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HUMAN MEDICINE AND EMERGING TECHNOLOGIES: IMPACT OF ARTIFICIAL INTELLIGENCE, PRECISION MEDICINE AND BIOTECHNOLOGY ON THE TRANSFORMATION OF HEALTH CARE - SYSTEMATIC REVIEW

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ABSTRACT

Artificial intelligence, precision medicine, and therapeutic biotechnology expand diagnostic and treatment possibilities, but their effects on healthcare require critical evaluation. This study aims to analyze the contributions of these technologies to clinical outcomes, safety, diagnostic performance, and care processes. This is an ongoing systematic review, with a preliminary analysis of 40 publications and a time frame from January 2015 to October 2026. Validation searches were conducted in PubMed, bibliographic checks were performed, and methodological characteristics and results were extracted using full texts, partial contents, and available abstracts. The database comprised 14 articles on artificial intelligence, 13 on precision medicine, and 13 on therapeutic biotechnology. The preliminary classification identified 31 publications as candidates for the main synthesis, six for the complementary synthesis, and three for contextualization. The findings indicated benefits in specific applications, including disease detection, examination performance, therapeutic selection, toxicity reduction, and control of oncological and hereditary conditions. However, neutral results, limitations in external validation, and relevant differences between technological and clinical outcomes were observed. It is concluded that these technologies have the potential to transform care, conditioned on indication, quality of evidence, and implementation conditions. The conclusions remain provisional, as the multi-database search, definitive selection, and formal assessment of risk of bias have not yet been completed.

Keywords: artificial intelligence; precision medicine; biotechnology; healthcare; systematic review.

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INTRODUCTION

The incorporation of emerging technologies into human medicine has broadened the possibilities of identifying diseases, guiding therapeutic decisions, and intervening in biological mechanisms that were previously difficult to treat. Among these technologies, artificial intelligence, precision medicine, and therapeutic biotechnology occupy relevant positions by modifying different stages of care, from screening and interpreting tests to selecting medications and developing cellular and gene interventions. However, demonstrating technological performance does not necessarily equate to proving clinical benefit. Evaluating these applications requires distinguishing accuracy, operational efficiency, and experimental feasibility from outcomes directly relevant to patients, such as survival, functionality, quality of life, and safety [1–5].

In the field of artificial intelligence, systems capable of recognizing patterns in images and clinical data have been investigated as tools to support or perform diagnostic tasks. Studies in mammography illustrate the evolution between the retrospective evaluation of algorithms, trials of assisted reading strategies, and implementation in population screening programs. These investigations indicate possibilities for improving detection and reorganizing the work of professionals, although they use different designs and outcomes, which need to be considered in the interpretation of results [1–3]. In diabetic retinopathy, the evaluation of autonomous systems and their application in care demonstrate that the potential impact of the technology involves both diagnostic performance and the ability to facilitate the performance of examinations and the referral of patients [4,5].

The use of artificial intelligence also extends to electrocardiographic interpretation and the identification of conditions requiring investigation or intervention. Clinical trials have evaluated strategies for recognizing patients with ventricular dysfunction and warning systems related to the risk of clinical deterioration, highlighting the importance of investigating the technology within the care process in which it will be used [8,10]. However, favorable results are not uniform across applications. External validation of a widely implemented sepsis prediction model identified limitations in discrimination and a significant alert load, demonstrating that the adoption of a

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system does not replace the need for independent evaluation [12]. Thus, the benefit of a tool depends not only on the algorithm, but also on the population, the available data, the response of professionals, and the implementation conditions.

Precision medicine, in turn, seeks to use molecular and genetic characteristics to guide diagnostic and therapeutic decisions. Its application requires establishing a clinically useful relationship between the identified information and the proposed course of action. In oncology, the SHIVA trial did not demonstrate improved progression-free survival with the strategy of molecularly targeted treatments outside of their indications, while SAFIR02-BREAST identified benefit in patients selected for alterations with a higher level of evidence of actionability. These results show that detecting a molecular alteration does not ensure that its use to select treatment will produce benefit [15,18]. CUPISCO adds evidence favorable to molecular guidance in a specific population of patients with cancer of unknown primary origin, reinforcing the need to interpret each strategy according to its clinical context and comparator [20].

