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Revolutionizing personalized medicine with generative AI: a systematic review

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Abstract

Background Precision medicine, targeting treatments to individual genetic and clinical profiles, faces challenges in data collection, costs, and privacy. Generative AI offers a promising solution by creating realistic, privacy-preserving patient data, potentially revolutionizing patient-centric healthcare.

Objective This review examines the role of deep generative models (DGMs) in clinical informatics, medical imaging, bioinformatics, and early diagnostics, showcasing their impact on precision medicine.

Methods Adhering to PRISMA guidelines, the review analyzes studies from databases such as Scopus and PubMed, focusing on AI's impact in precision medicine and DGMs' applications in synthetic data generation.

Results DGMs, particularly Generative Adversarial Networks (GANs), have improved synthetic data generation, enhancing accuracy and privacy. However, limitations exist, especially in the accuracy of foundation models like Large Language Models (LLMs) in digital diagnostics.

Conclusion Overcoming data scarcity and ensuring realistic, privacy-safe synthetic data generation are crucial for advancing personalized medicine. Further development of LLMs is essential for improving diagnostic precision. The application of generative AI in personalized medicine is emerging, highlighting the need for more interdisciplinary research to advance this field.

Keywords Generative AI · Artificial Intelligence · Deep Generative Models (DGMs) · Foundation Models (FM) · Precision Medicine · Personalized Medicine · Personalized treatment · Generative Adversarial Networks (GANs) · Chat Generative Pre-Trained Transformer (ChatGPT) · Individualized Treatment Effect (ITE) · Large Language Models (LLMs)

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Abbreviations

3D	Three-Dimensional
ACC	Accuracy
ADS-GAN	Anonymization through Data Synthesis using Generative Adversarial Networks
AD	Alzheimer's Disease
AI	Artificial Intelligence
AMD	Age-Related Macular Degeneration
AUC	Area Under the Curve
AUC_RANO_criteria	Area Under the Curve for RANO Criteria
AUC_Wasserstein-GAN	Area Under the Curve for Wasserstein-GAN
AIBL	Australian Imaging, Biomarkers & Lifestyle Flagship Study of Aging
BN	Bayesian Network
BRATS	Brain Tumor Segmentation
CCGAN	Clinical Conditional Generative Adversarial Network
CNN	Convolutional Neural Network
CSE	Clinical Synthetic Fidelity
CT	Computed Tomography
CVAE-GAN	Conditional Variational Autoencoder-Generative Adversarial Network
DGMs	Deep Generative Models
Dr.VAE	Doctor Variational Autoencoder
EHR	Electronic Health Record
FCN	Fully Connected Network
FM	Foundation Model
GDSC	Genomics of Cancer Drug Sensitivity
GEO	Gene Expression Omnibus
GFN	Genomic Synthetic Fidelity
GNN	Graph Neural Network
GP	Gene Expression Profiles
GANDA	Generative Adversarial Network for Distribution Analysis
GAN	Generative Adversarial Network
GANCMLAE	Generative Adversarial Network Constrained Multiple Loss Autoencoder
GP-GAN	Growth Prediction Generative Adversarial Network
GSEA	Gene-Set Enrichment Analysis
GTEx	Genotype-Tissue Expression
ICC	Intraclass Correlation Coefficient
KIRC	Kidney Renal Clear Cell Carcinoma
KNN	K-Nearest Neighbors
LGG	Lower-Grade Glioma
LLMs	Large Language Models
LINCS	Library integrated Network-based Cellular Signatures
LR	Logistic Regression
MAE	Mean Absolute Error
MAGGIC	Meta-Analysis Global Group In Chronic Heart Failure
MCI	Mild Cognitive Impairment
MIMIC-III	Medical Information Mart for Intensive Care III

MLP	Multi-Layer Perceptron
MOICVAE	Multi-Omics Integrated Collective Variational Autoencoders
MRI	Magnetic Resonance Imaging
MSE	Mean Squared Error
NST	Neoadjuvant Systemic Therapy
NIH	National Institutes of Health
NS-VQ-VAE	Supervised Vector-Quantized Variational Autoencoder
NSCLC	Non-Small Cell Lung Cancer
OCT	Optical Coherence Tomography
OASI	Open Access Series of Imaging Studies
PATE-GAN	Private Aggregation of Teacher Ensembles—Generative Adversarial Network
PopHR	Population Health Record
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PSNR	Peak Signal-to-Noise Ratio
QDs	Quantum Dots
RForest	Random Forest
RMFN	Residual-Based Multi-Level Fusion Network
RNA-seq	Ribonucleic Acid Sequencing
S-VQ-VAE	Supervised Vector-Quantized Variational Autoencoder
SDI	Standard Deviation
SMP	Small Molecule Perturbation
SVM	Support Vector Machine
TXIT	Radiation Oncology In-Training Exam
U-HPNet	Uncertainty Handling Prediction Network
UNOS	United Network for Organ Sharing
VEGF	Vascular Endothelial Growth Factor
VAE	Variational Autoencoder
ZINC	Zinc Database

1 Introduction

Precision medicine marks a departure from traditional clinical care, focusing on tailoring the most effective therapeutic interventions to the unique genetic and clinical profiles of individual patients. This approach involves personalizing clinical decisions based on each patient's specific medical history and current condition, integrating clinical parameters with genomic profiling to formulate innovative diagnostic and therapeutic strategies (Ali and Aittokallio 2019; Collins and Varmus 2015; Moon et al. 2023; Shin et al. 2017).

Generative AI, a specialized subset of artificial intelligence (AI), is dedicated to the creation of new content, data, or solutions encompassing diverse forms such as text, images, and synthetic data. This innovative field employs machine learning models, with a strong emphasis on deep learning techniques, to produce outputs that are both novel and realistic. These outputs are derived from discerning and replicating patterns and structures found in existing data. In precision medicine, generative AI, particularly through advanced deep generative models (DGMs) such as Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs), has become an indispensable

technology. These sophisticated AI models adeptly tackle difficult challenges such as data scarcity, privacy issues, and the complexities of modeling complex human health data. By generating synthetic patient data that maintains realism and authenticity, these models significantly enhance data analysis and interpretation, thereby advancing precision medicine (Barbiero et al. 2021; Goodfellow et al. 2014; Kipf and Welling 2016; Openai 2016).

In Fig. 1 we illustrate a comprehensive overview of the versatile applications of generative AI in the context of precision medicine. It visually portrays the extensive utilization of generative AI techniques across a spectrum of critical healthcare domains. These include the analysis of Electronic Health Record (EHR) data, the interpretation and generation of medical imaging, the exploration of omics and biomarkers for drug discovery and response prediction, as well as the examination of physiological data and patient-reported information for digital diagnosis and decision-making support.

This review paper systematically examines the role of generative AI in precision medicine, focusing on its performance, limitations, and future directions. It highlights how generative AI, particularly DGMs, contributes to advancing personalized healthcare by generating high-quality synthetic data, enhancing diagnostic accuracy, and facilitating the development of personalized treatment plans. Unlike other reviews that broadly cover AI or machine learning in precision medicine, this paper specifically concentrates on the unique and up-to-date contributions and challenges of generative AI methodologies. It underscores the need for further interdisciplinary research to fully realize the potential of generative AI in transforming healthcare practices (Balla et al., n.d.; Bečulić et al., n.d.; Davri et al. 2022; Egger et al. 2022; Giannakopoulou et al. 2022; Kloczkowski et al. 2023; Rezayi et al. 2022; Sallam 2023; Song et al. 2023; Zerka et al. 2020).

To encapsulate the vast array of terminologies and core themes prevalent within the field of generative AI and its applications to precision medicine, we have synthesized a comprehensive word cloud from a curated collection of article titles, abstracts, and keywords. This visualization, represented in Fig. 1, serves not only as a testament to the rich vocabulary intrinsic to this interdisciplinary field but also as a beacon guiding us through the dense fog of complex concepts that characterize current research trends (Fig. 2).

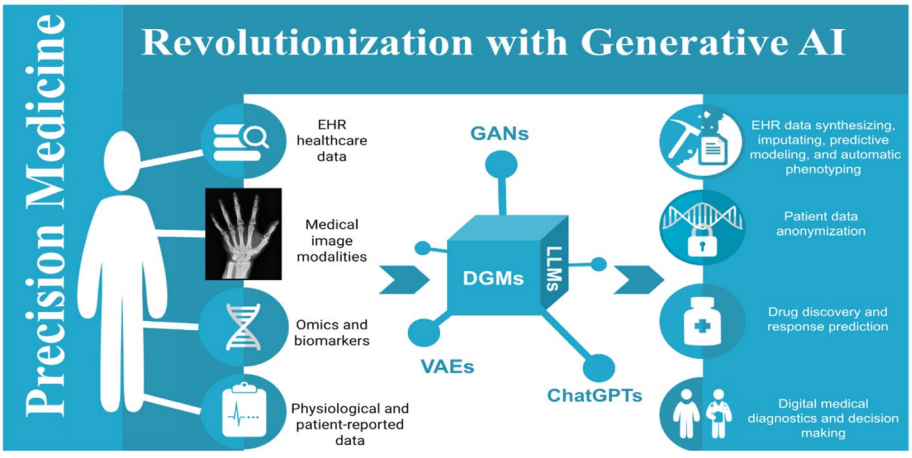

Fig. 1 The groundbreaking impact of Generative AI on Precision Medicine, spanning from clinical informatics and medical imaging to bioinformatics

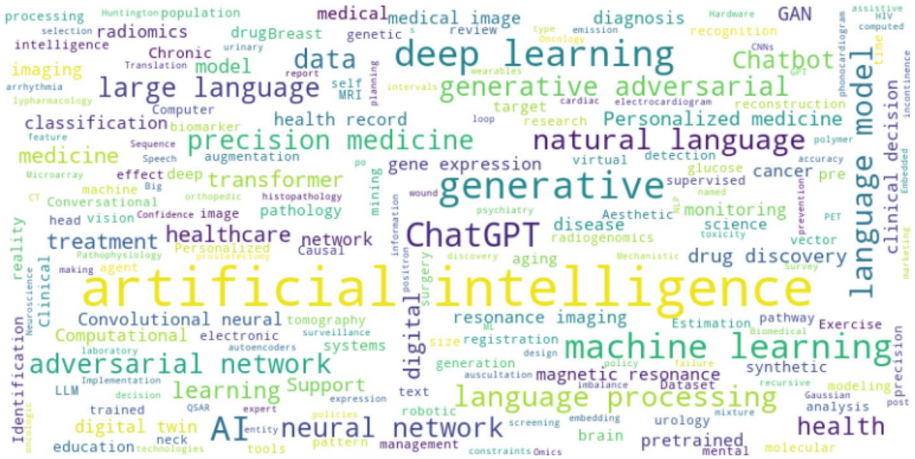

Fig. 2 Visual exploration of key themes: A word cloud representation of analysis of generative AI in personalized medicine

Upon examination of the word cloud, several key findings emerge, painting a vivid picture of the current state of research in generative AI and precision medicine. Firstly, the prominence of terms related to "AI", "data", and "model" show a significant leaning towards computational methodologies and the harnessing of vast datasets to drive innovation in healthcare. This indicates not only the centrality of data-driven approaches but also the reliance on advanced modeling techniques to interpret complex biological information. Secondly, the visibility of specific methodologies, such as "deep learning" and "bioinformatics", hints at the cutting-edge tools being employed to navigate and decipher the multilayered information intrinsic to personalized medicine. These tools represent the sharpened edge of the scalpel, meticulously carving out new pathways for treatment and diagnosis.

