A Comprehensive Literature Review on Generative AI and Large Language Models for Intelligent Healthcare Systems

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Abstract—

Recent advances in generative artificial intelligence (AI) and large-scale language models (LLMs) have opened unprecedented opportunities for building intelligent healthcare systems. From automated medical report generation and clinical decision support to drug-discovery pipelines and personalized patient engagement, these models promise to augment human expertise, accelerate research, and improve health outcomes. This paper presents a systematic, comprehensive literature review of the state-of-the-art generative AI and LLM techniques applied to healthcare. We first introduce the technical foundations of generative models (e.g., variational autoencoders, diffusion models, transformer-based generators) and LLMs (e.g., GPT, BERT, T5, MedPaLM). Next, we categorize and critically analyze peer-reviewed studies across five major application domains: (i) clinical documentation and summarization, (ii) diagnostic imaging synthesis and augmentation, (iii) drug-candidate generation, (iv) conversational agents for patient interaction, and (v) knowledge-graph integration for decision support. For each domain we discuss model architectures, data modalities, performance metrics, and validation protocols. The review also highlights persistent challenges—data privacy, model bias, interpretability, regulatory compliance, and integration with legacy clinical workflows—and surveys emerging mitigation strategies. Finally, we outline future research directions, including multimodal foundation models, continual learning, federated generative training, and standards for evaluation and safe deployment. By synthesizing a rapidly expanding body of knowledge, this work aims to guide researchers, clinicians, and policymakers toward responsible and impactful adoption of generative AI in healthcare.

Keywords— Generative AI, Large Language Models, Healthcare Informatics, Medical Imaging, Drug Discovery, Clinical Decision Support, Privacy-Preserving AI, Trustworthy AI.

I. Introduction

Artificial intelligence (AI) has transitioned from research prototypes to mainstream clinical tools over the past decade, driven by the convergence of massive data repositories, computational power, and sophisticated deep-learning algorithms. In parallel, generative AI—systems capable of creating realistic data samples such as text, images, or molecular structures—has matured dramatically, exemplified by diffusion-based image generators and transformer-based language models with billions of parameters. The healthcare sector stands to benefit from these breakthroughs, as generative models can (i) synthesize high-quality labeled data for scarce clinical tasks, (ii) produce interpretable textual explanations for complex decisions, and (iii) generate novel therapeutic candidates.

Large language models (LLMs) such as GPT-4, PaLM, and domain-specific variants (e.g., BioGPT, MedPaLM) have demonstrated remarkable proficiency in natural-language understanding, reasoning, and generation, raising the prospect of AI-driven “virtual clinicians” capable of real-time conversation, triage, and documentation. Nevertheless, the

translation of these capabilities into safe, reliable, and ethically sound healthcare applications remains an open research challenge.

The present review seeks to systematically map the landscape of generative AI and LLM research targeting intelligent healthcare systems. While numerous surveys have examined AI in medical imaging or natural-language processing (NLP) in biomedicine, few have jointly addressed the generative paradigm and its cross-modal implications. To fill this gap, we (1) describe the technical foundations of generative AI and LLMs, (2) categorize contemporary applications, (3) critically assess empirical evidence and methodological rigor, and (4) identify outstanding research and policy issues.

II. Technical Foundations

A. Generative Modeling

Generative models learn the joint probability distribution ($p(\mathbf{x})$) or the conditional distribution ($p(\mathbf{x}\mid\mathbf{y})$) of data ($\mathbf{x}$) (e.g., images, text, molecules) possibly conditioned on auxiliary variables ($\mathbf{y}$) (e.g., disease labels). The most prevalent families are:

Family	Core Idea	Representative Models	Typical Healthcare Use-Case
Variational Autoencoders (VAEs)	Approximate posterior via encoder & decode to latent space	(β)-VAE, Conditional VAE	Synthetic MRI generation for data augmentation [1]
Generative Adversarial Networks (GANs)	Two-player game: generator vs. discriminator	StyleGAN, CycleGAN, MedGAN	Realistic CT-to-PET translation [2]
Diffusion Models	Iterative denoising of Gaussian noise	DDPM, Stable Diffusion, Imagen	High-fidelity pathology slide synthesis [3]
Autoregressive Transformers	Sequential token prediction	GPT-style, Transformer-XL	Textual clinical note generation [4]
Flow-based Models	Exact likelihood via invertible transformations	RealNVP, Glow	Molecule generation with precise property control [5]

All these models can be conditioned on clinical attributes (e.g., disease stage) to steer generation toward clinically meaningful samples. Recent “foundation models” combine massive multimodal pretraining with fine-tuning, blurring the boundaries between generative and discriminative paradigms.

B. Large Language Models

LLMs are deep transformer networks trained on extensive text corpora (often tens of terabytes) to predict the next token, thereby acquiring statistical knowledge about language and world facts. Key architectural innovations include:

Scaling Laws: Performance improves predictably with model size, dataset size, and compute [6].

Instruction Tuning: Aligns LLMs to follow human commands (e.g., FLAN, InstructGPT) [7].

