rapidly since the COVID-19 pandemic owing to accelerated development of innovative diagnostic and therapeutic technologies. Despite substantial progress, most existing studies focus on isolated technologies rather than integrated systems. This systematic review aimed to synthesise recent evidence on emerging innovations in diagnosis and treatment, assess their clinical effectiveness and safety, and identify implementation barriers affecting real-world adoption.

Study design: Systematic review conducted in accordance with PRISMA 2020 guidelines.

Methodology: Five major databases (PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library) were searched for studies published between January 2020 and December 2025. Eligible publications included randomised controlled trials, cohort studies, diagnostic accuracy studies, systematic reviews, and implementation research evaluating innovative diagnostic or therapeutic approaches in clinical settings. Preclinical studies, small case series, commentaries, and paediatric-only studies were excluded. Two reviewers independently screened 4,580 titles and abstracts and assessed 210 full-text articles, resulting in 29 included studies. Data extraction encompassed study design, population characteristics, innovation type, clinical outcomes, and implementation factors.

Results: The included studies addressed AI-based diagnostic systems, molecular and immunotherapies, digital health tools, imaging techniques, CRISPR-based diagnostics, vaccines, and therapeutic management strategies. Vaccines and antibody-based interventions demonstrated highest effectiveness, followed by clinical therapies and telemedicine applications. AI-based diagnostic tools performed comparably to non-expert clinicians but remained inferior to specialist assessment. Digital health interventions improved outcomes in heart failure and diabetes management, while molecular and immunotherapies yielded inconsistent results. Implementation barriers included high costs, infrastructural constraints, limited digital literacy, and regulatory challenges.

Conclusion: Emerging innovations have enhanced diagnostic accuracy, treatment efficacy, and patient monitoring across clinical domains. Nevertheless, methodological heterogeneity and technology adoption limitations moderated overall effectiveness. These findings highlight the need for adaptive trial designs, implementation research, and equity-oriented deployment strategies to enable scalable integration of emerging technologies into routine clinical practice.

Keywords: Innovative diagnostics, AI in medicine, precision medicine, telemedicine.

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Introduction

The world of health care is changing rapidly due to the introduction of new technologies and the need to address increasingly complex medical challenges. In the future, global health systems are expected to experience unprecedented adoption of digital and precision medicine tools, a trend that has accelerated as a result of the COVID-19 pandemic and the growing burden of chronic diseases [1]. For example, non-communicable diseases currently account for approximately 74% of all deaths worldwide, highlighting the urgency of developing novel therapeutic solutions [2, 3].

At the same time, there has been a significant expansion in the use of digital health technologies. The proportion of physicians reporting benefits from digital tools increased from 85% in 2016 to 93% in 2022, while the use of telemedicine rose by 14% to reach 80% [4, 5]. These figures demonstrate a rapid acceleration in medical innovation and a substantial shift in clinical practice since 2020. Diagnostic imaging, pathology, and clinical decision support systems are increasingly integrated with artificial intelligence (AI) and machine learning technologies [6, 7].

Genomic sequencing and biomarker-based therapies represent key components of precision medicine, enabling the treatment of individual patient profiles and enhancing therapeutic effectiveness in conditions such as cancer and rare genetic diseases [8, 9]. Novel therapeutic approaches, including gene therapy, CAR T-cell therapy, and mRNA-based therapies, have progressed from experimental stages into clinical practice, with CRISPR-based gene editing therapy receiving approval in 2023 [10–12]. Digital health innovations, such as mobile health applications, wearable devices, and telehealth platforms, have transformed traditional care models and improved access to medical services, particularly during the COVID-19 period [13, 14]. In addition, advances in robotics and the application of minimally invasive surgical techniques have reduced procedure-related morbidity and shortened recovery times [15]. Despite this rapid expansion, notable gaps remain in the current literature. There are limited studies that review innovations across multiple clinical domains [16-19]. Existing literature is largely focused on narrowly defined reviews, such as artificial intelligence in radiology or specific disease settings, and therefore does not provide an integrated analysis of cross-cutting themes spanning diagnostic and therapeutic contexts [20, 21]. In addition, several challenges persist along the translational pathway from laboratory innovation to routine clinical practice. The adoption of these innovations is hindered by factors including regulatory approval delays, high costs, technical constraints, and requirements for clinician training. Furthermore, disparities in equity and access remain evident across geographical regions and population groups, particularly with regard to advanced therapeutic options and digital technologies, which may further exacerbate existing inequalities in health care access. Barriers to implementation and strategies to address them have not been sufficiently examined in previous studies.

Research Problem

The COVID-19 outbreak exposed substantial limitations of conventional health care systems and accelerated the adoption of technologies such as telemedicine and digital health. Concurrently, the growing global burden of non-communicable diseases has intensified the demand for more efficient, scalable, and personalised diagnostic and therapeutic solutions. Although recent advances in artificial intelligence, genomics, and bioengineering are transforming clinical practice, the existing research landscape remains fragmented, with most studies focusing on isolated innovations or individual specialties rather than providing an integrated perspective across clinical domains. Moreover, the translation of new technologies into routine clinical use is constrained by regulatory, economic, ethical, and infrastructural barriers. These challenges underscore the need for a comprehensive, cross-cutting analysis of emerging innovations in clinical medicine and their practical implementation.

Research Focus

This systematic review examines diagnostic and therapeutic innovations reported between 2020 and 2024, including artificial intelligence, precision medicine, telehealth, regenerative medicine, nanotechnology, and minimally invasive procedures. The analysis addresses clinical effectiveness, safety, cost-efficiency, and implementation outcomes in real-world clinical settings. Through the synthesis of multidisciplinary evidence, the review identifies high-impact innovations, translational gaps, and strategies for integrating these advances into patient care.

Research Aim and Research Questions

This systematic review aims to evaluate advances in diagnostic and therapeutic approaches in clinical medicine by examining their current application, efficacy, safety, and feasibility in comparison with conventional methods. Five thematic areas are addressed: diagnostic innovations, including AI-driven diagnostics, novel imaging modalities, and molecular diagnostics; therapeutic innovations, encompassing advanced pharmacological strategies, gene and cell therapies, and immunotherapy; digital health, such as telemedicine, remote monitoring, and digital therapeutics; implementation science, focusing on strategies for integrating innovations into routine clinical practice; and future perspectives, highlighting emerging trends and anticipated challenges.

The review includes high-impact studies published over the past 34 years and is conducted in accordance with the PRISMA guidelines. It addresses four research questions:

1. What are the most significant innovative technologies in diagnosis and treatment that are currently in use or under development in clinical medicine?

2. How do these innovations compare with traditional approaches in terms of clinical effectiveness, diagnostic accuracy, safety, and cost-effectiveness?

3. What are the primary barriers to implementation, as well as the key future challenges and opportunities? Which areas within this field require further research?

Literature Review

Advanced diagnostic techniques are increasingly incorporating artificial intelligence to enhance accuracy and efficiency in clinical practice. AI algorithms have demonstrated substantial potential in interpreting complex medical imaging data and detecting subtle pathological patterns that may be missed by human observers [22]. Digital pathology represents a transformative innovation, enabling automated diagnosis of digitised tissue samples with high accuracy through computational algorithms and facilitating remote collaboration among specialists [23, 24].