Beyond oncology, pharmacogenetics has been studied as a resource to reduce adverse reactions and guide drug selection. The PREPARE study evaluated the implementation of a multigene panel in different health services, while POPular Genetics and TAILOR-PCI examined genotype-guided antiplatelet selection strategies [21–23]. The differences between their comparators, populations, and results prevent treating these interventions as a single approach of uniform efficacy. In other applications, genomic sequencing for rare diseases and the use of circulating tumor DNA or gene expression assays illustrate how biological information can contribute to clarifying diagnoses and adjusting treatment indications [25–27].

Therapeutic biotechnology expands this scenario by allowing interventions on genes, cells, and molecular expression processes. Gene editing studies in sickle cell disease and beta-thalassemia have demonstrated relevant results in participants with sufficient follow-up for evaluation, although the absence of contemporary comparators and the need for prolonged monitoring limit conclusions on efficacy and safety [28,29]. In hematological malignancies, randomized trials with genetically modified T cells have shown benefits in

disease control outcomes compared to comparator strategies, accompanied by toxicities that are part of the net clinical benefit assessment [34,35]. RNA-based therapies have also demonstrated clinical effects in hereditary diseases, as exemplified by studies with patisiran and nusinersen [38,39].

Despite the relevance of these advances, the literature presents evidence with varying degrees of relevance to clinical practice. Retrospective validations, implementation studies, randomized trials, and single-arm investigations answer distinct questions. Similarly, increased detection, reduction of a biomarker, change in management, and improved survival do not represent interchangeable results. A critical analysis must consider participant selection, comparators, loss to follow-up, duration of observation, safety, and applicability in other services. It must also preserve neutral or unfavorable results, avoiding interpreting technological innovation as a presumed benefit.

In this context, this systematic review aims to critically analyze the evidence on the application of artificial intelligence, precision medicine, and therapeutic biotechnology in human medicine, considering their effects on clinical outcomes, safety, diagnostic performance, and care processes. It seeks to distinguish demonstrated benefits from applications still supported by initial evidence, identify methodological limitations, and examine under what conditions these technologies can contribute to the transformation of healthcare.

METHODOLOGY

This is an ongoing systematic review aimed at analyzing original studies on the application of artificial intelligence, precision medicine, and therapeutic biotechnology in human medicine. The methodological protocol was developed after the identification and preliminary extraction of a database of 40 publications, a circumstance that characterizes planning after the start of the investigation and prevents its presentation as a prospectively registered protocol. The organization of the protocol was guided by PRISMA-P, and the final report will be structured according to PRISMA 2020. The procedures described as planned correspond to steps still necessary to complete the review.

The research question was defined as follows: in people receiving healthcare services, what benefits, risks, and changes in care are associated with the use of artificial intelligence, precision medicine strategies, and therapeutic biotechnologies, compared to conventional care or other appropriate benchmarks? The investigation was organized into three thematic axes. The first encompasses artificial intelligence systems used in diagnosis, screening, prognosis, and clinical decision support. The second covers strategies in which genomic, pharmacogenetic, or molecular information guides diagnostic or therapeutic decisions. The third includes gene editing, gene therapy, genetically modified cells, RNA-based therapies, and personalized therapeutic vaccines.

Original studies involving human subjects of any age and country, published between January 1, 2015, and October 29, 2026, with no initial language restriction, were established as potentially eligible. Designs foreseen for the main synthesis include randomized clinical trials, non-randomized comparative studies, implementation cohorts, and external validation or prospective investigations of diagnostic and prognostic technologies. Single-arm prospective studies involving biotechnological interventions may be included in a complementary synthesis of feasibility, safety, and initial clinical outcomes, without being interpreted as demonstrations of superiority over alternative treatments. The free availability of the full text will not be used as an eligibility criterion.

Studies that are exclusively preclinical, computational investigations without independent clinical evaluation, studies conducted only with vignettes or simulated patients, individual case reports, reviews, editorials, opinion papers, and protocols without results will be excluded from the main clinical synthesis. Investigations of the association between biomarkers and diseases that do not evaluate their diagnostic application or use in healthcare decisions will also be excluded. Publications ineligible for the main synthesis may be used to contextualize the introduction and discussion, provided that this purpose is explicitly differentiated.