Moreover, the commonality of certain terms within the word cloud suggests a shared language that bridges diverse research efforts, pointing towards a consensus on the critical elements and challenges that define the field. This shared vocabulary facilitates a cohesive understanding and collaboration across disciplines, essential for tackling the multifaceted problems at the intersection of technology and healthcare. Finally, the word cloud subtly reveals potential research gaps and areas of saturation through the distribution of terms. While heavily represented terms suggest well-trodden paths, the less prominent ones may indicate niches or emerging areas ripe for exploration, guiding researchers towards uncharted territories that hold promise for groundbreaking discoveries.

In essence, this word cloud acts as both a mirror reflecting the current landscape of generative AI in precision medicine and a compass pointing towards future research directions. It encapsulates the collective knowledge and aspirations of the scientific community, offering insights into the dynamics of research trends and illuminating the way forward.

This review comprehensively analyzes literature from major databases such as Scopus (https://www.scopus.com/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/), focusing specifically on the applications of generative AI in precision medicine. The paper is structured to provide an in-depth overview of generative AI technologies, their applications in various aspects of precision medicine, and the challenges they address, including data scarcity, privacy, and ethical considerations. The review then evaluates the performance of these AI

models in enhancing patient care and discusses their current limitations. It concludes by exploring potential future advancements and advocating for more collaborative research efforts. The aim is to offer a detailed understanding of how generative AI is shaping the future of precision medicine, distinguishing this review from more general analyses of AI in healthcare and emphasizing the transformative potential of generative AI in this field.

2 Method

2.1 Overview

Adhering to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Page et al. 2021) guidelines, the protocol for this paper was drafted and the review was conducted thoroughly. The approach involves a structured and transparent method for gathering, evaluating, and synthesizing the research study.

2.2 Information retrieval strategy

2.2.1 Search sources

A thorough search was conducted on the Scopus (https://www.scopus.com/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases to identify research papers specifically addressing the utilization of the generative AI models in personalized medicine on 06 December 2023. The initial search on these databases yielded 481 articles (129 from Scopus and 252 from PubMed).

2.2.2 Search terms

The search strategy for this systematic review was meticulously developed, drawing upon insights from existing literature. To capture the scope of our research accurately, we incorporated a range of terms specifically associated with generative AI, such as "generative adversarial networks" and "GANs," as well as terms relevant to precision medicine, including "personalized medicine" and "patient-centric medicine." Our searches in various bibliographic databases were conducted using carefully crafted combinations of these key terms, which are detailed in Appendix 1. We refined our search criteria further by focusing exclusively on English-language journal articles published within the last decade. This time frame was chosen to ensure that our review includes the most recent advancements and trends in the rapidly evolving fields of generative AI and precision medicine. The rationale behind these search parameters and the specific databases searched are outlined in the methodology section, ensuring transparency and reproducibility of our research process.

2.2.3 Study eligibility criteria

The inclusion criteria for this research article include original research papers that have been accepted and published, with a specific focus on exploring Generative AI and individualized medicine. The selected studies should fall within the 10-year timeframe spanning from 2013 to 2023. The chosen period coincides with the emergence of modern generative models (Bao et al. 2017; Naveed et al. 2023; Goodfellow et al. 2014). Any articles in the

English language, without country restrictions, and those involving proposals and forecasting generative-aimed subject topics are eligible for inclusion. Conversely, the exclusion criteria involve studies that concentrate on generic AI in precision medicine. Publications in languages other than English, those not peer-reviewed, and those derived from unreliable or non-original sources (such as Wikipedia, posters, reviews and survey studies, editorials, commentaries, or duplications) are excluded from consideration. These criteria aim to ensure the selection of high-quality and relevant research for the comprehensive review. Some of the eligibility criteria are applied utilizing the database search filter, and the study eligibility criteria are summarized in Table 1.

2.2.4 Study selection and screening process

Our study selection and screening process was meticulously designed and executed in three distinct phases to ensure only the most relevant and high-quality studies were considered. Initially, targeted searches were conducted to compile an initial set of studies. This was followed by a rigorous process to remove any duplicates. Subsequently, titles and abstracts were reviewed to filter out studies that did not align with our research objectives, allowing for a more focused evaluation of potentially relevant studies. The final phase involved a detailed full-text review against a set of predefined criteria, ensuring the inclusion of studies that truly contributed to our understanding of the field. Throughout this process, any discrepancies between reviewers were resolved through discussion to maintain the integrity of the research selection process. By adhering to these stringent criteria, we aimed to construct a solid foundation for our analysis, free from the influence of less relevant or lower-quality studies.

2.2.5 Data items and data extraction process

A granular exploration of the included papers was achieved through a meticulous and systematic analysis. This task was undertaken by a designated author for each study, ensuring a focused and comprehensive analysis. The extraction covered bibliographic details (including the first author, publication year, and title), specifics of the generative model employed (detailing any modifications and the intended purpose of the model), key findings, datasets and their characteristics, evaluation metrics used, and the reported accuracy,

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
• Studies that address application of generative AI in Precision Medicine • Studies published from 2013 onwards • Original research articles	• Grey literature (including materials like magazines, conference abstracts, etc.) • Non-peer-reviewed sources (including Wikipedia, posters, reviews, and survey studies) • Informal or opinion-based publications (including editorials, commentaries) • Studies solely on generative model implementation techniques • Papers investigating DGMs or FMs outside of the personalized medicine domain • Research limited to precision medicine without broader DGMs or FMs applications

strengths, and limitations of each study. This comprehensive examination ensured a deep understanding of each study's unique contribution to the field, revealing the intricacies and unique contributions of the research, thereby laying the groundwork for a substantive synthesis of the gathered insights.

2.2.6 Data synthesis

Upon analyzing the extracted data, we identified four clearly defined themes present in the selected papers. These themes encompassed various aspects of the application of generative AI in the medical field. The first theme highlighted the use of bioinformatics in the context of personalized medicine, showcasing how AI can be leveraged to tailor treatments to individual patients. The second theme focused on clinical informatics, illustrating how AI technologies can be utilized to streamline healthcare processes and improve patient care. The third theme delved into medical imaging informatics, demonstrating the role of AI in enhancing diagnostic capabilities through advanced imaging analysis. Lastly, the fourth theme highlighted the emergence of Large Language Models (LLMs) as a pivotal force in transforming personalized medical research and practice, indicating a significant shift in the field towards more sophisticated AI-driven approaches. These themes highlight the breadth and depth of current research endeavors and underscore the diverse applications of generative AI in the realm of personalized medicine.

2.2.7 Quality assessment

The assessment of each study incorporated into the review involved a careful examination of various factors to ensure a thorough and unbiased evaluation of the prevailing state of generative AI applications in the context of personalized medicine. This involved exploring several key factors, including the clarity and transparency of results presentation, ensuring that findings were easily understandable. Another critical criterion was the relevance of each study to the overarching theme of the review, highlighting the necessity of aligning the research with the specific focus on generative AI applications in precision medicine. This multifaceted approach to quality assessment was instrumental in curating a selection of studies that not only meet high academic standards but also directly contribute to the discourse on generative AI's applications in precision medicine.

2.2.8 Review of literature

The use of generative AI in patient-centric medicine is still in its early stages, but it has the potential to revolutionize the way we diagnose and treat diseases. The utilization of generative AI models within the domain of precision medicine has experienced exponential growth in the past decade. This significant interest can be attributed to the unique capabilities of these models in generating diverse data types, encompassing fundamental microscopic details, intricate imaging, varied modalities, and multidimensional representations. Figure 3 presents a quantitative analysis of publications dedicated to generative AI in personalized medicine, employing search data retrieved from the Scopus database for the period 2014–2023.

The graph shows that the number of publications on generative AI in personalized medicine has increased dramatically in recent years. In 2014, there were only 2 publications on the topic. However, by 2023, there were 52 publications. This represents a more than

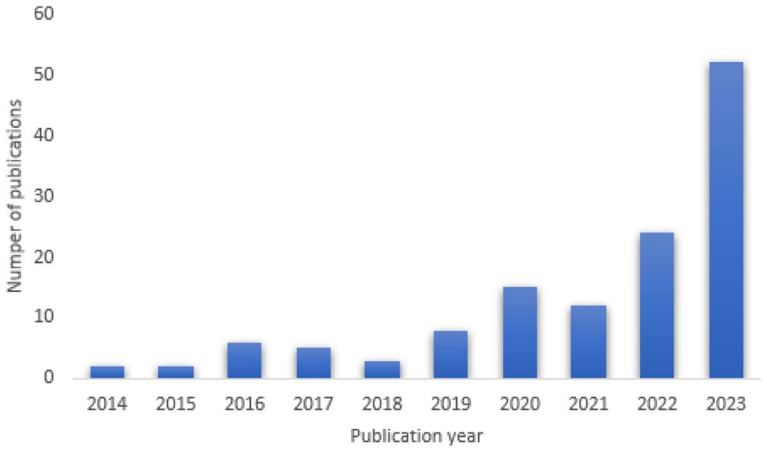

Fig. 3 Visualization of a decade of generative AI research trends in precision medicine

25-fold increase in the number of publications in just 9 years. This suggests that generative AI is having a major impact on the field of individualized medicine.

3 Results

3.1 Search and selection

From the initial search of the two electronic databases retrieved 481 citations, we meticulously applied our selection criteria. Following the removal of duplication and title/abstract screening, 407 were excluded. A close examination of the 50 remaining full-text articles resulted in the further exclusion of 21, as depicted in Fig. 4. Ultimately, only 29 studies aligned with our stringent criteria and were included in this systematic review.

3.2 Characteristics of the included studies

As shown in Table 2 it is evident from the increasing number of publications in this domain, rising from one article in 2019 to 17 articles in 2023. The global nature of this research is highlighted by the diverse geographic distribution of publications, with leading contributions from the United States and China. All the included publications that have been reviewed are journal articles with the majority focusing on applications in clinical informatics (31%), medical imaging (28%), and bioinformatics (31%).