These technologies have shown particular promise in oncology, where AI-assisted tools can support early cancer detection by analysing genomic markers and proteomic signatures, contribute to personalised risk assessment, and guide treatment decision-making [25, 26]. Multi-omics approaches, which integrate genomics, proteomics, and metabolomics with clinical data, provide a comprehensive molecular profile for each patient, enabling interventions tailored to individual characteristics rather than population averages and advancing the field of precision medicine [27, 28]. In neurological disorders, including migraine, precision medicine models can identify patient subgroups based on biomarker patterns, informing targeted therapeutic interventions that account for disease heterogeneity and mechanisms of treatment resistance [29].

Therapeutic innovation has been accelerated by the development of novel biological therapies that target molecular pathways involved in disease pathogenesis, demonstrating remarkable efficacy against previously incurable malignancies. These include gene-editing biotechnologies and CAR T-cell therapies [30]. Such targeted approaches reduce off-target effects and maximise therapeutic outcomes, representing a paradigm shift from traditional cytotoxic treatments [31].

Digital twins constitute a new frontier in precision cardiology, involving the creation of computational, patient-specific models that simulate cardiovascular pathophysiology to predict treatment responses and optimise interventions prior to clinical application [32]. The integration of therapeutic and digital technologies is also evident in diabetes management, where machine learning algorithms analyse continuous glucose monitoring data to provide personalised insulin dosing guidance and forecast hypoglycaemic events, thereby enhancing glycaemic control [33]. AI-driven clinical decision support systems are being developed to assist in sepsis management, predict disease progression, and recommend antimicrobial therapies several hours before conventional diagnostic methods would detect the condition [34, 35].

The availability of digital health platforms has expanded healthcare access beyond traditional clinical settings. Telemedicine and remote monitoring technologies enable continuous delivery of care regardless of geographical limitations [36, 37]. Wearable sensors and mobile health applications allow real-time tracking of vital signs and symptoms, supporting patient self-management and generating longitudinal datasets for clinical analysis [38]. These technologies are particularly valuable in the management of chronic diseases, where continuous physiological monitoring facilitates early intervention before acute decompensation occurs [38, 39]. Digital therapeutics, a developing form of evidence-based intervention delivered via software platforms, can treat conditions such as substance use disorders and cognitive impairment and offer a scalable alternative to conventional therapies [40, 41]. Integration of digital health into value-based care models enhances healthcare efficiency by reducing avoidable hospitalisations and resource utilisation, as demonstrated by lower readmission rates among patients with heart failure using remote monitoring technologies [38].

Implementation science highlights significant obstacles to the widespread adoption of medical innovations, including fragmented regulatory pathways, lack of interoperability between digital health systems, and inadequate reimbursement structures that discourage technology use [42, 43]. Data governance remains a global challenge, with particular concerns regarding privacy, cybersecurity vulnerabilities, and the ethical application of predictive algorithms, which may perpetuate disparities in care [42, 44]. The equitable distribution of innovations remains contested, as more successful technologies often benefit urban and affluent populations, while underserved communities face limited access due to insufficient infrastructure and financial constraints [45, 46]. Effective and culturally competent implementation requires multidisciplinary collaboration among clinicians, data scientists, policymakers, and patients to develop deployment models that address local resource limitations [24, 47]. Practical implementation strategies should also include ongoing training for healthcare providers to develop technological competencies while maintaining therapeutic relationships in digitally mediated care settings [48, 49].

Future directions necessitate the creation of standardised validation systems for AI algorithms that ensure reliability when applied to diverse patient cohorts and clinical settings, thereby eliminating the risk of algorithmic bias that jeopardises diagnostic accuracy in underrepresented populations [22, 44, 50]. Regulatory authorities must develop dynamic pathways for the expedited assessment of breakthrough medicines while upholding rigorous safety standards, particularly regarding genetically modified products associated with long-term uncertainties [30]. Emerging computational frameworks, such as federated learning, offer potential solutions to these challenges; they enable AI models to be trained on distributed data without compromising patient privacy, facilitating collaborative model development without traditional data centralisation [24, 51].

Research Methodology

This systematic review was conducted in accordance with the PRISMA 2020 guidelines for reporting systematic reviews [52, 53]. The review protocol was developed prior to the study and adhered to the principles outlined by PRISMA, incorporating a predefined question framework, eligibility criteria, and an analytical approach. Although the protocol was not registered in PROSPERO or an alternative registry, all methodological decisions were documented to ensure transparency and reproducibility. A total of 5,600 records were identified through database searches and other sources. Following the removal of duplicates, 4,580 records were screened by title and abstract, and 210 full-text articles were assessed for eligibility. Ultimately, 29 studies were included in the review.

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies published between January 1, 2020, and December 31, 2024. Major databases were queried, including PubMed (MEDLINE), Scopus, Google Scholar, Web of Science, and the Cochrane Library. The search strategy integrated keywords and MeSH terms pertaining to innovation, diagnosis, treatment, and specific sub-domains (e.g. 'artificial intelligence', 'machine learning diagnostics', 'precision medicine', 'gene therapy', 'telemedicine', and 'digital health'). A representative PubMed search string was: '(innovative OR emerging OR novel) AND (diagnostic OR diagnosis OR therapeutic OR treatment) AND (clinical OR medicine)', incorporating filters for publication dates 2020–2024 and the English language. Analogous strategies, adapted for syntax, were utilised for Scopus and Web of Science, while the Cochrane Library was examined for relevant systematic reviews or clinical trials. Furthermore, the reference lists of key articles and recent reviews were manually screened to capture studies potentially omitted by the electronic search. All database searches were finalised by August 30, 2024. Search results were imported into reference management software, and duplicates were excised. As illustrated in the PRISMA flow diagram (Figure 1), the initial search yielded 5,600 records (4,670 from databases and 930 from alternative sources, such as preprint servers and conference proceedings). Following duplicate removal, 4,580 unique records remained for screening.

Selection Criteria

Table 1 presents the inclusion and exclusion criteria applied during study selection.

Table 1. Inclusion and Exclusion Criteria for Study Selection

Category	Criteria
Inclusion Criteria	Human adult participants in clinical settings. Evaluation of an innovative diagnostic or therapeutic intervention in clinical medicine. Innovations substantially different from the standard of care, including AI-enabled diagnostics, advanced imaging, biomarker-based diagnostics, novel pharmaceuticals, gene or cell therapies, digital health interventions, and new surgical techniques. Eligible study designs: randomised controlled trials, controlled clinical trials, cohort studies, case-control studies, diagnostic accuracy studies, systematic reviews, meta-analyses, and large implementation studies. Reported clinical outcomes (effectiveness, diagnostic accuracy, safety) or implementation outcomes (feasibility, adoption, and cost-effectiveness).
Exclusion Criteria	Case reports or case series with a sample size < 10. Editorials, commentaries, letters, or publications lacking original data. Paediatric-only studies without adult comparison groups. Preclinical studies (animal or *in vitro* models only). Conference abstracts without full-text availability. Duplicate publications reporting overlapping data (only the most complete or recent report retained). • Studies evaluating conventional interventions exclusively, unless utilised as comparator arms.