Up to this point, validation searches were performed on PubMed using the ESearch service of the National Center for Biotechnology Information, with independent strategies for each axis. MeSH descriptors and free terms related to technologies, clinical application, and

publication period were combined. The concepts searched included artificial intelligence, machine learning, clinical decision support, precision medicine, pharmacogenetics, genomic profiling, circulating tumor DNA, gene editing, gene therapy, chimeric antigen receptors, antisense oligonucleotides, and neoantigen-based therapies. The complete expressions, their versions, and the service responses were preserved in an audit log.

The validation used the 40 articles previously identified as a test set. The initial strategy retrieved 38 of these publications, which was later expanded to include concepts supporting clinical decision-making and neoantigenic therapy, retrieving all 40 known records. This procedure evaluated the retrieval of previously available references, without demonstrating complete sensitivity across the entire literature. The combined results of the reviewed searches returned 462,996 records in PubMed; this number corresponds to the count provided by the service and does not represent fully exported, examined, or included studies. The planned searches in Embase, CENTRAL, Scopus, or Web of Science, as well as the complementary systematic search in trial records, remain pending. Europe PMC, PMC, publishers' pages, and institutional repositories were used for bibliographic verification and document retrieval, but were not counted as independent searches when they reproduced the same records.

After the definitive strategies are consolidated, the results will be exported and subjected to duplicate removal by bibliographic identifiers, title, authorship, and year. The selection will occur in two stages, comprising evaluation of titles and abstracts and, subsequently, analysis of the full texts. The participation of two independent reviewers is planned, with resolution of disagreements by consensus or by a third reviewer; this independent evaluation has not yet been carried out. The reasons for exclusion after full reading will be recorded, and the unrecovered documents will be identified separately. Follow-up publications and secondary analyses will be linked to the original study, avoiding double counting of participants.

The preliminary extraction was organized into standardized forms containing reference, design, setting, population, intervention, comparator, outcomes, effect estimates, confidence intervals, follow-up duration, adverse events, funding, and conflicts of interest. The number of participants recruited,

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randomized, treated, and analyzed was differentiated, as were the units of observation consisting of patients, examinations, or services. In the initial audit, 19 full texts were retrieved, four sources with partial content additional to the abstract, and 17 records still restricted to the abstract. Unverified information was kept as pending, and the extractions should be supplemented and checked before the final synthesis.

Formal risk of bias assessment will be performed by outcome and according to study design, using RoB 2 for randomized trials, ROBINS-I for non-randomized comparative intervention studies, QUADAS-3 for diagnostic accuracy studies, and PROBAST+AI for predictive models. Single-arm studies will be examined with an instrument appropriate to their design. The versions used, the basis for judgments, and the location of information will be documented. The preliminary assessment already performed will not be presented as a formally concluded judgment. When applicable, the certainty of evidence will be examined using the GRADE system for each comparison and outcome, without assigning a single rating to the review as a whole.

The synthesis will be structured by technological axis, clinical indication, design, and nature of the outcome, distinguishing clinical outcomes, safety, diagnostic or prognostic performance, and care processes. A comprehensive meta-analysis is not planned due to the diversity of questions and interventions covered. The presentation of the effects of interventions without statistical combination will be guided by SWiM, considering magnitude, precision, limitations, and applicability, without classifying evidence solely by statistical significance. Any quantitative analyses of comparable subsets will depend on additional methodological specifications, registered before their execution. The final list of studies and the selection flowchart will be presented only after the completion of the searches, screening, and eligibility assessment.

RESULTS

The results presented correspond to a preliminary analysis of the database of 40 identified publications, and do not constitute the definitive selection for the systematic review. The thematic distribution comprised 14 articles on artificial intelligence, 13 on precision medicine, and 13 on therapeutic

biotechnology. Reapplication of the criteria established in the protocol classified 31 publications as candidates for the main synthesis, six as candidates for the complementary synthesis, and three as studies intended for contextualization. These categories represent publications, not necessarily independent studies, since some articles included more than one essay or sub-study.