3.3 Findings of the included studies

DGMs are advancing in clinical informatics, including the generation of synthetic patient data, data anonymization, and the development of predictive models, contributing significantly to realizing the potential of precision medicine while addressing privacy and ethical concerns. These models also contribute significantly to advancing our understanding of complex biological processes, enabling personalized medicine, and improving treatment

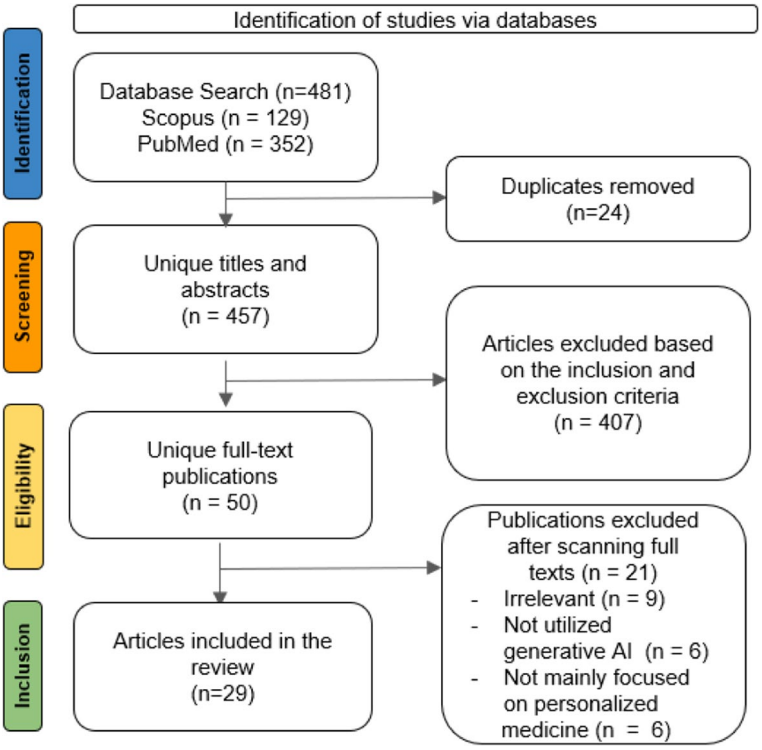

Fig. 4 PRISMA selection process of publication for review

Table 2 Characteristics of the included studies

Features	Values
Years of publications, n (%)	
2019	1 (3)
2020	4 (14)
2021	4 (14)
2022	3 (10)
2023	17 (59)
Country of publication, n (%)	
USA	8 (28)
China	7 (24)
Germany	3 (10)
others	11 (36)
Type of publications (n)	**articles (29)**
Application in the articles, n (%)	
Clinical Informatics	9 (31)
Medical Imaging	8 (28)
Bioinformatics	9 (31)
Foundation models in precision medicine	3 (10)

outcomes across various diseases. Meanwhile, in imaging informatics, the convergence of generative AI and medical imaging is propelling advancements in disease prognosis and diagnosis, exemplified by studies in pulmonary imaging, neuroimaging, retinal imaging, and cancer molecular imaging. These breakthroughs underscore the transformative potential of informatics and advanced technologies in shaping the future of healthcare and personalized medicine. In bioinformatics, the spotlight is mainly on VAEs and GANs, but also foundation models like LLMs for gene prioritization and knowledge-driven candidate selection, highlighting the capability of these models in uncovering hidden patterns within multi-omics data. Furthermore, the integration of LLMs in precision oncology and radiation oncology presents a paradigm shift in decision support for healthcare practitioners, offering complementary insights and potentially enhancing individualized clinical decision-making.

Table 3 provides an overview of the 29 included papers, presenting the applied DGMs or LLMs along with their modified or underlying generative model and the focus of their application.

3.3.1 Clinical informatics

Synthetic patient data generation A recent study (El Emam 2023) developed a method using conditional generative adversarial networks (cGANs) to generate synthetic patient data from real-world clinical and genomic sources for myeloid malignancies such as myelodysplastic syndromes and acute myeloid leukemia. The model was trained on over 7,000 patients' data and evaluated the synthetic data using a synthetic validation framework, finding high fidelity for clinical, demographic, genomic, and outcome features as well as strong privacy preservability. They showed the synthetic data could effectively recapitulate disease subgroups, prognostic scoring systems, and results from clinical trials. Additionally, generating augmented synthetic cohorts allowed for predicting later insights years ahead of real studies. A web portal (https://sdg-webserver-cloudrun-xkb3corsxq-ew.a.run.app/) was created for clinicians to generate synthetic cohorts, demonstrating the potential of this approach to enhance data use and accelerate personalized medicine in hematology.

By injecting realistic EHR data, clinical informatics can overcome data scarcity and unlock new possibilities for analysis and prediction. The paper (Bernardini et al. 2023) addresses this by proposing a data imputation technique called ccGAN (clinical conditional Generative Adversarial Network) to handle missing values in EHR datasets. The ccGAN approach conditions the generation of missing values for partially observed features (called yellow predictors) on both the available values of fully observed features (called green predictors) as well as other clinical information that is usually available in EHR datasets like age, weight, etc. This allows the ccGAN to capture nonlinear relationships between features when imputing missing values. The ccGAN approach is evaluated on a real multi-center diabetic dataset and is shown to outperform other state-of-the-art imputation techniques in terms of both imputation accuracy and predictive performance for diabetic retinopathy detection tasks. An additional experiment on a benchmark MIMIC-III dataset (Purushotham et al. 2018) further demonstrates the robustness of ccGAN across different missingness rates. Furthermore, the paper (Li et al. 2023) proposes a novel approach to improving prediction models trained on EHRs when labeled data is limited. The researchers introduce a network-based generative adversarial semi-supervised method that leverages graph representations of EHR datasets and a GAN to generate synthetic data. This synthetic data aims to bridge the density gap between classes in the real sample data. The approach also

Table 3 Overview of generative AI applications in precision medicine research

#	Ref	Year	Applied Generative Model	Underlying Generative Model	Focused Application
1	(Rampášek et al. 2019)	2019	Dr. VAE	VAE	Personalized drug response prediction
2	(Ge et al. 2020)	2020	MCGAN	GANITE	Personalized treatment effect (ITE)
3	(Xue et al. 2020)	2020	VAE, S-VQ-VAE	VAE	Representation of cellular states from gene expression data
4	(Elazab et al. 2020)	2020	GP-GAN	GAN	Growth prediction of gliomas (brain tumors)
5	(Yoon et al. 2020)	2020	ADS-GAN	GAN	Anonymization through data synthesis
6	(Barbiero et al. 2021)	2021	WGAN	GAN	Production realistic gene expression samples
7	(Sui et al. 2021)	2021	CVAE-GAN	VAE & GAN	Analyze the correlation between lung cancer imaging and gene expression data
8	(Tang et al. 2021)	2021	GANDA	GAN	Generation of intratumoral nanoparticles distribution (nps)
9	(Piacentino et al. 2021)	2021	GAN based ECG	GAN	Anonymize private healthcare data
10	(Ahmed et al. 2022)	2022	omicsGAN	GAN	Improved disease phenotype prediction
11	(Rafael-Palou et al. 2022)	2022	U-HPNet	U-Net	Predicting the progression of lung nodules
12	(Ahuja et al. 2022)	2022	MixEHR	LDA	large-scale automatic phenotyping using electronic health record (EHR) data
13	(Jahanyar et al. 2023)	2023	MS-ASGAN	GAN	Evaluating tabular biomedical data generated by GANs
14	(M. Shi et al. 2023a, b)	2023	CSAM-GAN	GAN	Predicting prognostic outcomes in cancer using multimodal data
15	(Wang et al. 2023)	2023	MOICVAE	VAE	Predict cancer drug response
16	(Yamanaka et al. 2023)	2023	DRAGONET	VAE	Generate new drug candidate molecules
17	(Strack et al. 2023)	2023	Wasserstein-GA	GAN	Monitor brain tumor changes
18	(Gao et al. 2023)	2023	BrainStatTrans-GAN	GAN	Generate corresponding healthy images of patients, which further used to decode individualized brain atrophy
19	(Moon et al. 2023)	2023	AttentionGAN	GAN	Predict short-term anatomical treatment outcomes for different anti-vascular endothelial growth factor agents
20	(R. Shi et al. 2023a, b)	2023	GANCMLAE	GAN	Precisely detect individual brain atrophy patterns in Alzheimer's disease (AD) and mild cognitive impairment (MCI)

Table 3 (continued)

#	Ref	Year	Applied Generative Model	Underlying Generative Model	Focused Application
21	(El Emam 2023)	2023	Conditional GAN	GAN	Synthetic patient cohorts that accurately
22	(Bernardini et al. 2023)	2023	CCGAN	GAN	Clinical data imputation
23	(Li et al. 2023)	2023	GAN-boosted SSL	GAN	Improve prediction models trained on electronic health records (EHRs)
24	(Hsu and Lin 2023)	2023	SCAN	VAE	Predicting cancer patient prognosis using small medical datasets
25	(Zhou et al. 2023)	2023	SCGAN	CGAN	Counterfactual explanations in breast cancer prediction
26	(Zhu et al. 2023)	2023	GluGAN	GAN	Personalized glucose monitoring
27	(Benary et al. 2023)	2023	ChatGPT, Galactica, Perplexity, and BioMedLM	LLMs	Supporting tool in Precision oncology
28	(Huang et al. 2023)	2023	ChatGPT-3 and ChatGPT-4	LLMs	Benchmarking ChatGPT-4 on a radiation oncology in-training exam and Red Journal Gray Zone cases
29	(Toufiq et al. 2023)	2023	GPT-3.5, GPT-4, Gemini and Claude	LLMs	Candidate gene prioritization and selection

incorporates a modified discriminator loss to enhance semi-supervised learning performance while generating privacy-preserving data. The paper presents experimental results on four datasets, demonstrating that their approach outperforms other semi-supervised methods and achieves performance comparable to supervised learning using only 10% of the labels. Similarly, the research paper (Ahuja et al. 2022) explores an automatic phenotyping method called MixEHR-Guided (MixEHR-G), which is a multimodal hierarchical Bayesian topic model that can efficiently model large-scale EHR data to identify latent phenotype structure and simultaneously predict up to 1515 well-defined phenotypes. MixEHR-G uses priori information from clinical coding systems like PheCodes (Wei et al. 2017) to guide the posterior topic inference, allowing it to learn interpretable and clinically meaningful phenotypes in an unsupervised manner. It was applied to the Population Health Record (PopHR) dataset (Yuan et al. 2017) containing administrative claims data for 1.3 million patients in Quebec, and the MIMIC-III dataset (Purushotham et al. 2018) containing intensive care unit observations.