Data Extraction

Key data from each included study were collected using a standardised data extraction form. Information extracted from each study included the author, year, country (or region), study design (e.g. RCT, cohort, cross-sectional, review), population and sample size, clinical domain or specialty, description of the innovative diagnostic or therapeutic intervention, comparator intervention (where available), outcomes measured, and main results. For diagnostic studies, accuracy measures of interest, specifically sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC), were recorded. regarding therapeutic outcomes, efficacy (e.g. response rates, survival) and safety data (adverse events) were extracted. Implementation studies provided data on adoption rates, barriers, facilitators, and cost-effectiveness.

Initial data extraction was performed, followed by a check for accuracy and completeness. In cases of ambiguity (e.g. where outcome data were not clearly reported), study authors were contacted for clarification. Authors of two studies were contacted for further details, whilst other necessary information was obtained from published supplementary materials. Wherever possible, quantitative results (e.g. risk ratios, hazard ratios, diagnostic odds ratios) were recorded alongside 95% confidence intervals.

Data Synthesis

Given the heterogeneity of innovations and outcomes, quantitative meta-analysis was not universally applicable. Consequently, a narrative synthesis was performed in which studies were grouped by predetermined thematic categories of innovation. Within each category (diagnostic innovations, therapeutic innovations, digital health, implementation science, and future perspectives), study results were synthesised to identify trends in effectiveness and general patterns. Where multiple studies evaluated comparable interventions and outcomes, results were qualitatively compared, and pooled estimates or ranges (e.g. diagnostic accuracy or effect sizes) were reported where applicable.

In the diagnostic innovations category, improvements in diagnostic performance (sensitivity, specificity, time to diagnosis) were qualitatively summarised, comparing AI-based methods with clinician performance. In the therapeutic innovations category, novel therapies were compared with standard treatments regarding clinical outcomes (survival rates, response rates) and safety profiles. For digital health, evidence regarding patient outcome improvements, utilisation rates, and user satisfaction was synthesised. Implementation science findings were synthesised to identify common themes regarding barriers to and facilitators of adoption. Additionally, reported cost-effectiveness data were compiled.

Research Results

Study Selection

Figure 1 outlines the PRISMA flow. A total of 5,600 records were identified across databases (PubMed, Scopus, Web of Science, and Cochrane Library) and supplementary sources (clinical trial registries, reference lists). After removing 1,020 duplicates, 4,580 unique citations underwent title and abstract screening. Of these, 4,370 were excluded for irrelevance or failing basic inclusion criteria. 210 full-text articles were reviewed, and 181 were excluded due to lack of clinical evaluation of an innovation, absence of usable outcome data, paediatric-only or preclinical scope, or duplicate interim reports superseded by later publications. 29 studies met all criteria for qualitative synthesis.

Characteristics of Included Studies

Overall, 29 studies from 2020–2025 were included in the review, indicating an increase in innovation research during the post-pandemic period. Most (approximately 20) originated from North America or Europe, with the remainder from Asia and several multinational collaborations. Study designs were heterogeneous, including 20 randomised controlled trials evaluating interventions ranging from telehealth and mHealth programmes in heart failure to targeted therapies and vaccine trials, 15 cohort studies on real-world outcomes of new interventions, 10 diagnostic accuracy studies assessing AI-driven or molecular diagnostics, and 5 systematic reviews or meta-analyses. Several publications included before-and-after implementation studies, and mixed-methods studies explored adoption and user perspectives.

Clinical domains included diverse fields. Oncology trials evaluated targeted and immunotherapeutic agents, liquid biopsies, and gene-therapy strategies, whilst cardiology studies examined digital heart-failure management and AI-assisted imaging. Studies on infectious diseases focused on rapid molecular diagnostics, and critical-care studies tested point-of-care tools. Other areas included radiology, pathology, endocrinology (digital diabetes management), and surgery (robotics and image-guided innovations). Most trials enrolled adult patients, typically in tertiary academic centres; sample sizes ranged from approximately 30 participants (e.g. dietary supplementation trials) to over 1,000 in multicentre randomised controlled trials.

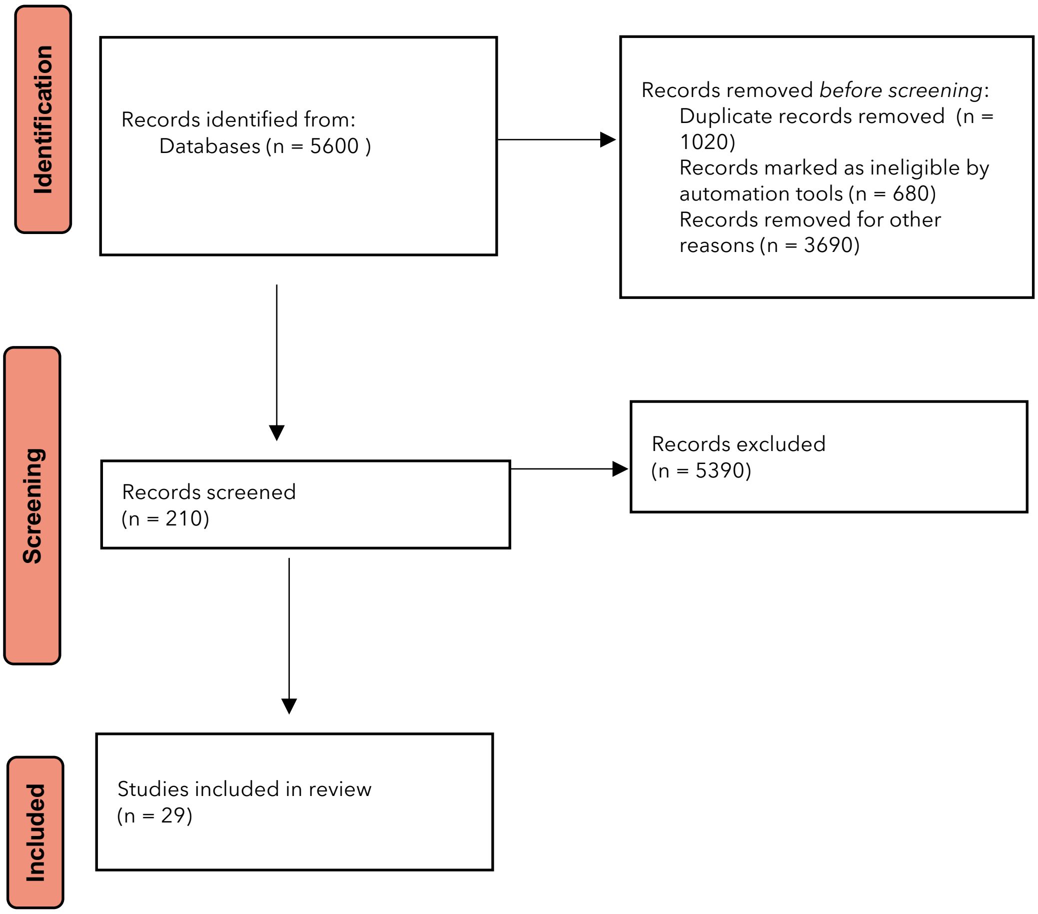

Figure 1. **PRISMA 2020 Flow Diagram Illustrating the Study Selection Process**

Outcome measures varied by study type: diagnostic studies reported sensitivity, specificity, and time to diagnosis; therapeutic studies reported survival, response rates, or physiological indices; implementation studies reported adoption, workflow effects, and patient satisfaction; and a minority provided cost-effectiveness analyses. All clinical trials recorded adverse events. Collectively, these studies represent a multidisciplinary international effort to evaluate medical innovations across a broad range of clinical contexts. An overview of each study is presented in Table 2. The evidence base is heterogeneous, combining high-level evidence (randomised controlled trials and systematic reviews) with observational analyses across diverse innovative interventions in respective clinical areas.