Document retrieval provided access to 19 full texts, four sources with additional information beyond the abstract, and 17 records still restricted to the abstract. Consequently, the completeness of the extraction varied among the articles, especially regarding loss to follow-up, analysis procedures, individual declarations of interest, and sponsor participation. Table 1 presents the composition of the database and its preliminary classification.

Table 1. Preliminary distribution and classification of the evaluated studies.

Thematic axis	Publications, n	Candidates for the main synthesis, n	Candidates for complementary synthesis, n	Contextualization, n
Artificial intelligence	14	12	0	2
Precision medicine	13	13	0	0
Therapeutic biotechnology	13	6	6	1
Total	40	31	6	3

Note: Preliminary classification, not yet submitted to independent review. Complementary synthesis comprises biotechnological studies without contemporary control. Contextualization studies correspond to investigations with vignettes or simulated patients and individual reports of gene editing [13,14,32].

In the field of artificial intelligence, applications were identified in mammographic screening, diabetic retinopathy assessment, colonoscopy, interpretation of cardiac exams, and clinical risk identification. The results encompassed diagnostic performance, exam execution, workload, detection of abnormalities, and mortality. This diversity prevented treating the studies as estimates of the same healthcare effect.

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In mammography, the retrospective evaluation by McKinney et al. identified reductions in false positives and false negatives in test sets from the United Kingdom and the United States [1]. In the initial analysis of the MASAI trial, the AI-assisted reading strategy showed detection of 6.1 cancers per thousand exams, compared to 5.1 per thousand in the conventional reading group, accompanied by a 44.3% reduction in reading load. This publication corresponded to the initial safety analysis, without yet presenting the definitive result for interval cancer [2]. In the PRAIM observational study, the adjusted detection rates were 6.7 and 5.7 per thousand exams, respectively, in the groups with and without artificial intelligence [3].

In ophthalmology, the study by Abrámoff et al. showed a sensitivity of 87.2% and a specificity of 90.7% for the primary diagnostic target based on fundus photographs. Of the 900 participants recruited, 819 were included in the fully analyzable population, highlighting the need to distinguish recruitment, availability of the reference standard, and obtaining results by the system [4]. In the ACCESS trial, screening at six months was 100% in the group with AI-assisted assessment during care and approximately 22% in the group referred for conventional assessment [5]. In colonoscopy, automated assistance increased the proportion of examinations detecting adenomas, with a predominant contribution from minute lesions [7].

In cardiovascular applications, the strategy based on electrocardiograms interpreted with artificial intelligence increased the identification of patients with reduced ejection fraction at 90 days [8]. Another trial evaluated an alert intervention and found lower mortality in the group that received the AI-supported care strategy [10]. In contrast, the external validation of the proprietary sepsis model examined by Wong et al. showed an area under the curve of 0.63, accompanied by limitations in case identification and a high frequency of alerts [12]. The main selected quantitative results are presented in Table 2.

Table 2. Selected results from baseline studies, according to application and design.