Data anonymization and privacy preservation While EHRs offer exciting possibilities in the digital healthcare arena, data privacy and ethical issues remain a prominent concern. To address this, research papers (Yoon et al. 2020) and (Piacentino et al. 2021) propose utilizing GANs in the synthetize of data in the health sector focusing on anonymizing users' information. The paper (Yoon et al. 2020) discusses a novel framework called ADS-GAN (Anonymization through Data Synthesis using Generative Adversarial Networks) to generate synthetic EHR data that closely approximates the joint distributions of variables in the original dataset while satisfying a quantifiable definition of identifiability. ADS-GAN modifies the conditional GAN framework by optimizing the conditioning variables for each patient to improve data quality while ensuring no combination of features can readily identify a patient. It also uses WGAN-GP to improve training stability. Experiments on four real-world healthcare datasets demonstrate that ADS-GAN outperforms other methods in preserving data characteristics and distributions across different identifiability levels. Predictive models trained on ADS-GAN synthetic data perform similarly to those trained on real data, showing it can generate useful realistic synthetic datasets that address both data distribution and privacy constraints to enable wider sharing of healthcare data for AI research and development while protecting patient confidentiality. Following the same line of thought, the paper (Piacentino et al. 2021) proposes a procedure for GAN-based anonymization of general health data, including both images and raw static data in the context of electrocardiograms (ECGs).

Prediction models and prognosis DGMs have also proven instrumental in enhancing the understanding and prediction of prognosis and diagnosis from patients' data. In the study (Hsu and Lin 2023), a new machine learning framework called SCAN (Semi-supervised Cancer prognosis classifier with Bayesian variational auto-encoder) was proposed for predicting cancer patient prognosis using small medical datasets. SCAN utilizes both labeled and unlabeled patient data in a semi-supervised manner to train deep-learning models. It is tested on breast cancer and non-small cell lung cancer (NSCLC) datasets for predicting 5-year survival rates. The performance gains observed stemmed from SCAN's ability to fully leverage all available patient information. Another innovative framework is demonstrated in the paper (Zhu et al. 2023) in which a deep learning model GluGAN is designed for generating personalized glucose time series data using GANs that provide additional support for decision-making in the management of Type 1 Diabetes (T1D). GluGAN

incorporates recurrent neural network modules and a combination of unsupervised and supervised training to learn the temporal dynamics in latent spaces. It is evaluated on three clinical datasets containing data from 47 T1D patients, and it outperforms four baseline GAN models according to various quantitative metrics assessing the quality of synthetic data. The paper also discusses an application of GluGAN, where it is used to augment training data for glucose prediction algorithms, leading to a significant reduction in prediction errors.

Counterfactual explanations and causal inference A recent scholarly article (Pearl 2018) contended that counterfactual explanations have the potential to offer the utmost interpretability in machine learning models and can serve as a foundation for generating causal inferences. Taking this into account the paper (Zhou et al. 2023) proposes a new method called Sparse CounteRGAN (SCGAN) to generate counterfactual explanations for predicting the response of breast cancer patients to neoadjuvant systemic therapy (NST). SCGAN aims to overcome the limitations of existing counterfactual generation methods by producing counterfactuals that are sparse, diverse, and plausible while maintaining proximity to the original instances. It utilizes a generative adversarial network with dropout training of the discriminator to encourage sparsity and introduces a diversity term to maximize the distance between counterfactuals. A masking approach is also used to handle immutable features and ensure plausibility. Evaluation of benchmark datasets and a breast cancer MRI dataset shows SCGAN can generate counterfactuals with higher prediction probabilities and sparser feature changes compared to baseline methods, helping to identify causal relationships between imaging phenotypes, clinical information, molecular features, and pathologic response to NST to guide more informed treatment decisions.

3.3.2 Medical imaging informatics

Pulmonary imaging Generative models have seen a lot of use recently in a variety of medical imaging domains, such as label-to-image, mask-to-image, and medical cross-modality translation (Ben-Cohen et al. 2017; Goodfellow et al. 2014; Nie et al. 2017; Schlegl et al. 2017; Uzunova et al. 2020; Wang et al. 2021; Yao et al. 2021). Consequently, the paper (Sui et al. 2021) proposes a deep learning-based radio genomics framework to analyze the correlation between lung cancer imaging and gene expression data. It first segments tumor regions from CT images using U-Net. Then it uses a conditional auto-encoder to extract multi-level image features under gene expression conditions. Various analyses like survival prediction and genomic data using gene-set enrichment analysis (GSEA) are performed to validate the correlation between image features, genes, and prognosis data. Finally, a modified CVAE-GAN (Bao et al. 2017) is used to generate tumor images from gene expression data for visualization purposes. This allows for the exploration of the relationship between gene expression and tumor imaging, providing a means to visually represent the correlation between the two data modalities. Similar to this theme, a recent study (Rafael-Palou et al. 2022) also discusses U-HPNet, a deep-learning model created to forecast the advancement of lung nodules identified in CT scans. U-HPNet is specifically designed to tackle the uncertainty linked to image noise in medical images and discrepancies in annotations made by different radiologists. It takes an initial CT image of a nodule as its input and generates predictions regarding its growth, estimates the anticipated size of future growth, and provides a probabilistic segmentation outlining the expected appearance of the nodule at a later time point. The paper's primary emphasis is on the creation and assessment of

U-HPNet as a tool for foreseeing lung nodule progression, with potential implications for influencing clinical decision-making and enhancing patient care.

Longitudinal neuroimaging analysis of glioblastoma patients (Elazab et al. 2020) introduced GP-GAN, a novel brain tumor growth prediction method using 3D generative adversarial networks. By analyzing longitudinal MRI scans, GP-GAN predicts future tumor boundaries more accurately, utilizing a modified 3D U-Net generator and a new L1 and Dice loss-based objective function. Tested on 18 subjects, it surpassed traditional and deep learning models in several metrics, showcasing GANs' effectiveness in data-driven tumor prediction. Further advancements are seen in (Strack et al. 2023), where personalized neural networks, trained on individual patient MRI data, utilized Wasserstein GANs for tumor change detection, proving effective in glioblastoma tumor monitoring and modified RANO classification.

Alzheimer's' disease and mild cognitive impairment detection The importance of individualized brain atrophy in Alzheimer's disease (AD) and mild cognitive impairment (MCI) lies in its ability to underscore the variability in disease progression and treatment responses among patients. This understanding could lead to more personalized treatments, enhancing their effectiveness. The paper by (Gao et al. 2023) introduces a novel method, BrainStatTrans-GAN, to decode individual brain atrophy in AD and MCI. This approach uses a generative adversarial network to transform diseased brain images into healthy ones, with a residual-based multi-level fusion network (RMFN) aiding in disease classification and diagnosis. Tested on 1,739 subjects across three datasets, this method outperforms others in the classification and interpretation of individual changes, underlining its significance in tackling the complexity of neurodegenerative diseases.

Furthermore, (R. Shi et al. 2023a, b) present another framework, GANCMLAE (Generative Adversarial Network Constrained Multiple Loss Autoencoder), focusing on detecting individual atrophy patterns in AD and MCI. Leveraging structural MRI data from the ADNI cohort, this model demonstrates robust image reconstruction and the potential to identify varying MCI atrophy patterns, surpassing traditional group-level methods. Its ability to predict MCI conversion to dementia highlights GANCMLAE's promise for precise, individualized diagnosis and monitoring of AD and MCI.

Retinal imaging Age-related macular degeneration (AMD) with new blood vessel growth can cause severe vision loss (Bressler et al. 1982). For neovascular AMD, blocking anti-vascular endothelial growth factor (VEGF) remains the primary line of defense (Solomon et al. 2019). The paper (Moon et al. 2023) proposes an AI model using attentionGAN to predict short-term anatomical treatment outcomes for different anti-VEGF agents in patients with neovascular age-related macular degeneration (AMD). The researchers aim to leverage the capabilities of attentionGAN, a type of generative adversarial network (GAN), to make predictions related to treatment outcomes for this specific medical condition. Notably, the AI model outperforms human examiners in predicting the presence of residual fluid after treatment, but its performance is comparable to or slightly lower than examiners in predicting the complete resolution of retinal fluid. The study emphasizes the importance of predicting fluid status for selecting appropriate anti-VEGF agents in personalized medicine.

Synthesis and biodistribution of QDs for breast cancer imaging The frontiers of cancer molecular imaging are being pushed by nanotechnology, with quantum dots (QDs) emerging as a groundbreaking probe due to their exceptional optical and electronic properties, unlocking possibilities for both in vitro and in vivo applications (Fang et al. 2012). The study (Tang et al. 2021) introduces a sophisticated generative model named Generative Adversarial Network for Distribution Analysis (GANDA) to characterize and conditionally produce the intertumoral distribution of QDs in breast cancer tissues following intravenous administration. GANDA undergoes training by breaking down entire-slide images of tumor sections into patches that carry information about tumor vessels, cell nuclei, and QDs. It is capable of accurately generating the QD distribution based on the provided vessels and nuclei channels. The generated QD distribution allows for quantitative analysis, enabling calculations such as extravasation distance and subarea distribution. GANDA showcases the potential for predictive modeling of nanoparticle distribution, offering insights into customizing the design of nanomedicine for individual cases.

3.3.3 Bioinformatics: integrated omics and biomarkers profiling

Drug response prediction Predicting prognostic outcomes is crucial for advancing personalized medicine in cancer treatment, as emphasized by (M. Shi et al. 2023a, b). (Wang et al. 2023) contributed significantly to this field by developing the Multi-Omics Integrated Collective Variational Autoencoders (MOICVAE), a novel deep-learning framework for predicting cancer drug sensitivity. This model utilizes integrated genomic and transcriptomic data, employing a multimodal deep autoencoder and a collective variational autoencoder for enhanced prediction accuracy. MOICVAE's effectiveness was demonstrated through high AUCs on major datasets such as the Genomics of Cancer Drug Sensitivity (GDSC) and the Cancer Cell Line Encyclopedia (CCLE), highlighting its potential in personalizing cancer treatment. Additionally, (Rampášek et al. 2019) introduced Dr.VAE, a semi-supervised variational autoencoder designed for generative modeling of post-treatment gene expression. Dr.VAE's capability was evaluated through the expected root mean square error (RMSE) in both latent and gene spaces, offering valuable insights into its predictive accuracy compared to baseline models.