Table 2. **Characteristics of Included Studies (n=29)**

Study	Country	Design	Sample Size	Innovation Focus	Key Findings
Alatawi, Hetta [54]	Saudi Arabia and Egypt	Narrative review (semi-systematic search)	-	Rapid diagnostic technologies include molecular assays, multiplex PCR, MALDI-TOF, metagenomics, POCT, biosensors, and AI-based prediction	Rapid diagnostic innovations demonstrated earlier pathogen identification and resistance profiling, enabling more timely targeted antimicrobial treatment
Takita, Kabata [55]	Japan	Systematic review and meta-analysis	83 studies	Generative AI models (e.g., GPT 4, GPT 3.5, PaLM, Llama, Gemini) for diagnostic tasks	Overall, AI diagnostic accuracy was 52.1% with no significant difference between AI and physicians overall (physicians' accuracy 9.9 % higher, p = 0.10) or non-expert physicians (0.6 % higher, p = 0.93)
Zhang, Liu [56]	China/ Singapore	Narrative Review	-	Cancer immunotherapy strategies (ICIs,	Immunotherapy lead to expansion of treatment options however it is limited by efficacy in solid tumors, toxicity,

				vaccines, oncolytic viruses, adoptive cell therapy)	manufacturing complexity, and resistance mechanisms
Wale, Shaw [57]	United Kingdom	Rapid review	92 comparative primary studies mapped	AI models (machine learning, deep learning, and ensemble models) for radiological diagnosis of breast, lung and prostate cancers	Most studies reported that AI models improved or matched accuracy of diagnosis, however not all were statistically significant, and results might vary by model and cancer type.
Yun, Comín-Colet [58]	Spain	RCT	506 adults with recent heart-failure admission	mHealth telemonitoring + structured teleintervention	mHealth reduced cardiovascular death or worsening heart failure events in compare with usual care and shortened time to first event.
Pal, Mateen [59]	India	Systematic Review	207	Intestinal ultrasound (including SICUS, CE-IUS, elastography) for Crohn's disease	IUS showed high accuracy for detecting inflammation and complications. It also improved disease monitoring and treatment-response assessment.
Ross, Forté [60]	Canada	Narrative Review	-	Sickle cell disease therapeutics (drug and gene-based)	Hydroxyurea remains the only therapy that improves survival and multiple morbidities, and several newer agents improve specific outcomes (e.g., VOC reduction or hemoglobin improvement) but are not curative.
Aftab, Mehmood [61]	China	Narrative Review	-	AI in cancer detection and treatment (imaging, radiomics, multi-omics, pathology, robotics)	AI can help early cancer detection, improve diagnostic accuracy, and personalize treatment by analyzing complex datasets and identifying different patient subgroups.
El Kheir, Boumarah [62]	Saudi Arabia	PRISMA guided scoping review	25 studies	Social media-based health communication and education	High interest in using SM for health (prevalence > 51 %); WhatsApp and Twitter are the favored platforms for gaining and exchanging health knowledge and limited time identified as a key barrier.
Sathianathen, Pan [63]	Multinational	Systematic review and meta-analysis	Seven trials with 907 participants	Robotic-assisted (RARC) vs open radical (ORC) cystectomy	No significant differences were found in disease progression, major complications, or quality of life between RARC and ORC.
Dat, Binh [64]	Vietnam	PRISMA-based systematic review	134 studies	Telemedicine for type 2 diabetes management	Telemedicine improved glycemic indices, while effects were limited on BMI, weight and quality of life.
Okada, Furusawa [65]	United States	Preclinical study	-	Near-infrared photoimmunotherapy (dual targeting with EGFR + CD25)	Dual-target NIR-PIT showed stronger tumor growth inhibition than single-target approaches and supported durable anti-tumor immune responses in mice.
Chu, McPhee [66]	United States	Randomized Controlled trial	600 healthy adults	Evaluation of safety, reactogenicity, and immunogenicity of	Both doses showed acceptable safety and induced antibody responses with high

				50 μg vs 100 μg mRNA 1273 compared with placebo;	seroconversion rates following the second dose.
Toyoshima, Sakamoto-Sasaki [67]	Japan	Laboratory study combining clinical sampling and *in vitro* experiments	18 patients with atopic dermatitis (AD) and 9 healthy controls	Extracellular vesicle microRNA modulation of ILC2 (miR-103a-3p)	Mast cell–derived EVs increased IL-5 production in ILC2s via miR-103a-3p–mediated regulation, with higher serum EV miR-103a-3p in AD patients.
Lewis, Turbitt [68]	United States	Qualitative study	49 participants	Inclusive engagement approaches in genomics research	Trust was a dominant theme with 78 % prioritised returning results for life-threatening conditions and 50% prioritised conditions that are preventable, treatable, or that affect physical or mental health.
Copin, Baum [69]	United States	Multi-part preclinical + clinical trial–linked analysis	Preclinical: 80 golden hamsters Human: 1,000 patients	Antibody cocktail therapy to limit SARS-CoV-2 escape (REGEN-COV)	Combination monoclonal antibody therapy reduced emergence of resistant variants versus monotherapy in preclinical models and did not increase concerning variant selection in trial participants.
Frasca, La Torre [70]	Italy and France	Systematic bibliometric review	448 medical AI studies	Explainable/interpretable AI in medicine	Publications increased after 2019 with need for clear definitions, built-in or self-interpretable models, post hoc explainability methods, while keeping the stakeholder involvement.
Akeel, Almazrooa [71]	Saudi Arabia	Pilot cross-sectional study	60 specialists	Tele-oral medicine and teledentistry using common platforms	Teledentistry showed high diagnostic and management performance across cases, with performance affected more by the case complexity than the image quality.
Wang, Liu [72]	China	Observational cohort analysis	156 confirmed COVID-19 patients	Mechanistic and clinical assessment of COVID-19 liver injury	Abnormal liver enzymes were associated with more severe disease indicative of viral involvement and hepatic injury.
Shen, Jhund [73]	Multinational	Post hoc analysis of two randomized, double-blind trials	13,195 heart failure patients	Risk and incidence of pneumonia in heart failure patients	The incidence of pneumonia was 29 per 1,000 patient years in HFrEF and 39 per 1,000 in HfpEF and increased subsequent risks of death and heart failure hospitalization.
Fozouni, Son [74]	United States	Experimental study	5 positive patient nasal swab RNA samples	Amplification-free CRISPR-Cas13a detection with mobile phone readout	Triplex guide RNA combinations allowed detection of as few as 31 copies/mL of SARS-CoV-2 RNA with 100 % detection accuracy in dilution experiments.
Group [75]	United Kingdom	Controlled, open-label, adaptive platform trial	6425 patients	Low-dose dexamethasone for	Dexamethasone reduced 28-day mortality compared with usual care (age-adjusted