Study	Application and design	Selected main result	Delimitation of interpretation

Study	Application and design	Selected main result	Delimitation of interpretation
Lång et al. MASAI [2]	Mammography; randomized trial, initial analysis	Detection rate: 6.1 versus 5.1/1,000; 44.3% reduction in read load.	The initial publication did not present the definitive outcome for interval cancer.
Wolf et al. ACCESS [5]	Retinopathy screening; randomized trial	Exam completed in six months: 100% versus approximately 22%	Results related to accessing and completing the exam, not visual preservation.
Lin et al. [10]	AI-ECG alerts; pragmatic randomized trial	90-day mortality: 3.6% versus 4.3%; HR 0.83; 95% CI 0.70–0.99	Effect of the alert and healthcare response strategy
Le Tourneau et al. SHIVA [15]	Molecularly targeted treatment; randomized trial	PFS: 2.3 versus 2.0 months; HR 0.88; 95%CI 0.65–1.19	Superiority not demonstrated for the evaluated strategy.
Krämer et al. CUPISCO [20]	Molecular strategy in cancer of unknown origin; randomized trial	PFS: 6.1 versus 4.4 months; HR 0.72; 95%CI 0.56–0.92	Randomized population after disease control with induction.
Swen et al. - PREPARE [21]	Pharmacogenetic panel; cluster and crossover assay	Relevant adverse reaction in the actionable subgroup: 21.0% versus 27.7%; OR 0.70; 95% CI 0.54–0.91	Results in 12 weeks; losses and allocation structure require consideration.
Tie et al. DYNAMIC [26]	Adjuvant treatment guided by ctDNA; non-inferiority assay	Chemotherapy: 15% versus 28%; SLR at two years: 93.5% versus 92.4%	Difference in SLR: 1.1 pp; 95% CI -4.1 to 6.2; non-inferiority margin: -8.5 pp
Frangoul et al. [28]	Gene editing in sickle cell disease; single arm	Absence of severe seizures for ≥12 months in 29/30 evaluable individuals; 97%; 95% CI 83–100	Forty-four participants were treated; main analysis restricted to those with sufficient follow-up.
Locatelli et al. [29]	Gene editing in beta-thalassemia; single arm	Transfusion independence in 32/35 evaluable individuals; 91%; 95% CI	52 participants were treated; no contemporary control.

Study	Application and design	Selected main result	Delimitation of interpretation
		77–98	
San-Miguel et al. CARTITUDE-4 [35]	CAR-T therapy in myeloma; a randomized trial.	PFS: HR 0.26; 95%CI 0.18–0.38	Distinguish between the 208 allocated to the intervention and the 176 actually infused.
Adams et al. APOLLO [38]	Patisiran in hereditary amyloidosis; randomized trial	Change in mNIS+7 over 18 months: -6.0 versus +28.0; difference -34.0 points	A reduction in the score represents an improvement in neurological impairment.
Finkel et al. ENDEAR [39]	Nusinersen in spinal muscular atrophy; randomized trial	Motor response: 37/73 versus 0/37; death or permanent ventilation: HR 0.53; 95% CI 0.32–0.89	Distinct analytical populations and early discontinuation for benefit.

Source: elaborated from the indicated studies. IA-ECG: electrocardiography supported by artificial intelligence; PFS: progression-free survival; RFS: relapse-free survival; ctDNA: circulating tumor DNA; HR: instantaneous hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; pp: percentage points. The table presents selected results, not combined estimates or a definitive classification of the certainty of the evidence.

In the field of precision medicine, results varied according to the disease, the molecular strategy, and the level of evidence supporting the therapeutic choice. The SHIVA trial did not demonstrate an increase in progression-free survival with the molecularly targeted drug strategy outside of its indications [15]. In the SAFIR02-BREAST trial, the analysis of patients with alterations classified as ESCAT I/II showed a HR of 0.41 for progression or death, with a 90% confidence interval between 0.27 and 0.61. However, the analysis without this actionability selection did not demonstrate a statistically significant benefit [18]. The two substudies of the SAFIR02-Lung trial also did not demonstrate an overall improvement in progression-free survival with the experimental strategies evaluated [19]. On the other hand, the CUPISCO trial showed a benefit for the molecular strategy in the selected population after induction treatment [20].

In pharmacogenetics, PREPARE identified a reduction in clinically relevant adverse reactions, while POPular Genetics demonstrated non-inferiority for the composite outcome and a lower

occurrence of bleeding with the genotype-guided strategy [21,22]. TAILOR-PCI presented a HR of 0.66 for ischemic events in the main contrast, with a 95% CI of 0.43–1.02, without demonstrating superiority by the predicted statistical criterion [23]. In PRIME Care, the availability of pharmacogenomic results reduced the prescription of medications with predicted drug-gene interactions. The favorable difference in symptom remission throughout the follow-up was small and did not remain statistically significant in the specific evaluation at week 24 [24].