Further advancements in the field were made by (Xue et al. 2020), who utilized two different deep generative models (DGMs)—the variational autoencoder (VAE) and the supervised vector-quantized variational autoencoder (S-VQ-VAE). These models were trained on datasets containing gene expression profiles influenced by small molecules or gene knockdowns. Their study revealed that VAE could effectively regenerate gene expression data and encapsulate relationships between perturbagens. Additionally, S-VQ-VAE's embedding space sheds light on the shared mechanisms of action among perturbagen classes. In a separate study, (M. Shi et al. 2023a, b) developed CSAM-GAN, a generative adversarial network enhanced with sequential channel-spatial attention modules. This method, applied to datasets like lower-grade glioma (LGG) and kidney renal clear cell carcinoma (KIRC) from TCGA, showcased the potential of integrating multimodal data (miRNA expression, mRNA expression, histopathological images) for accurate cancer prognostic outcome prediction.

Drug candidate generation The paper (Yamanaka et al. 2023) introduces a novel computational method named DRAGONET, designed for the generation of potential drug candidates tailored to specific diseases using patient gene expression profiles and deep learning.

DRAGONET leverages gene expression data from patients afflicted with a particular disease to discern patterns associated with that ailment. Subsequently, it employs a generative neural network, specifically a variational autoencoder, to create novel molecular structures that are computationally predicted to target disease-associated genes and biological processes. The underlying transformer-based variational autoencoder (TransVAE) maps these molecules to latent space coordinates, facilitating the production of new molecules through the exploration of this space. The methodology was applied to generate drug molecules targeting gastric cancer, atopic dermatitis, and Alzheimer's disease. The newly generated drugs exhibited a closer structural resemblance to registered drugs for each disease when compared to the initial disease reversal molecules.

Individualized treatment effects The publication (Ge et al. 2020) examines the development of precision oncology through the use of a counterfactual generator in the imputation block, which is a non-linear function of various vectors and random variables. The proposed MGANITE was applied to 256 newly diagnosed acute myeloid leukemia (AML) patients, and the data were obtained from the M. D. Anderson Cancer Center database. MGANITE is a modified GAN that refers to "Modified Generative Adversarial Network for Individualized Treatment Effects". MGANITE is designed to improve the accuracy of estimating individualized treatment effects and to identify optimal treatment strategies for patients, particularly in the context of precision oncology. It extends the capabilities of previous conditional generative adversarial network (CGAN)-based causal inference methods by enabling the estimation of individualized effects of continuous treatments, developing new network structures for the generator and discriminator in the CGANs, and combining sparse techniques for the selection of biomarkers to predict the best treatment for each patient.

Clinical endpoints simulation The study (Barbiero et al. 2021) demonstrates the development of a digital patient model using a Generative Adversarial Network (GAN) and a Graph Neural Network (GNN) to simulate and forecast clinical endpoints. The model is trained and validated using a learning process lasting 50 epochs with a learning rate of 0.01. The results include a 95% confidence interval estimation of the evolution of each variable over time, and the assessment of prediction uncertainty using dropout techniques. In the study, the GAN model is extended to address the specific problem related to gene expression samples by simultaneously accounting for multiple tissue types from the same donor. The extension involves building on a Wasserstein GAN with gradient penalty (WGAN-GP) to estimate a generative model via an adversarial process. The generator in the GAN model aims at producing samples from the conditional P (X|M, R, Q), where X represents gene expression values, and M, R, and Q are different parameters. The model is designed to generate gene expression data for synthetic patients in every modeled tissue type without any missing values, facilitating the cross-tissue analysis of gene expression. This extension allows for a more comprehensive and integrated analysis of gene expression samples across multiple tissue types, addressing the specific problem of joint observations for different tissue types in real datasets. In addition, the generative model is used for transcriptomics data to simulate the effects of SARS-CoV-2 (i.e., the virus responsible for the COVID-19 pandemic) infection on gene expression in various tissues.

Gene expression augmentation It is prominent to develop frameworks for generating and evaluating diverse and reliable genetic data, which can ultimately lead to more personalized

and effective medical interventions for individual patients. The paper (Jahanyar et al. 2023) proposes a modified auxiliary classifier generative adversarial network (MS-ACGAN) for augmenting schizophrenia gene expression microarray data. It downloaded two schizophrenia microarray datasets from NCBI and performed feature selection to select the most relevant genes. It then implemented four types of GANs (basic GAN, modified GAN, ACGAN, MS-ACGAN proposed in the paper) and five classifiers (LR, KNN, SVM, MLP, 1DCNN) for generating and evaluating samples. Five different volumes of data were generated based on stopping criteria. The proposed MS-ACGAN feeds the generator with restricted Gaussian noise based on mean and standard deviation of training data. The model was evaluated using quantitative measures like GAN-test, and GAN-train that measure the quality and diversity of generated data respectively. Statistical techniques like calibration plots, Brier score, and confidence intervals were used to characterize model reliability. The experimental results showed that MS-ACGAN outperformed other models in terms of data quality, diversity, and reliability.

Multi-omics data integration The study (Ahmed et al. 2022) shows a framework known as omicsGAN, designed to revolutionize the integration of multi-omics data and their biological interaction networks. The process began by inputting mRNA and miRNA expression data, along with their interaction network, into the omicsGAN model. Through an intricate series of iterations, an adversarial game unfolded between a generator and a critic, resulting in the updating of the input omics data. In study refers to a component of the omicsGAN model, which is a generative adversarial network (GAN) tailored for multi-omics data integration. The generator meticulously synthesized new mRNA and miRNA datasets, harnessing information from the input omics and their interaction network, while the critic diligently discerned between real and synthetic data. Upon completion of the training, the model produced final synthetic mRNA and miRNA datasets, enriched with comprehensive information from the input omics and their interactions. These synthetic datasets were then leveraged for disease phenotype prediction tasks, such as cancer classification and survival analysis. The study's experiments on real cancer datasets showcased the remarkable predictive performance of the synthetic omics data generated by omicsGAN, underscoring its success in seamlessly integrating multi-omics and network information to enhance disease outcome predictions.

3.3.4 Utilization of foundation models (FMs)

Precision oncology with LLMs support Healthcare practitioners can utilize the support of LLMs like ChatGPT to enhance clinical decision-making, despite their current limitations compared to human experts. (Benary et al. 2023) demonstrated this in precision oncology, comparing treatment recommendations from human experts and LLMs for ten fictional cancer cases. The LLMs evaluated were BioMed LM (MosaicML; Stanford University), Perplexity.ai (University of California, Berkeley), ChatGPT (OpenAI), and Galactica (Meta), using metrics like precision and recall. A molecular tumor board (MTB) then assessed the usefulness of these recommendations. Although LLMs didn't reach the expertise level of humans, they offered valuable complementary insights. Another study by (Huang et al. 2023)benchmarked ChatGPT-4 in radiation oncology. Using the radiation oncology in-training exam (TXIT) with 300 questions and 15 clinical cases, ChatGPT-4's performance in providing accurate treatment recommendations was evaluated, underscoring its potential in complex medical fields.

LLMs in multi-omics data exploration As microscopes of information, LLMs are also peering into the depths of multi-omics data, revealing hidden patterns and connections that hold the key to unleashing the next level of personalized medicine. The paper (Toufiq et al. 2023) explored the potential for using LLMs to assist with knowledge-driven candidate gene prioritization and selection. The researchers first evaluated four LLMs (GPT-3.5, GPT-4, Gemini, and Claude) on tasks like identifying functional relationships between genes and scoring genes against relevance criteria. This identified GPT-4 and Claude as the best-performing models. They then established a multi-step workflow for these LLMs, which involved: selecting candidate gene modules, identifying functional themes among genes, scoring genes, summarizing justifications, validating justifications with references, and selecting top candidates. This workflow was applied to prioritize 11 modules associated with an erythroid signature. The LLMs incorporated profiling data to finalize top gene picks, and their selections were generally agreed upon. The results demonstrated LLMs can enhance gene prioritization efficiency with minimal human input, though limitations like the potential for incorrect information still need addressing for broader adoption as research tools. As the field of artificial intelligence continues to evolve, studies like these contribute significantly to our understanding of the capabilities and limitations of LLMs, paving the way for their responsible integration into various personalized medical disciplines.

Table 4 compiles the results from the examination of 29 papers focused on generative artificial intelligence in precision medicine. It provides comprehensive analysis aims to understand how these methods operate in diverse datasets, assesses the metrics used to quantify their performance, and quantifies the accuracy levels attained in the context of personalized medicine applications. The papers under consideration make use of diverse datasets for their studies in generative artificial intelligence across various domains. These datasets encompass a wide range of medical and biological contexts. Notable datasets include: The Cancer Genome Atlas (TCGA), Medical Information Mart for Intensive Care (MIMIC-III), the Gene-expression omnibus (GEO) archive, Library of Integrated Network-based Cellular Signatures (LINCS), and Alzheimer's Disease Neuroimaging Initiative (ADNI). In the publications, various performance metrics were reported based on the nature of the tasks and the type of data being analyzed. The selection of metrics is contingent upon the particular tasks and goals of each study. These metrics encompass standard machine learning measures such as accuracy (AUC), precision, F1 score, recall, and extend to task-specific metrics like imputation accuracy, clinical and genomic syntenic fidelity, Jaccard index, Dice coefficient, among others. The collective outcomes of these studies highlight a varied and encouraging scenario for the utilization of generative methods across diverse domains, especially within the realm of personalized medicine.

In Table 5 we present a concise summary of various research studies focusing on the development and application of generative models in the field of precision medicine. Each row of the table highlights a specific study, citing its strengths and limitations. The strengths column emphasizes the key advancements and achievements of each model, such as improved performance, ability to handle complex data, or generation of synthetic data for rare clinical scenarios. The limitations column, on the other hand, outlines the challenges or potential areas of improvement for each model, including issues like data limitations, training instability, generalizability concerns, and interpretability challenges. This comparative analysis provides a highlight of the current state of research in generative models within precision medicine, offering insights into both their potential and the hurdles that need to be addressed.