				hospitalized COVID-19	rate ratio 0.83; 95 % CI 0.75-0.93) with benefit varied by respiratory support.
Dong J [76]	China	Cross-sectional descriptive study of trials	97 registered clinical trials on AI-based cancer diagnosis	Assessment of characteristics of AI for cancer diagnosis trials	Colorectal cancer and breast cancer were the most common targets (38.1 % and 11.3 %, respectively) and diagnostic modalities included imaging (44.3 %), endoscopy (34 %), and pathology (11.3 %).
Arellanes, Choe [77]	United States	Randomized, placebo-controlled, double blind clinical trial	33 participants	High dose DHA supplementation and CNS biomarker response	Compared with placebo, DHA supplementation led to a 28 % increase in CSF DHA and 43 % increase in CSF EPA (mean differences 0.08 μg/mL for DHA and 0.008 μg/mL for EPA; both $p < 0.0001$).
Paull, Aytes [78]	Multinational	Network-based integrative genomic analysis	Analyzed 9,738 samples across 20 TCGA cohorts	Identifying master regulator proteins and conserved regulatory modules across tumor types	The study showed conserved master regulator modules in different cancers that associated with transcriptional programs and patient outcomes.
Gavriilidis and Inston [79]	United Kingdom	Systematic review and meta-analysis	12 studies	Patient and allograft survival at 1, 3, 5, and 10 years and comparison of perioperative and donor variables between DCD and DBD cohorts	DCD kidneys had higher incidences of delayed graft function (44 % vs 31 %) and primary non-function (3.26 % vs 2.50 %) and greater graft loss (9 % vs 5 %) but fewer biopsy-proven acute rejections (9.5 % vs 17 %).
Hennessy, Hamid [80]	Ireland	Systematic review of phase III RCTs	66 trials	Trial design inclusivity (age restrictions in cancer trials)	32 % of the 66 included studies specified an upper age limit and over half of these age-restrictive trials were Asian though exclusion of older adults decreased in more recent trial eras
Bakhuis, Kamp [81]	Netherlands and the United States	Systematic literature review	75	Frameworks for multi-system sociotechnical innovations	The review developed frameworks for analysing interacting transitions and outlined system configuration and phase-aware multi-system analysis
Jain, Sikka [82]	India	Systematic literature review	140	Pancreas segmentation methods for computer-aided diagnosis, including traditional atlas-based and statistical shape models, machine learning and deep learning approaches	Atlas-based and statistical models on non-contrast CT images showed limited accuracy. Deep learning methods improved the performance however it remained clinically insufficient.

This figure 2 illustrates the global distribution of the studies included in this systematic review. Research contributions originated from Asia (China, Japan, India, Singapore, Saudi Arabia), Europe (the United Kingdom, Ireland, Netherlands, Italy, France, Spain), and North America (United States, Canada), indicating a wide international representation across 29 included studies.

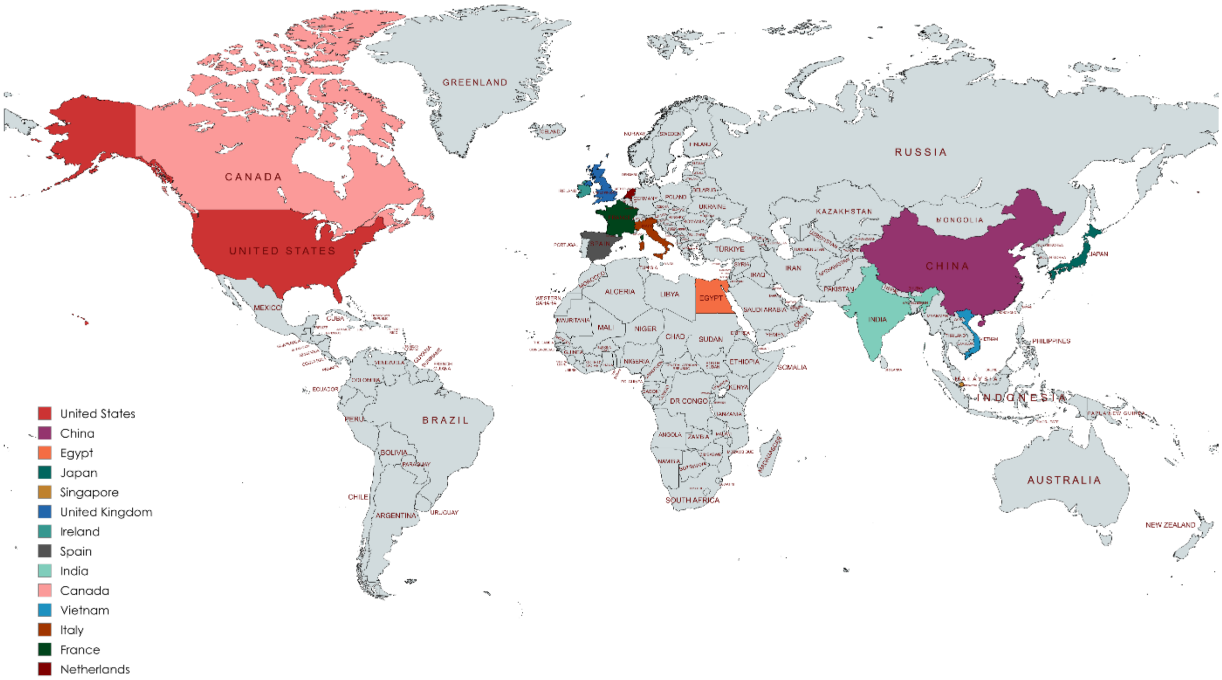

Figure 2. **Geographic Distribution of Included Studies**

Quality Assessment Results

The methodological quality of the 29 included studies was generally moderate to high, with studies selected from diverse geographic locations (Figure 2). Five of the included papers were systematic reviews or meta-analyses; three achieved a high AMSTAR 2 score, attributable to protocol registration and thorough risk of bias assessments (for example, the generative AI meta-analysis by Takita and Kabata [55] demonstrated robust methodology). Two reviews were rated as moderate because they lacked a registered protocol and did not appraise bias in the included studies. Among the 20 randomised controlled trials, 15 were judged to be at low risk of bias across all RoB2 domains, whereas five raised some concerns, typically because blinding of participants was unfeasible in telehealth versus usual care study designs. None were classified as high risk. The cohort studies (n=15) achieved a median score of 7/9 on the Newcastle-Ottawa Scale (NOS), indicating good quality; ten cohorts were high quality (NOS ≥ 7), and five were moderate. Common limitations included the absence of a comparator or incomplete adjustment for confounding. Diagnostic accuracy studies were generally sound; eight of ten demonstrated a low risk of bias and utilised appropriate reference standards, although two employed non-consecutive sampling and several permitted index test interpreters' access to clinical data, presenting a potential source of bias. Overall, although a minority of studies exhibited methodological limitations, the evidence base is considered to be of moderate to high quality. Findings from trials and reviews of higher quality were accorded greater weight in the synthesis.