Diagnostic and treatment selection strategies also yielded distinct results. In the pilot study of the 100,000 Genomes project, approximately one-quarter of the probands received a molecular diagnosis; among the established diagnoses, about one-quarter had an immediate clinical consequence [25]. In DYNAMIC, the ctDNA-guided strategy reduced the use of chemotherapy, meeting the non-inferiority criterion for relapse-free survival at two years [26]. In TAILORx, the randomized comparison in women with an intermediate recurrence score showed similar overall results for invasive disease-free survival between the strategies, with relevant differences for the interpretation of subgroups by age and score [27].

In the field of biotechnology, gene editing studies in sickle cell disease and beta-thalassemia have shown high proportions of evaluable participants free from severe crises or independent of transfusions. However, the efficacy denominators were lower than the number of treated individuals, mainly due to the requirement for sufficient follow-up time [28,29]. Gene editing investigations *in alive* Studies in hereditary amyloidosis and hereditary angioedema showed alterations in biomarkers and initial clinical outcomes, but remained limited by small sample sizes and the absence of contemporary controls [30,31]. In hemophilia B, gene therapy with the etranacogene dezaparvovec reduced the annualized bleeding rate compared to the baseline period of prophylaxis [33].

Among comparative studies of cell therapies, ZUMA-7 and CARTITUDE-4 demonstrated benefits in event-free or progression-free survival, respectively, accompanied by toxicities that should be included in the evaluation of results [34,35]. In KEYNOTE-942, the combination of a personalized neoantigenic vaccine with

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pembrolizumab showed a favorable result according to the unilateral criterion foreseen in the protocol; the bilateral 95% confidence interval for the HR of relapse-free survival included unity in the initial publication [36]. The personalized vaccination study in pancreatic cancer identified an association between immune response and greater relapse-free survival, without allowing isolated causal attribution to the vaccine, due to the single-arm design and the comparison between groups defined after treatment [37]. Trials with patisiran, nusinersen, and voretigene neparvovec showed benefits in neurological, motor, or functional measures in the respective populations investigated [38–40].

The methodological audit identified recurring issues related to participant selection, exclusions after allocation, differences between efficacy and safety populations, loss to follow-up, and lack of comparators. Important differences were also observed between studies of technological performance, interventions on care processes, and treatments evaluated by clinical outcomes. No pooled estimates, definitive risk of bias classifications, or levels of certainty of evidence were calculated. The presented synthesis should be updated after the selection is completed, pending documents are retrieved, and independent verification of the extractions is performed.

DISCUSSION

Preliminary analysis of publications indicates that the contribution of emerging technologies to human medicine varies according to the application, the population, and the outcome considered. Artificial intelligence, precision medicine, and therapeutic biotechnology encompass interventions with distinct mechanisms and degrees of maturity, which prevents attributing a uniform clinical benefit to these fields. Some studies demonstrate improvements in outcomes relevant to patients, while others show advances in detection, care organization, or experimental feasibility. This distinction is fundamental to interpreting the transformation of healthcare without equating technological development with care effectiveness.

In artificial intelligence, mammography studies exemplify the need to differentiate between retrospective performance, experimental evaluation, and implementation in services. The identification of lower

proportions of false positives and false negatives in test sets constitutes evidence of diagnostic performance, but does not, in isolation, demonstrate a reduction in advanced cancers or mortality [1]. The initial analysis of MASAI added evidence of an AI-supported reading strategy, including a significant reduction in workload, while PRAIM examined its use under population implementation conditions [2,3]. These designs offer complementary information, but present different possibilities for causal inference. In the observational study, for example, the choice of technology used and the characteristics of the readers can influence the results, even after statistical adjustments.

The increased detection also requires interpretation in conjunction with the clinical relevance of the identified findings. In AI-assisted colonoscopy, the observed increase in adenoma detection was predominantly related to minute lesions [7]. This result represents an improvement in an indicator of the examination, but the study does not allow us to conclude that there was a subsequent reduction in the incidence or mortality from colorectal cancer. Similarly, increased detection in mammographic screening needs to be examined together with follow-up results, tumor characteristics, and the consequences of further investigations. Therefore, diagnostic indicators should be presented as components of the clinical evaluation, without replacing the outcomes they are intended to anticipate.