Table 4 The performance evaluation of generative AI methods in precision medicine encompasses an examination of dataset characteristics, evaluation measures employed, and the performance achieved

#	Ref	Dataset	Type	Evaluation Measure	Performance
1	(Rampášek et al. 2019)	860 cell lines and 481 drug compounds from CTRPv2 (Rees et al., 2015); 77 cell lines and 811 drug compounds from CMap-L1000v1, NIH LINCS Consortium (Subramanian et al., 2017)	Pharmacogenomics data	Random Forest (RForest)	RForest achieved 23/26
2	(Elazab et al. 2020)	BRATS 2014 (9 High-Grade Glioma subjects) and Guangzhou General Hospital (9 Low-Grade Glioma subjects) BRATS Dataset (https://www.virtualskeleton.ch/BRATS/Start2014)	MRI images	Jaccard index and Dice coefficient	Jaccard index = 78.97% and Dice coefficien = 88.26%
3	(Ge et al. 2020)	256 newly diagnosed AML patients, M. D. Anderson Cancer Center AML-RPPA Database (http://bioinformatics.mdanderson.org/Supplements/Kornblau-AML-RPPA/aml-rppa.xls) and Related Study (https://pubmed.ncbi.nlm.nih.gov/18840713/)	Biological processes (apoptosis, cell-cycle, signal transduction pathways)	Mean Squared Error (MSE), Standard Deviation (STD), Accuracy (ACC)	MSE = 0.062, STD = 0.235 and ACC = 0.938
4	(Xue et al. 2020)	116,782 expression profiles from 9 cell lines (GP) and 85,183 profiles from 7 cell lines (SMP), LINCS Project (Keenan et al., 2018; Subramanian et al., 2017)	Gene expression data		The models are effective in uncovering connections between cellular perturbagens and identifying the affected genes by each drug

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
5	(Yoon et al. 2020)	MAGGIC (30,389 patients) (Pocock et al., 2013); UNOS Transplant datasets—Heart-Transplant (56,822 patients), Lung-Transplant (26,854 patients), Heart-Wait-list (23,706 patients) UNOS Data. (https://www.unos.org/ data/)	Binary and Continuous data	AUROC	ADS-GAN surpassed PATE-GAN and DP-GAN in downstream prediction performance, maintaining 0.1-identifiability constraint, and showed dependability in joint distributions
6	(Barbiero et al. 2021)	Genotype-Tissue Expression (GTEx) project (15,201 RNA-Seq samples from 49 tissues of 838 donors) (Aguet et al., 2019)	Gene expression measurements		Utilized GNN and GAN for monitoring and forecasting clinically relevant endpoints, offering a comprehensive view of patient health states
7	(Piacentino et al. 2021)	Fingerprints database (ChaLearn-http://chalearnlap.cvc.uab.es/dataset /32/description/); Iris database (IIT Delhi); Thyroid database (KEEL—https://sci2s.ugr.es/keel/dataset.php?cod=67); Cardiogram database (Physionet—https://physionet.org/physiobank/database/ptbdb/)	Various (including ECGs, iris images, thyroid data)		Demonstrated the efficacy of GANs in anonymizing data, particularly ECGs
8	(Sui et al. 2021)	211 subjects from an NSCLC cohort (Clark et al., 2013)	Radio genomic image data		Implemented a deep learning framework for radiogenomic research
9	(Tang et al. 2021)	27,775 patches from whole-slide images of T1 breast cancer sections	Whole-slide images	MSE, ICC	MSE = 1.871; ICC for QDs extravasation distance = 0.95, sub-area distribution = 0.99

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
10	(Ahmed et al. 2022)	The Cancer Genome Atlas (TCGA) for BRCA, LUAD, and OV (TCGA https://cancergenome.nih.gov/)	RNA-seq, mRNA e and miRNA expressions	AUC	AUC for synthetic mRNA and miRNA expressions in various cancer types (0.708 to 0.949)
11	(Ahuja et al. 2022)	Population Health Record (PopHR) dataset (Yuan et al. 2017); MIMIC-III dataset (38,597 ICU patients) (Purushotham et al. 2018)	Clinical notes, codes, lab tests, prescriptions		MixEHR-G outperformed in phenotype label annotation and phenotype prevalence estimation
12	(Rafael-Palou et al. 2022)	160 pulmonary tumors with two CT scan images	CT images	MAE, DSC, AUC_tumor_growth	MAE = 1.74 mm, DSC = 78%, AUC_tumor_growth = 84%
13	(Benary et al. 2023)	10 fictional cancer patients (4 with lung cancer, 6 with other types) https://cdn.jamanetwork.com/ama/content_public/journal/jamanetworkopen/939254	Molecular alterations	Precision, F1 score, and Recall	Precision = 0.29, Recall = 0.29 and F1-score = 0.29
14	(Bernardini et al. 2023)	Multi-Diabetic Centers (MDC) dataset (120 K diabetic patients), MIMIC-III dataset (Purushotham et al. 2018)	Demographics (ID, gender, birth year, diabetes diagnosis date), pathological (ID, ICD-9 codes, diagnosis date), lab tests (ID, codes, values, prescription date)	Imputation accuracy, predictive performance for diabetic retinopathy detection	ccGAN significantly outperformed leading methods in imputation (approx. 19.79% improvement) and predictive performance (up to 1.60% advantage). Demonstrated robustness across varying levels of missing data (up to 1.61% advantage under high missingness rates)

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
15	(El Emam 2023)	2043 MDS patients from GenoMed4All cohort (Bersanelli et al., 2021); 2,957 MDS from IWG-PM (Bernard et al., 2022); 1,002 AML from GenoMed4All (Bersanelli et al., 2021)	Hematologic malignancies (genomic data, patient characteristics, disease subtypes, risk classifications, etc.)	Clinical Synthetic Fidelity (CSF), Genomic Synthetic Fidelity (GSF)	CSF=93%, GSF=90%
16	(Gao et al. 2023)	ADNI (https://adni.loni.usc.edu), AIBL (https://ida.loni.usc.edu/home/projectPage.jsp?project=AIBL), and OASI (https://www.oasis-brains.org/). Total subjects: 1,739	T1w-MRI image data		The method outperforms current techniques by modeling personalized brain atrophy, enhancing disease diagnosis and interpretation
17	(Hsu and Lin 2023)	METABRIC (Curtis et al., 2012), Gene Expression Omnibus (GEO) for breast and NSCLC patients (GEO Repository). (https://www.ncbi.nlm.nih.gov/geo)	Gene expression	AUROC	SCAN significantly outperformed existing benchmarks, including previous bimodal neural network classifiers, with AUROC scores of 81.73% for breast cancer and 80.46% for NSCLC (compared to 77.71% and 78.67% respectively). Independent validation showed SCAN's AUROC scores of 74.74% for breast cancer and 72.80% for NSCLC, outperforming the bimodal classifiers (64.13% and 67.07% respectively)

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
18	(Huang et al. 2023)	The 38th ACR Radiation Oncology In-Training Exam (TXIT) with 300 questions (ACR TXIT Exam—https://www.acr.org/-/media/ACR/Files/DXIT-TXIT/ACR-2021-TXIT-am—) and 2022 Red Journal Gray Zone cases (Red Journal Gray Zone—https://www.redjournal.org/content/grayzone)	Medical questions & complex cases	Exam Score, Case Evaluation Performance	ChatGPT-3.5 scored 62.05%, and ChatGPT-4 scored 78.77% in the TXIT Exam
19	(Jahanyar et al. 2023)	Gene-expression omnibus (GEO) archive (GEO Archive). (https:/www.ncbi.nlm.nih.gov/)	Gene expressions	Confidence Interval	Utilized confidence intervals for a more reliable prediction range, enhancing the credibility of performance measure estimates
20	(M. Shi et al. 2023a, b)	LGG & KIRC from TCGA (TCGA). (https://cancergenome.nih.gov/)	miRNA, mRNA, and pathological image data		SAM-GAN, combining a multilayer deep neural network and GAN, excelled in analyzing multimodal datasets for lower-grade glioma and kidney renal clear cell carcinoma
21	(Moon et al. 2023)	1684 OCT images from 842 patients treated with ranibizumab or aflibercept	OCT images	Sensitivity and Specificity	AI model showed varied sensitivity and specificity between ranibizumab and aflibercept treatments, outperforming human examiners in some aspects. In 18.5% of cases, posttreatment image fluid status differed between the two treatments

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
22	(Li et al. 2023)	University of California Irvine Machine Learning Repository Type 2 Diabetes 30-Day Readmission (61,675 recods) (Eby et al., 2015), Surveillance, Epidemiology, and End Results Ovarian Cancer (10,038 records), Surveillance, Epidemiology, and End Results Colorectal Cancer (40,014 records) (https://www.seer.cancer.gov), and Second Affiliated Hospital of Zhejiang University (1244 records)		AUC	Average AUCs were 0.945, 0.673, 0.611, and 0.588. Outperformed graph-based learning and label propagation methods, and showed competitive AUCs even with only 10% labeled data. Also addressed data synthesis and privacy concerns
23	(R. Shi et al. 2023a, b)	ADNI http://adni.loni.usc.edu/ and Xuanwu cohorts (Sino Longitudinal Study on Cognitive Decline)	Structural MRI data	SSIM, PSNR, MSE, AUC	SSIM = 0.929, PSNR = 31.04, MSE = 0.0014. AUCs for AD and MCI were 0.867 and 0.752, respectively
24	(Strack et al. 2023)	Local dataset including longitudinal follow-up scans from 15 patients diagnosed with recurrent Grade IV glioblastoma & TCIA (Clark et al., 2013) (20 patients newly diagnosed with glioblastoma)	MRI images	AUC for Wasserstein-GAN and RANO criteria	AUC_Wasserstein-GAN = 0.87, AUC_RANO_criteria = 0.66
25	(Toufiq et al. 2023)	BloodGen3 (co-expression gene set (M9.2) Erythroid cell modules (11)) https://drinchai.shinyapps.io/BloodGen3Module/	Erythroid coexpression gene signature		Claude from Anthropic and GPT-4 from OpenAI showed superior performance in candidate gene prioritization and selection

Table 4 (continued)

#	Ref	Dataset	Type	Evaluation Measure	Performance
26	(Wang et al. 2023)	GDSC (426 cell lines, 191 drugs) (Yang et al., 2013); CCLE (401 cell lines, 24 drugs) (Barretina et al., 2012); TCGA (Cerami et al., 2012)	Multi-omics data	AUC score	AUC scores were 0.856 for GDSC, 0.808 for CCLE, and 0.91 for TCGA
27	(Yamanaka et al. 2023)	ZINC database (249,455 molecules) (Irwin & Shoichet, 2005); LINCS (20,655 molecules) (Subramanian et al., 2017)	Drug Molecules		The model is capable of building molecules with changing substructures by exploring the latent space
28	(Zhou et al. 2023)	Pima Indians Diabetes (768 instances) (Sigillito et al., 1989); Ionosphere (351 instances) (Smith et al., 1988); Breast Cancer DCE-MRI (922 instances) (Saha et al., 2018)	Numerical features, radiomic features, binary classification labels		SCGAN generates sparse, diverse, plausible, and feasible counterfactual instances, aiding in understanding causal links between features and treatment response
29	(Zhu et al. 2023)	OhioT1DM (12 T1D subjects) (Marling & Bunescu, 2020); ARISES (12 T1D subjects); ABC4D (25 T1D subjects)	Glucose levels		GluGAN effectively generates high-quality synthetic glucose time series, useful for evaluating insulin delivery algorithms and potentially replacing pre-clinical trials

Table 5 Comparative analysis of recent advances in generative models for precision medicine data