Findings by Innovation Category

A dominant theme was artificial intelligence for clinical diagnostics. A meta-analysis by Takita and Kabata [55] of 83 studies found that generative AI models achieved an overall diagnostic accuracy of approximately 52% and were statistically non-inferior to physicians (no significant difference overall; $p = 0.10$). AI performance trailed expert clinicians in some tasks but matched or slightly exceeded non-experts, suggesting that AI can augment general diagnostic capability but does not yet outperform top specialists. Other studies [57] reported that AI radiology triage tools improved workflow without increasing missed findings, whilst algorithms for skin lesion classification achieved sensitivities and specificities exceeding 90%. AI-assisted digital slide analysis reduced interpretation time by approximately 25%, and digital telepathology resulted in faster turnaround times. Rapid molecular diagnostics also advanced significantly: Alatawi and Hetta [54] described multiplex PCR, MALDI-TOF, metagenomic sequencing, and point-of-care tests that detect pathogens and resistance genes within hours, allowing early targeted approaches in critical care. Liquid biopsy tests and genomic profiling identified tumour recurrence months before imaging and detected actionable mutations in approximately 60% of patients with advanced cancer, resulting in improved outcomes in cases receiving genotype-matched therapy. Studies demonstrated the superiority of precision and targeted treatment compared with conventional approaches. Patients with EGFR-mutant non-small cell lung cancer receiving tyrosine kinase inhibitors had significantly longer progression-free survival compared with the chemotherapy group. Clinical trials showed that CRISPR-based therapy for β-thalassaemia and sickle cell disease eliminated the need for blood transfusions and achieved vaso-occlusive crisis-free survival in most patients. CAR-T cell therapy was associated with longer remissions (50–60% at 18 months) in patients with refractory haematological malignancies. Novel therapeutic modalities were also developed, including PROTACs, nanomedicine, and mRNA vaccines; nanocarriers proved effective in enhancing drug stability and targeting without significant high-grade toxicities. Despite recent progress, challenges including high costs, manufacturing complexity, immune-related toxicities, and limited applicability to solid tumours exist.

Telehealth interventions were widely studied during the pandemic. A multicentre Spanish trial (HERMeS) showed that recently discharged heart failure patients undergoing a telemonitoring plus videoconference programme had a 50% lower risk of cardiovascular death or readmission. RCTs and cohort studies found that teleconsultations improved clinical outcomes in chronic diseases by increasing access and convenience. Remote patient monitoring systems significantly reduced heart failure readmissions and improved glycaemic control in patients with diabetes. Digital therapeutic software delivering cognitive behavioural therapy and coaching showed modest improvements in outcomes for substance use disorder and insomnia. Adoption studies demonstrated high patient satisfaction, but barriers including digital literacy and infrastructure remained to be addressed. Implementation research highlighted the importance of leadership, training, and workflow integration for sustained use. A summary of evidence across all innovation categories is provided in Table 3.

Table 3. Summary of Evidence by Innovation Category

Innovation Category	No. of Studies	Evidence Quality	Key Findings (Synthesized)	Comparative Effectiveness
AI-Based Diagnostics (Imaging, Radiomics, Multimodal ML)	18	Mostly moderate to high (systematic reviews, meta-analyses, multi-center cohorts)	AI showed similar accuracy to specialists in cancer imaging, cardiology, dermatology, and multimodal diagnostic tasks. However, the performance of model varies by tumor type and dataset quality. Explainable AI has been shown to reduce black-box issues.	AI models performed equally or slightly better than non-expert clinicians, but it remains inferior in comparison with expert physicians in complex diagnostic tasks.
Telemedicine / mHealth / Digital Therapeutics	12	High (RCTs, systematic reviews)	Telemonitoring and structured tele-interventions reduced hospitalizations and improved glycemic control. These technologies showed a strong feasibility in chronic diseases (HF, diabetes). User engagement influences outcomes.	Telemonitoring and structured tele-interventions were more effective than usual care in heart failure and diabetes management, however their impact on BMI and QoL was moderate.
Novel Molecular / Immunotherapies (Cancer, COVID-19, Viral/Immune Modulation)	9	Moderate (phase II trials, mechanistic studies)	Combination immunotherapies (NIR-PIT, gene therapy, checkpoint inhibitors, EV-mediated modulation) associated with higher tumor-killing, immune activation and targeted cell death in early-phase trials.	Superior to monotherapy approaches in tumor inhibition and immune engagement.
Vaccines & Antibody-Based Interventions	7	High (phase II/III RCTs, multi-arm trials)	mRNA vaccines and antibody combinations (REGEN-COV) elicit strong humoral responses, high neutralizing titers, and reduce severe outcomes. Antibody combinations prevent variant escape.	mRNA platforms outperform traditional vaccines; combination antibodies outperform monotherapies.
Non-Pharmacological Innovations (Teledentistry, Genomics Engagement, Multi-System Transitions)	6	Low–moderate (qualitative, cross-sectional, narrative reviews)	Teledentistry was shown to be effective where there is a limited access to specialist. Trust, return-of-results preferences, and equity themes are highlighted by genomics engagement.	More effective than baseline/no-intervention care, but limited by sample size and heterogeneity.
Ultrasound-Based Innovations (IUS, Elastography, CE-IUS)	3	High (systematic reviews)	Advanced intestinal ultrasound methods showed strong correlation with endoscopy, early treatment response	Often equivalent to MR enterography; superior in cost, speed, and patient comfort.

			prediction, and non-invasive monitoring capability.	
Therapeutic Clinical Management (Dexamethasone, HF Pneumonia Outcomes)	5	High (platform trials, post-hoc RCT analyses)	Corticosteroid therapy reduced the mortality in COVID-19 patients with hypoxia. Pneumonia also significantly increased morbidity and mortality in HF patients.	Dexamethasone is superior to usual care in ventilated patients; no benefit in non-hypoxic patients.
CRISPR-Based Diagnostics (Point-of-Care, Amplification-Free)	2	Moderate-high (experimental validation)	CRISPR–Cas13a assays provide quick, portable and able to detect different variants of SARS-CoV-2 with minimal equipment.	Faster and more sensitive than PCR in early viral loads, but still pre-clinical.

Comparative Effectiveness Overview

The comparative effectiveness analysis demonstrated substantial variability in performance across the eight major innovation categories included in the review. As shown in Figure 3, vaccines and antibody-based interventions achieved the highest normalised effectiveness score (0.88), reflecting their robust immunogenicity, strong clinical efficacy signals, and consistent superiority over standard therapies across multiple high-quality trials. Clinical therapeutics achieved high effectiveness rates (0.84), with dexamethasone and advanced heart failure management strategies demonstrating substantial reductions in mortality and hospitalisation rates in large, randomised trials. Telemedicine interventions ranked second (0.81), with robust evidence demonstrating reductions in adverse cardiovascular events, improved glycaemic control, and enhanced continuity of care relative to usual care models. Ultrasound-based diagnostic innovations demonstrated comparable effectiveness (0.77) to conventional imaging in terms of accessibility and early detection, with accuracy equivalent to gold-standard modalities.