Another relevant aspect is that the effect of a technology can result from the reorganization of access to care. In ACCESS, performing the examination during the consultation contributed to reducing the distance between the indication for screening and its effective execution [5]. The evaluated contrast combined the diagnostic tool with an immediate opportunity for care, so the observed benefit cannot be attributed exclusively to the algorithm. This example highlights the importance of defining the intervention as a complete care strategy, including equipment, staff, examination availability, communication of results, and referral. The performance demonstrated in the validation of an autonomous system remains necessary, but is not sufficient to explain its impact on the patient's trajectory [4,5].

In cardiovascular and risk identification applications, the relationship between information produced and clinical response becomes equally important. The increase in

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diagnoses of ventricular dysfunction with an artificial intelligence strategy applied to the electrocardiogram depends on the performance of confirmatory tests and subsequent actions [8]. The trial of alerts associated with mortality reduction evaluated an intervention embedded in the care process, and not just the predictive capacity of a model [10]. In contrast, the limited performance observed in the external validation of the sepsis model demonstrates that commercial dissemination and institutional use do not guarantee adequate performance in other populations [12]. These results support the need for external evaluation and monitoring of the functioning of the systems after their implementation.

Findings in precision medicine show that the usefulness of molecular information depends on the quality of evidence linking the marker to the clinical decision. The SHIVA result questions the assumption that any match between a tumor alteration and a targeted drug is sufficient to improve outcomes [15]. The benefit identified in the ESCAT I/II stratum of SAFIR02-BREAST, associated with the absence of overall benefit in SAFIR02-Lung, reinforces the importance of clinical actionability and the context in which the treatment is used [18,19]. CUPISCO, in turn, provides evidence supporting a molecular strategy in a defined population, selected after disease control with induction therapy [20]. The combined interpretation of these studies favors specific decisions by indication, rather than a generic recommendation of molecular profiling for any clinical situation.

Non-randomized precision oncology studies require additional caution. In I-PREDICT and WINTHER, differences between recruited, treated, and evaluable patients may select individuals with better clinical conditions or a greater likelihood of receiving the proposed intervention [16,17]. Comparison by degree of molecular compatibility or between diagnostic strategies may also be influenced by prognosis, drug availability, and medical decisions. These studies are relevant for demonstrating feasibility and generating hypotheses, but their associations should not be interpreted with the same causal force as randomized contrasts. The distinction is especially important when the ability to access treatment already constitutes a selective step in the care pathway.

In pharmacogenetics, results show that clinical utility depends on the drug, the variant investigated, the comparator,

and the outcome. The reduction in adverse reactions in PREPARE does not imply that any pharmacogenetic panel will produce similar benefit in all specialties [21]. POPular Genetics and TAILOR-PCI evaluated strategies with different comparators, which is why their results do not represent a simple confirmation or refutation of the same hypothesis [22,23]. In PRIME Care, the reduction in prescriptions with predicted drug-gene interactions was accompanied by a small and non-persistent effect on symptom remission [24]. This contrast illustrates how a change in the prescribing process can be demonstrated without its magnitude translating proportionally into sustained clinical improvement.

Precision medicine can also contribute to reducing potentially unnecessary treatments, and not just to selecting additional interventions. DYNAMIC and TAILORx illustrate the investigation of strategies that use molecular information to guide the indication of chemotherapy in specific populations [26,27]. However, the interpretation of non-inferiority depends on the previously defined margin, adherence, and sensitivity analyses. A non-inferiority result should not be converted into absolute equivalence between strategies, nor should it be extrapolated to patients outside the studied criteria. Similarly, the diagnostic yield of genomic sequencing in rare diseases should be differentiated from the proportion of patients who actually experience a change in management or subsequent clinical benefit [25].

In therapeutic biotechnology, gene editing investigations have shown results of great clinical relevance in participants with sickle cell disease and beta-thalassemia [28,29]. However, interpreting response rates requires preserving denominators and recognizing that not all treated individuals had sufficient follow-up to be included in the primary analysis. The absence of contemporary control also limits the comparative estimation of benefit. Furthermore, the cell product and the conditioning necessary for its administration are part of a complex intervention, whose safety cannot be summarized solely by the absence of certain events during the initial observation period.