#	Ref	Main Strength	Main Limitation
1	(Rampášek et al. 2019)	The Dr.VAE model partially models drug perturbation effects	■ Reliance solely on gene expression data, overlooking the benefits of multi-omic integration ■ A mismatch between features and sample sizes affecting model performance ■ Overfitting in neural networks and the need for models to handle sparse, heterogeneous data more effectively
2	(Elazab et al. 2020)	Demonstrates superior quantitative and qualitative performance of GP-GAN compared to state-of-the-art reaction–diffusion based and deep learning-based methods for both LGG and HGG datasets	■ Absence of a detailed tumor model and assumption of constant tumor growth, neglecting scenarios of tumor reduction due to treatment ■ The study's reliance on a limited dataset of only 18 subjects, reducing generalizability ■ Recognition of mode collapse as an unresolved issue in GANs, compounded by limited data affecting the diversity of tumor shapes generated
3	(Ge et al. 2020)	Unleashing GANITE's full potential by estimating effects beyond binary treatments	■ Training GANs can be unstable, leading to inaccurate individual treatment effect (ITE) estimates ■ Assumes the absence of unobserved confounders, risking biased outcomes ■ Relies on a small real data set for method comparison and primarily uses LASSO for feature selection, leaving other techniques unexplored
4	(Xue et al. 2020)	Demonstrated DGMs like VAE ability to learn complex patterns in high-dimensional biological data like gene expression profiles	■ The model's representations lack direct correlation to specific biological entities such as proteins or pathways ■ Performance heavily reliant on architectural tuning ■ Limited data restricts learning, especially for rare perturbations ■ While distributions are accurate, generated profiles may not completely reflect true biological responses
5	(Yoon et al. 2020)	Generating synthetic healthcare data that addresses the challenge of balancing data utility and patient identifiability	■ Uncertain applicability of ADS-GAN across various healthcare data sources and settings ■ Lack of comprehensive analysis of ethical and legal implications of using synthetic healthcare data

Table 5 (continued)

#	Ref	Main Strength	Main Limitation
6	(Barbiero et al. 2021)	The generative model can produce synthetic data representing biological states that may not be observed in reality, allowing for the simulation of rare clinical scenarios and personalized experiments in a virtual environment	■ Difficulty in comprehending the generative model's behavior and decisions, hindering its healthcare application ■ Needs thorough validation and careful interpretation for reliable and accurate outcomes ■ Model effectiveness hinges on the quality and representativeness of input data, like data from GTEx
7	(Piacentino et al. 2021)	Validates the anonymization approach through qualitative and quantitative analysis of the generated synthetic ECGs compared to real data	■ The generated ECGs are primarily assessed visually, lacking quantitative analysis ■ Reliance on a limited dataset from only one source ■ Synthetic ECGs require validation by expert physicians ■ Issues like privacy breaches from data leakage and biases in synthetic data remain unexplored
8	(Sui et al. 2021)	Enables the establishment of an effective correlation between genomic and radiology information using hierarchical features	■ A potentially insufficient dataset size, affecting model generalizability ■ Issues with uneven distribution within the dataset ■ Detection of anomalies, especially around lung edges and other organs like the heart ■ Lack of complete independence in tumor characteristics due to coupling in generation
9	(Tang et al. 2021)	Demonstration of the feasibility of using DGMs to investigate complex tumor-nano interactions with pixel-level accuracy and high reliability	■ The study is constrained by a single tumor model and focuses only on staining specific cell types, overlooking the diversity of tumor models and broader tumor microenvironment components ■ Inconsistencies in immunohistochemistry staining methods across labs, coupled with GANDA's current limitation to 2D imaging, necessitating adaptation for 3D analysis
10	(Ahmed et al. 2022)	Demonstrates the ability of omicsGAN to integrate multiple omics data types, such as miRNA and gene expression, and their interaction networks, leading to improved predictive performance for cancer phenotype classification and survival prediction	■ The study's concentration on particular cancers like breast, lung, and ovarian limits its direct applicability to other cancer types or diseases ■ The absence of specific quantitative metrics for assessing omicsGAN's performance, apart from AUC scores ■ The study omits external validation using independent datasets, crucial for establishing the generalizability and robustness of its results

Table 5 (continued)

#	Ref	Main Strength	Main Limitation
11	(Ahuja et al. 2022)	The topics inferred by MixEHR-G align effectively with the corresponding phenotypes and complement rule-based phenotyping algorithms	■ Requirement to convert continuous variables and summarize time-based observations ■ Challenges in handling data from multiple centers with demographic and coding differences ■ Need to confirm specific associations, like bipolar disease and hypothyroidism ■ Reliance on age and sex in the Bayesian topic prior may limit applicability to diverse patient profiles
12	(Rafael-Palou et al. 2022)	Holds promise in delivering valuable predictions regarding the progression of lung nodules	■ Low number of analyzed tumor cases ■ The segmentations were generated semi-automatically based on original diameter, growth, and centroid annotations, with final validation by a visual expert ■ Relies on a single axial slice of the tumor to predict tumor growth
13	(Benary et al. 2023)	Addresses the challenge of integrating multidimensional data beyond established guidelines, showcasing the potential of LLMs in dealing with complex medical decision-making	■ Small Sample Size which may impact the generalizability of the results ■ Limited Conclusions due to the rapid development of new LLM models and versions ■ Experienced challenges related to the interpretation of results
14	(Bernardini et al. 2023)	The proposed ccGAN strategy exhibits reliable imputation performance compared to baseline GAN-based methods, particularly in handling missing values in the clinical MDC dataset under the MCAR assumption	■ Excludes high-missingness predictors, potentially missing key diabetes features ■ Challenges in applying findings broadly, with key data fields like examinations and medications omitted ■ The study lacks comprehensive evaluation of the long-term impact of using synthetic data in myeloid malignancy research
15	(El Emam 2023)	Offered evidence that synthetic data using cGAN can accelerate translational research in hematology	■ Applicability of findings primarily restricted to specific malignancies, with limited extension to other cancer types ■ Inadequate assessment and evaluation of the long-term effects and sustainability of using synthetic data in myeloid malignancy research

Table 5 (continued)

#	Ref	Main Strength	Main Limitation
16	(Gao et al. 2023)	Innovative approach to modeling individualized brain atrophy patterns has the potential to aid in the	■ Significant resources needed for generating and analyzing personalized brain atrophy patterns ■ Difficulties in decoding outputs from complex methods like BrainStatTrans-GAN ■ Essential to test and validate on varied datasets for broader model applicability
17	(Hsu and Lin 2023)	SCAN effectively utilizes both labeled and unlabeled patient data in a semi-supervised manner for predicting cancer patient prognosis	■ SCAN's enhanced performance heavily relies on the availability of unlabeled data ■ Initial performance gains from duplicated unlabeled data, but effectiveness decreases beyond a certain threshold ■ Utilizing synthetic data from advanced GANs does not endlessly boost the model's performance ■ The study is constrained by the scope and size of the datasets used
18	(Huang et al. 2023)	Explores the vast potential of ChatGPT-4, in assisting with medical diagnoses and patient care	■ Limited assessment scope, missing a comprehensive comparison with medical LLMs like Med-PaLM ■ Time-specific benchmarks influenced by model updates ■ Challenges arise from inconsistencies in complex case evaluation, reliance on external tools, and the requirement for internet browsing for up-to-date information
19	(Jahanyar et al. 2023)	The study provides insights into reliable data generation and evaluation for microarray data, specifically related to schizophrenia gene expression	■ Single omics focus may overlook complex disease patterns revealed by multi-omics analysis ■ Method's specificity to schizophrenia gene expression data limits applicability to other diseases or data types ■ Missing details on computational demands, implementation time, and generalizability beyond schizophrenia restrict broader use
20	(M. Shi et al. 2023a, b)	Introducing a novel GAN architecture with an attention mechanism that enables the model to assign different weights to input parts based on their relevance to the task	■ Limited prognosis prediction with multimodal data ■ Prone to overfitting ■ Low feature dimension (k) may limit performance

Table 5 (continued)

#	Ref	Main Strength	Main Limitation
21	(Moon et al. 2023)	Generation of more realistic post-therapeutic OCT images and superior performance compared to human examiners	■ Single-center retrospective study limits generalizability ■ Evaluation focuses on short-term outcomes ■ Limited OCT image variety ■ Small study population (842 patients) ■ Absence of noise reduction ■ Minimal exploration of AI models
22	(Li et al. 2023)	The model fully utilizes the inner graphical structure of Electronic Health Records (EHRs), enhancing its ability to extract meaningful information	■ Unclear impact on data quality and prediction ■ Limited applicability in varying label-rate scenarios ■ Lack of defined switching thresholds between algorithms ■ Requires improved patient privacy and IP protection
23	(R. Shi et al. 2023a, b)	The GANCMLAE model combines GAN, AE, and multiple loss functions, improving the detection of individual brain atrophy in AD and MCI patients	■ Resolution mismatch between generated and input images ■ Lack of exploration into physiological mechanisms for AD and MCI ■ Exclusive use of 2D images due to processing limitations ■ Small sample size leads to higher p-values and limited comparisons
24	(Strack et al. 2023)	Fully unsupervised, requiring no manual annotations or large pre-trained models. It only needs two MR images from the same patient at different timepoints	■ Ground truth generated by a neural network, not medical experts ■ Performance sensitivity to MRI image quality and resolution ■ Limitation due to reliance on data from one patient ■ Insufficient capture of patient case variability ■ Limited resources due to lack of external funding ■ Modified RANO criteria may not align with clinical standards, affecting clinical applicability
25	(Toufiq et al. 2023)	Establishes a standardized workflow for how LLMs can be integrated into the candidate gene prioritization process in a systematic way	■ Factual accuracy concerns ■ Risk of information hallucination ■ Dependency on LLMs' training data ■ LLMs cannot replace traditional scientific methods
26	(Wang et al. 2023)	· Demonstrated the potential to predict drug responses in different cancer types and revealed differences in survival outcomes	■ Lacks clinical validation for practical treatment ■ Limited to two omics integrations, potentially overlooking other influential factors

Table 5 (continued)

#	Ref	Main Strength	Main Limitation
27	(Yamanaka et al. 2023)	The method can generate new drug candidate molecules for diseases with unknown therapeutic target proteins, which is a significant contribution to precision medicine	■ Need for broader disease applicability validation ■ Limitations of structural similarity in assessing therapeutic effects ■ Evaluation required for generating molecules across numerous diseases
28	(Zhou et al. 2023)	Introduce new method, SCGAN, to produce sparse, diverse, and plausible counterfactuals while maintaining proximity to the original instances	■ Limited comparison with other counterfactual generation methods ■ Generalizability constrained to breast cancer datasets ■ Potential biases from specific open-source data ■ Concerns about SCGAN's scalability and computational efficiency in clinical settings
29	(Zhu et al. 2023)	Creating individualized glucose time series data	■ Absence of standardized GAN model validation criteria and hyper-parameter tuning ■ Unusual responses to certain conditional inputs, like unexpected glucose level changes ■ Implementation challenges for a personalized T1D simulator ■ Limited evaluation scope to clinical datasets, warranting broader demographic and clinical profile assessment

4 Discussion

This paper lightens the developments of the cutting-edge applications of generative AI methods in precision medicine, to improve treatment outcomes and patient care through personalized and data-driven approaches. The methodology employed in the review involved a systematic and rigorous approach to identify, select, and evaluate relevant literature on the applications of generative models in personalized medicine, ensuring a comprehensive and unbiased review of the current state of the field. The review of the 29 final refined papers focuses on exploring the potential of DGMs and LLMs in various aspects that constitute individualized medicine including clinical informatics, bioinformatics, and medical imaging.