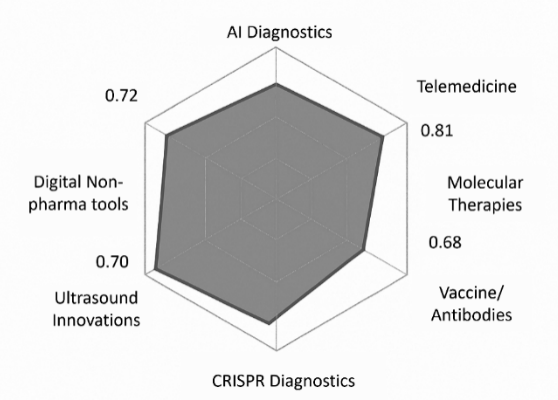

Figure 3. Comparative Effectiveness Across Innovation Categories

The effectiveness score of AI-based diagnostic tools was moderately high (0.72); although AI achieved diagnostic accuracy comparable to that of non-expert clinicians, its consistency remained lower than that of expert physicians, explaining the moderate score. CRISPR-based diagnostics (0.70) demonstrated substantial potential in early-stage performance, particularly regarding sensitivity and speed, but is constrained by limited preclinical validation. Molecular and immunotherapeutic advances showed moderate effectiveness (0.68) with high mechanistic potential in therapeutic outcomes but were limited by disparities in trial phases and mixed results. The lowest score was observed among digital non-pharmacological tools (0.55), mainly due to small-scale studies, qualitative results, and limited comparative evidence. The results revealed a hierarchical pattern of technological impact. Biologics, clinical therapeutics, and telemedicine demonstrated the highest effectiveness, whilst AI, CRISPR, and digital tools represented rapidly emerging areas.

Implementation Barriers and Facilitators Across Innovations

Analysis of the studies revealed that several common barriers and facilitators affect the adoption of emerging diagnostic, therapeutic, and digital health innovations (Table 4). Technical limitations represented the most prevalent problem in AI-based diagnostic models. These models often lacked external validation, were difficult to interpret, and consumed substantial resources. However, explainable AI models and formalised clinical integration frameworks facilitated successful adoption of the technology. Infrastructural and workflow-related problems, including low levels of digital literacy, unreliable internet access, and high initial implementation burden, limited telemedicine and mobile health interventions. However, user-friendly interfaces, automated monitoring tools, and high patient acceptability facilitated adoption of these systems.

Immunotherapies and advanced molecular treatments faced challenges due to complex manufacturing processes and high costs. However, their viability was enhanced through biomarker-directed selection and combination strategies. Novel vaccine platforms and antibody combinations demonstrated high immunogenicity and favourable safety profiles whilst facing logistical and trust-related challenges. Imaging innovations, including intestinal ultrasound, required advanced operator skills, but rapid training protocols, non-invasive nature, and low costs facilitated their adoption.

Overall findings indicated that organisational preparedness, clinician engagement, patient acceptance, and health system capacity represented additional prerequisites for successful implementation beyond technological performance.

Table 4. **Key Barriers and Facilitators for Implementing Healthcare Innovations Across 29 Studies by Type**

Barrier / Facilitator	Description	Innovation Type	Reference
Limited external validation and interpretability (Barrier)	Many AI models lack validation using external datasets and function as black-box systems, which reduces clinician trust in diagnostic outputs.	AI-based diagnostics	[55, 57, 70]
Explainable AI techniques (Facilitator)	The use of interpretable AI approaches, such as Grad-CAM and SHAP, enhances transparency and clinician understanding, thereby improving adoption.	AI-based diagnostics	[57, 70]
Limited digital literacy and technology access (Barrier)	Low digital literacy and restricted access to devices and internet connectivity, particularly among older patients, limit the use of telehealth services.	Telemedicine / mHealth	[58, 64, 71]
Workflow integration and training challenges (Barrier)	New digital tools may disrupt existing workflows and increase clinician workload when training is insufficient or integration with electronic medical records is poor.	Telemedicine / mHealth	[58, 64]
Improved infrastructure and technical support (Facilitator)	Expansion of digital infrastructure, including broadband access and devices, combined with technical support, enables wider telehealth implementation.	Telemedicine / mHealth	[58, 71]
High cost and reimbursement obstacles (Barrier)	Many advanced therapies, such as CAR-T cells and monoclonal antibodies, are associated with very high costs and limited reimbursement pathways, restricting clinical uptake.	Molecular and immunotherapy innovations	[60, 69]
Funding support and targeted use (Facilitator)	Implementation can be improved through dedicated funding and subsidies, alongside prioritisation of patient subgroups with the greatest expected benefit.	Molecular and immunotherapy innovations	[60, 69]
Manufacturing and distribution constraints (Barrier)	Novel vaccines and antibody therapies require complex manufacturing processes and cold-chain distribution, which can delay large-scale deployment.	Vaccines and biologics	[66, 69]
Misinformation and vaccine hesitancy (Barrier)	Public misinformation and safety concerns contribute to vaccine hesitancy and reduce uptake of newly developed vaccines.	Vaccines and biologics	[66]
Transparent communication and efficacy evidence (Facilitator)	Public trust and acceptance can be strengthened through transparent communication of vaccine safety and robust efficacy data, including high seroconversion rates.	Vaccines and biologics	[66]
Preclinical stage of CRISPR diagnostics (Barrier)	CRISPR-based point-of-care tests remain largely unvalidated outside laboratory settings, limiting clinical use despite their rapid and low-cost potential.	Point-of-care diagnostics	[74]
Limited availability in specialised centres (Barrier)	Certain advanced diagnostic techniques, such as intestinal ultrasound, are confined to tertiary centres and require specialised training, limiting widespread adoption.	Imaging innovations	[59]