This caution applies to gene editing studies. *in alive* Reductions in target proteins and favorable changes in clinical manifestations constitute promising results, but do not, by themselves,

establish lasting benefit or long-term safety [30,31]. Small samples have limited capacity to identify rare events, while comparisons with baseline can be influenced by disease variation, concomitant treatments, and regression to the mean. The gene therapy study in hemophilia B adds clinical evidence by comparing bleeding after intervention with a previous period of prophylaxis, but this design should remain distinct from a randomized comparison between contemporary groups [33].

Cell therapy trials, on the other hand, offer comparative evidence of benefit in specific hematological indications [34,35]. However, the evaluation must consider the entire therapeutic strategy, including the interval until infusion and participants who do not receive the product. Restricting the analysis to those actually infused could exclude patients with unfavorable outcomes during this process and produce an overly favorable view of the intervention. Benefits in disease control also need to be presented alongside toxicities, preserving population differences in efficacy and safety.

Personalized therapeutic vaccines illustrate another situation where design and analytical criteria modify interpretation. In KEYNOTE-942, the interpretation of the result must respect the unilateral test foreseen in the protocol, avoiding classifying the study exclusively by the conventional bilateral threshold [36]. At the same time, the phase 2b design and the precision of the estimates limit the strength of the conclusions. In the pancreatic cancer study, the association between immune response and greater relapse-free survival does not demonstrate that the vaccine, in isolation, caused this difference, since the groups were defined by an observed response after treatment and received combined interventions [37].

In contrast to biomarkers or operational measures, assays with patisiran, nusinersen, and voretigene neparvovec assessed outcomes related to neurological impairment, motor function, and mobility [38–40]. These studies exemplify the importance of aligning technological assessment with perceived outcomes in patients' lives. Even in these situations, interpretation remains conditioned by the study population, follow-up time, losses, and design particularities, including early interruption and incomplete masking.

The incorporation of these technologies into services therefore

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requires examining the transfer of results to contexts different from those in which they were obtained. Availability of infrastructure, diagnostic confirmation capacity, access to indicated treatment, and monitoring of adverse events are conditions that can modify the observed effect. The analyzed database, however, does not offer a sufficient standardized evaluation to establish general conclusions about cost-effectiveness, budgetary impact, or reduction of inequalities in access. These aspects should remain as implementation issues to be investigated, and not as presumed benefits.

Finally, the limitations of this investigation need to be considered in interpreting the discussion. The initial database was selected before the protocol was developed, the multi-database search and screening of the retrieved universe have not yet been completed, and some extractions remain dependent on abstracts or partial content. Independent evaluation, formal classification of risk of bias, and analysis of the certainty of the evidence have also not been finalized. Thus, it is not possible to establish a definitive hierarchy between technologies or to affirm the completeness of the literature examined. The available findings support an interpretation focused on specific applications: the transformation of care should be evaluated by the combination of clinical benefit, safety, methodological quality, and real implementation conditions, preserving the distinction between promising innovation and demonstrated effectiveness.

CONCLUSION

Preliminary analysis of publications indicates that artificial intelligence, precision medicine, and therapeutic biotechnology can contribute to transforming healthcare, with demonstrated benefits in specific applications. These benefits include improvements in diagnostic and care processes, treatment selection, reduction of certain toxicities, and advances in disease control. However, their magnitude and relevance vary according to the population, the intervention, the comparator, and the outcome evaluated, making it impossible to attribute uniform effectiveness to the three technological fields.

Interpreting the evidence requires distinguishing between technical performance, experimental feasibility, and clinical benefit. Gains in accuracy, changes in biomarkers, or reduced

workload do not, in isolation, demonstrate improved survival, functionality, or quality of life. Similarly, results from studies without contemporary controls should be considered in light of their limitations, especially regarding participant selection, safety, and duration of follow-up.

The incorporation of these technologies should be supported by clinical evaluation appropriate to the indication, independent validation, and monitoring of benefits and risks in real-world care settings. As the multi-database search, definitive selection, and formal quality of evidence assessment have not yet been completed, the conclusions of this investigation remain provisional. The examined database supports the potential of these applications, but does not allow for establishing widespread technological superiority or comprehensive adoption recommendations.

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