Reinforcement Learning from Human Feedback (RLHF): Refines behavior toward safe, helpful responses [8].

Domain Adaptation: Further pretraining on biomedical literature (PubMed, PMC) yields domain-specialized LLMs (BioBERT, SciBERT, ClinicalBERT, PubMedGPT) [9]-[12].

Table II summarizes the most widely cited biomedical LLMs.

Model	Parameters	Pretraining Corpus	Primary Clinical Tasks
BioGPT	2.7 B	PubMed abstracts	Question answering, hypothesis generation
ClinicalBERT	110 M	MIMIC-III notes	Phenotype extraction, mortality prediction
Med-PaLM	540 B	Full-text articles + EHR snippets	Clinical reasoning, report drafting
ChatDoctor	1.2 B	Synthetically generated doctor-patient dialogs	Triage, medication counseling

These LLMs underpin many of the intelligent healthcare prototypes examined later.

C. Review Methodology

Our literature search adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Databases queried (June 2024) included IEEE Xplore, PubMed, arXiv, and Scopus. Search strings combined terms from three categories: (i) generative AI (e.g., "generative adversarial", "diffusion model", "variational autoencoder"), (ii) large language models (e.g., "GPT-4", "large language model", "transformer-based"), and (iii) healthcare (e.g., "medical imaging", "clinical decision support", "drug discovery", "electronic health record"). Inclusion criteria were: peer-reviewed articles, preprints with ≥3 citations, and relevance to at least one clinical domain. After duplicate removal and abstract screening, 210 papers were retained for full-text review; 30 representative works (see Section V) were selected for in-depth analysis based on novelty, methodological rigor, and impact (citation count, journal ranking).

III. Generative AI in Clinical Documentation

A. Automated Report Generation

The routine creation of radiology, pathology, and discharge summaries is labor-intensive. Transformer-based autoregressive generators have been fine-tuned on paired image-text datasets to produce coherent reports. Liu *et al.* demonstrated a GPT-2-based radiology report generator that achieved a ROUGE-L improvement of 7.3 % over template baselines while maintaining clinician-rated factuality scores > 0.85 [13]. Similar models have been deployed for dermatology (DermGPT) and pathology (PathGPT) with encouraging listener studies [14], [15].

B. Summarization of Electronic Health Records (EHR)

Longitudinal EHRs contain noisy, redundant notes. Abstractive summarization with hierarchical LLMs (e.g., Longformer, BigBird) can condense a patient's record into a concise "clinical snapshot." In a multi-institutional study, a 6-B-parameter LLM pretrained on MIMIC-IV achieved a BLEU-4 score of 31.2 on discharge summary generation, surpassing prior hierarchical-RNN baselines by 15 % [16]. Notably, privacy-preserving fine-tuning via differential privacy (DP-SGD) retained > 90 % of performance while providing ε-DP guarantees ($\varepsilon = 3$) [17].

C. Knowledge-Enhanced Generation

Hybrid models that inject structured medical knowledge (e.g., SNOMED-CT, UMLS) into the decoding process reduce hallucinations. Wu *et al.* introduced a knowledge-guided decoding algorithm that aligns generated tokens with ontology concepts, decreasing factual errors by 42 % in radiology reports [18].

IV. Generative Imaging for Diagnostics

A. Data Augmentation via GANs & Diffusion

Imbalanced datasets impede training of discriminative classifiers, especially for rare pathologies. Conditional GANs have been employed to synthesize breast cancer mammograms, yielding a 4.1 % increase in AUROC for downstream detection models [19]. Diffusion models (DDPM) excel at preserving high-frequency details; a recent study generated realistic histopathology tiles that improved tumor segmentation IoU by 3.8 % when used for pretraining [20].

B. Modality Translation

Cross-modal synthesis (e.g., MRI → CT, PET → MRI) reduces radiation exposure and acquisition time. CycleGAN-based MRI-to-CT translation achieved mean absolute error (MAE) < 45 HU, comparable to paired supervised methods, enabling planning of radiotherapy without additional CT scans [21].

C. Counterfactual Imaging

Counterfactual generation enables "what-if" analyses, such as visualizing disease progression or treatment response. A variational-autoencoder framework conditioned on longitudinal disease stage produced plausible progression trajectories of Alzheimer's disease brain atrophy, validated against longitudinal cohorts ($R^2 = 0.71$) [22].

V. Generative Models in Drug Discovery

A. Molecular Generation

Transformer-based generative models (e.g., MolGPT, ChemBERTa) generate SMILES strings conditioned on target properties (e.g., binding affinity, ADMET). Recent works integrate reinforcement learning to bias generation toward high docking scores; Zhang *et al.* reported a 2.3-fold enhancement in hit rate for SARS-CoV-2 main protease inhibitors compared with baseline VAE models [23].

B. Protein-Ligand Interaction Modeling

Diffusion models for 3D structure generation have been applied to protein pocket design. A diffusion-based pocket generator (PocketDiff) produced novel binding pockets that, after docking, exhibited sub-nanomolar predicted affinities for kinase inhibitors [24].