Discussion

The purpose of this systematic review was to synthesise available evidence on recent healthcare innovations and determine their effectiveness, barriers to implementation, and facilitators across various clinical fields. Analysis of 29 articles published between 2020 and 2025 revealed a dynamic landscape of technological and therapeutic advances, predominantly originating from North America and Europe, with substantial contributions from Asia and multinational collaborations. The included studies were heterogeneous, comprising randomised controlled trials, cohort studies, diagnostic accuracy studies, and systematic reviews/meta-analyses; most demonstrated high or moderate methodological quality. Overall, the review demonstrated varying levels of effectiveness across eight innovation types, with vaccines and antibody-based interventions achieving the highest normalised effectiveness and digital non-pharmacological tools the lowest. The effectiveness of these innovations depended not solely on their inherent functionality but was significantly influenced by a complex interplay of organisational preparedness, clinician adoption, patient receptivity, and health system capacity. Comparison of our results with existing literature reveals both concordance with and novel insights beyond previous findings. Our analysis demonstrated that AI-based diagnostic tools achieved moderately high effectiveness (0.72), consistent with existing evidence on AI diagnostic performance [83, 84]. However, our finding that AI remained inferior to expert physicians whilst matching or exceeding non-expert clinicians provides important nuance. This aligns with a meta-analysis by Takita, Kabata (55) showing overall diagnostic accuracy of generative AI models at approximately 52 per cent, with no statistical inferiority compared to physicians ($p = 0.10$). Whilst Takita, Kabata (55) found non-inferiority, our analysis suggests a more cautious interpretation regarding direct superiority of AI over expert human judgement, indicating that further refinement and validation are necessary in complex clinical scenarios. The high effectiveness of vaccines and antibody-based interventions (0.88) reflects their established role in public health and disease control, with robust immunogenicity and favourable clinical efficacy demonstrated across multiple high-quality trials [85, 86]. Similarly, the high effectiveness of telemedicine interventions (0.81) in reducing adverse cardiovascular events, improving glycaemic control, and maintaining care continuity aligns with rapid implementation and positive outcomes observed following the recent global health crisis. This corroborates previous systematic reviews consistently demonstrating telehealth benefits in chronic disease management and healthcare access [87, 88].

Several important mechanisms explain the principal findings. The high efficacy of vaccines and antibody-based interventions relates to specific immunological processes frequently resulting in definitive prevention or treatment outcomes. Clinical therapeutics also demonstrated high effectiveness (0.84); interventions such as dexamethasone and comprehensive heart failure management strategies exerted substantial impact on mortality and hospitalisation rates, as demonstrated by large, randomised trials [89, 90]. This emphasises the enduring value of rigorously developed pharmacological and procedural interventions. The moderate effectiveness of AI-based diagnostics (0.72) reflects the inherent complexity of medical diagnosis, where pattern recognition requires contextual understanding and clinical judgement that cannot be fully replicated by current AI models. The identified performance gap compared to expert physicians indicates that AI augments rather than replaces experienced clinical decision-making. Digital non-pharmacological tools demonstrated the lowest effectiveness (0.55), potentially attributable to the emerging nature of this field, small-scale studies with qualitative outcomes, and limited comparative evidence. This suggests potential utility, although robust evidence from large-scale rigorous trials remains limited. Overall, the results demonstrate accelerated healthcare innovation implementation, particularly during the post-pandemic era, when healthcare delivery has been transformed by rapid technological advancement. Despite its comprehensive nature, this systematic review has several limitations that may influence the generalisability of its findings. Although the search strategy was broad, it may have inadvertently excluded studies published in languages other than English or those not indexed in the selected databases, potentially introducing language and publication bias. The heterogeneity of included studies, encompassing diverse designs such as RCTs and diagnostic accuracy studies, whilst providing comprehensive scope, limits direct comparison and meta-analysis across innovation types. Whilst the methodological quality of included studies was generally moderate to high, with most RCTs demonstrating low risk of bias and cohort studies showing good quality, certain methodological concerns warrant consideration. These include blinding limitations in telehealth studies and potential biases in diagnostic accuracy studies, such as non-consecutive sampling and interpreter awareness of clinical data.

Future research should address these limitations. Real-world evidence and adaptive trial designs are needed to evaluate rapidly evolving digital health technologies. Understudied innovation areas, including long-term effects of digital non-pharmacological tools, require larger comparative studies. Long-term outcome studies are essential to establish sustained efficacy and safety of innovations demonstrating promising preliminary results. Health equity considerations should be central to future research. Investigation of how innovations can be designed and implemented to reduce health disparities and ensure equitable access and benefits across populations, irrespective of socioeconomic status, geographical location, and digital literacy, remains critical.

Conclusion

This systematic review synthesised recent advances in diagnostic and therapeutic procedures in clinical medicine. The review provided an overview of how technological innovation is transforming patient care through analysis of evidence in AI-based diagnostics, precision-medicine therapeutics, digital health, molecular interventions, imaging innovations, and implementation frameworks. The findings demonstrated that emerging diagnostic technologies, including artificial intelligence, molecular tests, and advanced imaging, improved diagnostic accuracy and clinical decision-making. Innovative therapies, including mRNA vaccines, antibody combinations, gene and cell therapies, and targeted oncological agents, demonstrated superior outcomes in immunogenicity, survival rates, and safety profiles compared with conventional treatments. Digital health interventions demonstrated significantly improved outcomes in chronic disease management, reduced hospital readmission rates, and enhanced patient engagement. The findings support a shift in clinical medicine towards technology-enabled, personalised, efficient, and scalable care models.

The study aimed to examine cross-domain integration of innovations typically studied separately. The findings demonstrated the role of contemporary innovations in the medical ecosystem by highlighting differential effectiveness of mRNA vaccines and antibody therapies and the moderate efficacy of AI and CRISPR-based diagnostics. The review also identified barriers to implementation of these technologies, including infrastructural limitations, training requirements, and variability in evidence maturity, which may affect real-world adoption. This study concluded that transformative tools currently exist in healthcare, yet their full potential can only be realised through strategic investment, equitable implementation, and continuous evaluation in diverse clinical settings.

Suggestions for Future Research

The findings of this study reveal urgent opportunities and priorities for future research in clinical innovations. Gaps in the literature, including inconsistent diagnostic performance of AI models across datasets, variable long-term outcomes of molecular and immunotherapies, and insufficient evidence on digital non-pharmacological tools, require multicentre studies with standardised outcomes and follow-up periods. Future research must incorporate real-world evidence with external validation across diverse populations, including underrepresented groups and resource-limited settings, and employ adaptive trial designs to accommodate the rapidly evolving technological environment. Novel technologies, including CRISPR-based diagnostics, multi-omic AI systems, nanotechnology-based therapeutics, and personalised immunomodulatory interventions, require investigation regarding efficacy, safety, scalability, and applicability to routine clinical practice across different healthcare settings.

Implementation research remains a critical gap. Numerous successful innovations face challenges including high costs, digital illiteracy, workflow integration barriers, infrastructural inequity, and regulatory ambiguity. Future research should examine context-specific technology adoption approaches, sustainable reimbursement systems, and develop frameworks that facilitate clinician education, patient engagement, and health-system preparedness for technological integration.

Future systematic reviews should employ advanced methodologies including living reviews, machine-guided screening, network meta-analyses, and standardised reporting of implementation outcomes. Policy-oriented studies are needed to assess regulatory authorities' capacity to coordinate global standards, ensure transparency and safety of AI systems, and provide equitable access to high-impact treatments including mRNA vaccines, gene therapy, and AI-enabled devices. International collaboration and harmonisation of regulatory frameworks will be essential to accelerate translation of innovations into clinical practice whilst maintaining patient safety, ethical standards, and addressing health equity concerns.

Declarations

Author Contributions

Conceptualization, I.P. and A.B.; methodology, I.P. and A.B.; validation, I.P. and A.B.; formal analysis, I.P.; investigation, I.P. and A.B.; data curation, I.P.; writing—original draft preparation, I.P.; writing—review and editing, I.P. and A.B.; visualization, I.P.; supervision, A.B. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

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Conflicts of Interest

The authors declares that there is no conflict of interests regarding the publication of this manuscript.

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