4.1 Interpretation of results

A diverse array of generative models is tailored for personalized clinical, biomedical, and healthcare applications. These models, such as omicsGAN, GANITE, Dr.VAE, and innovativeGAN architectures with attention mechanisms, demonstrate their efficacy in tasks ranging from cancer phenotype classification to drug response prediction. Notably, they contribute to data generation, simulation of rare scenarios, and personalized experiments in a virtual environment. These models exhibit capabilities in handling high-dimensional biological data, predicting disease progression, and generating synthetic healthcare data for translational research. In imaging informatics generative models such as are U-HPNet model are designed to forecast lung nodule progression, addressing uncertainties in medical images and radiologist annotations. For brain tumor growth prediction, the Growth Prediction (GP-GAN) method utilizes stacked 3D generative adversarial networks, outperforming existing models in accuracy. In Alzheimer's and mild cognitive impairment, BrainStatTrans-GAN and GANCMLAE are proposed to decode individualized brain atrophy patterns, providing a crucial approach for more personalized interventions. Other studies introduced ccGAN for imputing missing values in EHR datasets, excelling in diabetic retinopathy detection, while others proposed a semi-supervised method using graph representations and GANs to generate synthetic data, outperforming alternative approaches with minimal labels. Generative models, such as MixEHR-G, a Bayesian topic model facilitating automatic phenotyping in large-scale EHR data, have proven effective in predicting phenotypes and revealing associations between diseases. In data anonymization, ADS-GAN and extended GAN-based approaches demonstrated anonymization for general health data, ensuring patient confidentiality and preserving data characteristics while maintaining identifiability. For prognosis, modified generative models such as SCAN, a semi-supervised cancer prognosis classifier, and GluGAN, for personalized glucose time series data generation, have shown promise in enhancing glucose prediction algorithms, respectively. In counterfactual explanations, SCGAN has provided sparse, diverse, and plausible explanations for breast cancer patient response predictions, contributing to interpretability and causal understanding. These advancements collectively drive progress in precision medicine, clinical research, and healthcare data privacy. Additionally, the review highlights the potential of advanced foundation models like ChatGPT-4 in medical decision-making and proposes standardized workflows for integrating large language models into candidate gene prioritization processes. The collective impact of these models spans diverse aspects of healthcare, from molecular interactions to patient prognosis and diagnostic support.

4.2 Challenges and limitations of deep generative models in precision medicine

Challenges in the present ecosystem of deep generative modes and foundation models like LLMs in precision medicine are underscored by their limitations. These challenges involve issues such as restricted generalizability, insufficient model evaluation metrics, and a lack of external validation across diverse datasets. The intricacies of model architectures and their dependencies on data quality and representativeness present additional hurdles, along with concerns about training process stability, potential biases stemming from unobserved confounders, and the risk of overfitting. Additionally, the limited consideration of multi-omics complexities, sparse modeling techniques, and a focus on specific diseases emphasize the necessity for improvements in the applicability, interpretability, and clinical validation of these models for practical use in healthcare settings. These limitations of the studies highlight the complexities and challenges faced in various scientific and medical research endeavors, emphasizing the ongoing need for careful consideration, validation, and improvement in generative methodologies. Table 5 provides a comprehensive overview of the strengths and limitations of each generative model. Addressing these limitations and implementing the suggested recommendations will contribute to the advancement of generative AI and its potential for personalized clinical applications is provided in Table 6.

4.3 Limitations of the review process

This systematic review is subject to several limitations that warrant acknowledgment. Firstly, there is a possibility that the review might have overlooked certain publications that could contribute valuable insights and data pertinent to the scope of the study. The vast and continually evolving nature of medical literature poses a challenge, and despite comprehensive search strategies, some relevant studies may have been inadvertently omitted. Recognizing these limitations is crucial for a subtle interpretation of the review's findings and underscores the importance of future updates or supplementary reviews conducted with the input of medical professionals to enhance the comprehensiveness and accuracy of the analysis.

4.4 Future research and directions

In navigating the future trajectory of research, numerous pathways emerge with the potential to transcend current boundaries and rectify existing limitations. These avenues necessitate a collaborative effort to confront prevailing constraints, bolster model robustness, enhance generalizability, and advocate for the conscientious and effective utilization of DGMs and FMs in precision medicine. One key direction involves cultivating enhanced generalizability through the development and training of models on diverse datasets encompassing a spectrum of cancer types and diseases. Moreover, adopting quantitative metrics beyond accuracy scores and emphasizing external validation on independent datasets becomes imperative for rigorous evaluation. Simultaneously, prioritizing model interpretability, investing in research to elucidate generative model decision-making processes, and fostering transparency cater to the needs of healthcare practitioners. This involves simplifying model architectures, implementing standardized validation procedures, and addressing challenges related to data quality to

Table 6 Summary of main limitations and recommendations of generative AI in precision medicine

Common limitations	Suggested recommendations
Limited generalizability to other diseases	Include diverse datasets covering a broader spectrum of diseases to enhance the model's applicability
Lack of comprehensive evaluation metrics	Utilize a variety of quantitative metrics beyond AUC scores to thoroughly evaluate model performance
Absence of external validation	Validate and strengthen findings through external validation on independent datasets
Complexity and lack of interpretability in generative models	Improve model interpretability, possibly employing visualization tools, to foster understanding and trust in healthcare applications
Complex model architecture	Rigorously validate and interpret the results of the advanced model architecture to ensure reliability and accuracy
Dependency on data quality and representativeness	Improve the quality and representativeness of input data, considering alternative sources if necessary
Instability in training GANs	Stabilize GAN training to improve the accuracy of Individual Treatment Effect (ITE) estimation, address and mitigate identified drawbacks associated with GANs, and systematically tune hyperparameters to enhance the stability and performance of GANs
Assumption of no unobserved confounders	Explicitly consider and address potential unobserved confounders to mitigate bias in results
Small real data example size	Increase the sample size for real data example, address the imbalance in data features versus samples and consider alternative approaches or augmentation techniques to address data size limitations
Sparse modeling techniques	Explore alternative feature selection algorithms alongside LASSO techniques
Limitation to single omics data analysis	Emphasize the importance of multi-omics studies and expand the integration of multi-omics data beyond genomes and transcriptomes
Disease-specific methodology	Ensure methods are adaptable to different types of data and diseases
Inadequate consideration of computational resources	Address the computational resources and time required for practical implementation
Focus on single modality (gene expression)	Explore multi-omics predictors
Overfitting issues with discriminative neural networks	Implement strategies and regularization techniques to mitigate potential overfitting issues
Need for predictive models with heterogeneous data	Develop models that effectively utilize sparsely sampled data
Poor prognosis outcome prediction for multimodal data	Focus on improving prognosis outcome prediction for patients
Lack of clinical validation for practical treatment	Conduct rigorous clinical validation to ensure the practical efficacy of proposed treatment methods
Non-interpretable learned representations	Work on developing models with more interpretable representations
Dependency on Parameters like Architecture	Explore architectures that are less sensitive to parameter variations
Inability to Infer Causality	Acknowledge the limitations in causal inference and communicate results as statistical correlations

Table 6 (continued)

Common limitations	Suggested recommendations
Challenges in generating realistic new data	Continuously refine methods to generate more realistic data along
Method's Applicability to a Broader Range of Diseases	Extend validation efforts to ensure the method's applicability across a broader range of diseases

contribute to the reliability and accuracy of models, facilitating their adoption in clinical settings. The integration of multi-omics data and an understanding of system biology expands the depth of disease comprehension, ensuring clinical applicability through validation and focusing on ethical considerations, patient privacy, and continuous evaluation underscore the commitment to responsible model deployment. Strategies such as heterogeneous data utilization, improved model robustness, and interdisciplinary collaboration further fortify the models' efficacy. Furthermore, the exploration of advanced architectures, refined validation criteria, disease-specific tailoring, and real-world implementation considerations contributes to the evolution of generative models. Continuous learning from new data, advancements in foundation models for medical imaging, exploration of new model paradigms, and human-in-the-loop approaches propel the field forward, anticipating and addressing challenges for a comprehensive and impactful advancement in healthcare technology.

5 Conclusion

In conclusion, despite certain limitations such as restricted generalizability, insufficient model evaluation metrics, and a lack of external validation across diverse datasets, the integration of generative artificial intelligence (AI) models into personalized healthcare holds immense potential to revolutionize disease diagnosis and treatment. The continuous advancement and sophistication of generative AI models are expected to fuel further growth in precision medicine. Various future paths and recommendations outlined in this review offer opportunities to expand research boundaries and overcome existing limitations. A collective effort is required to confront current constraints, enhance model robustness, improve generalizability, and promote the responsible and effective application of deep generative models and foundation models in this field. Overcoming challenges such as data scarcity and ensuring the generation of realistic, privacy-preserving synthetic patient data are crucial steps toward surpassing limitations in real patient data collection. Additionally, the ongoing development and refinement of LLMs-based diagnostics are essential for improving diagnostic accuracy, precision, and medical recommendation capabilities across various medical conditions. The application of generative AI methods to personalized medicine is still in its early stages, highlighting the need for more interdisciplinary and collaborative research efforts to advance this field collectively.

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Author contributions IG, NZ, and RD collaboratively contributed to the conceptualization, methodology, and the writing of the original draft of the paper, with NZ taking a leading role in formulating the research question, defining the scope of the literature review, and overseeing the project's supervision. All authors were actively involved in data curation, writing, review, and editing of the manuscript, with IG playing a pivotal role in gathering and curating relevant literature to ensure thorough coverage of the topic. Furthermore, each author equally contributed to the investigation and analysis aspects of the research.

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Declarations

Competing Interests The authors declare that they have no potential conflicts or competing of interest.

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