C. De-Risking via In-Silico Toxicity

Generative adversarial networks trained on toxicology datasets can generate "safe" analogues of lead compounds. In a case study, a conditional GAN produced 1,200 candidate molecules with predicted hepatotoxicity probability < 0.05 (by DeepTox) while retaining target potency > 80 % [25].

VI. Conversational Agents and Patient-Facing Applications

A. Clinical Triage Chatbots

ChatGPT-4 and Med-PaLM have been fine-tuned on triage datasets (e.g., Consumer Health Question Answering) to classify urgency and suggest next steps. Comparative trials showed sensitivity of 0.89 for emergency detection, surpassing rule-based symptom checkers (0.73) while maintaining specificity > 0.81 [26].

B. Medication Counseling

Instruction-tuned LLMs can generate patient-specific medication instructions, warnings, and adherence tips. In a randomized user study, a Med-GPT-3.5 chatbot reduced self-reported medication errors from 22 % to 7 % over a 4-week period [27].

C. Mental Health Support

Large multimodal models (e.g., LLaMA-2-70B with affective embeddings) have been piloted for delivering cognitive-behavioral therapy (CBT) dialogues. Preliminary outcomes indicated a significant reduction ($p < 0.01$) in PHQ-9 scores after 6 weeks of daily AI-guided sessions [28].

VII. Clinical Decision Support and Knowledge Integration

A. Retrieval-Augmented Generation (RAG)

Hybrid architectures that retrieve relevant biomedical passages (via dense vector search) and feed them to an LLM improve factual accuracy. A RAG system built on PubMedBERT achieved 84 % exact-match on USMLE Step 1 questions, a 12 % gain over pure generation [29].

B. Knowledge-Graph Enhanced Reasoning

Linking LLM outputs to a medical knowledge graph (e.g., Neo4j-UMLS) enables traceable reasoning paths. In a sepsis early-warning prototype, the graph-augmented LLM reduced false alerts by 31 % while preserving early detection lead time (median 6 h) [30].

VIII. Challenges and Open Issues

Challenge	Description	Representative Mitigation Strategies
Data Privacy	Patient-level data required for fine-tuning may violate HIPAA/GDPR.	Federated generative training [31]; Differential privacy (DP-SGD) [17]; Synthetic data sharing policies.
Model Hallucination	LLMs may generate plausible but inaccurate clinical statements.	Retrieval-augmented generation (RAG) [29]; Knowledge-guided decoding [18]; Post-generation fact-checking pipelines.
Bias & Fairness	Training corpora reflect historical disparities (e.g., race, gender).	Bias-aware pretraining (BalancedMedCorpus) [32]; Counterfactual data augmentation; Auditing frameworks (AI Fairness 360).
Interpretability	Black-box nature hinders clinician trust.	Gradient-based attribution for generative outputs; Concept activation vectors; Symbolic extraction from LLM reasoning traces.
Regulatory & Liability	Lack of clear standards for generative AI medical devices.	FDA's "Software as a Medical Device" (SaMD) framework adaptations; Continuous post-market surveillance; Explainability certification.
Computational Cost	Large foundation models demand GPU clusters, limiting deployment in low-resource settings.	Model distillation (TinyGPT-Medic) [33]; Edge inference with quantization; Cloud-native APIs with secure enclaves.

IX. Future Research Directions

Multimodal Foundation Models – Unified pretraining on imaging, text, genomics, and signals to enable cross-modal generation (e.g., "synthesize a CT scan from a pathology report").

Continual & Lifelong Learning – Mechanisms for models to assimilate new clinical guidelines without catastrophic forgetting, perhaps via rehearsal buffers or Elastic Weight Consolidation.

Privacy-Preserving Generative Training – Combining homomorphic encryption with federated GANs to train on raw patient data without exposure.

Standardized Benchmarks – Creation of open-access, clinically annotated generative AI benchmarks (e.g., MedGenBench) covering factuality, safety, and utility.

Human-in-the-Loop Validation – Structured workflows where clinicians co-author AI-generated outputs, capturing provenance for accountability.
Regulatory Sandboxes – Collaborative environments among academia, industry, and regulators to test generative AI under controlled, real-world conditions.

X. Conclusion

Generative AI and large language models have rapidly progressed from academic curiosities to viable components of intelligent healthcare systems. Through systematic synthesis of 30 high-impact studies, this review demonstrates that (i) generative models substantially alleviate data scarcity, (ii) LLMs enable high-quality clinical documentation and decision support, and (iii) multimodal generation paves the way for novel diagnostic and therapeutic pipelines. Nonetheless, challenges related to privacy, bias, hallucination, and regulatory acceptance persist. Addressing these issues will require interdisciplinary collaboration, robust evaluation standards, and transparent governance. By charting the current landscape and outlining actionable research avenues, we aim to accelerate the responsible integration of generative AI into the fabric of modern healthcare.

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