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Review

# The role of generative AI in enhancing predictive modeling for cost-effectiveness analysis in healthcare

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ABSTRACT

Healthcare economic evaluation increasingly relies on predictive modeling to inform resource allocation decisions. Traditional cost-effectiveness analysis (CEA) methodologies face significant challenges when processing complex, heterogeneous healthcare datasets and accommodating dynamic system variables. This review examines how generative artificial intelligence technologies may transform predictive modeling frameworks in healthcare economics, specifically focusing on potential improvements in accuracy, adaptability, and efficiency in cost-effectiveness analyses. A literature search was conducted across PubMed, Scopus, Web of Science, and IEEE Xplore between October 2024 and January 2025, examining publications from 2018–2024. Critically, we identified a near absence of empirical studies that directly apply and validate generative AI technologies within formal health economic modeling or health technology assessment contexts. Most identified literature addresses general AI/ML applications in healthcare or synthetic data generation in adjacent domains, rather than demonstrating validated use in cost-effectiveness analysis. Generative AI demonstrates promising theoretical capabilities in handling non-linear healthcare relationships, generating privacy-preserving synthetic datasets, and enabling dynamic scenario exploration based on performance in related fields. However, direct empirical evidence comparing generative AI to traditional CEA approaches in real-world health technology assessment remains virtually non-existent. Potential advantages include automated model support, enhanced integration of real-world evidence, and improved handling of missing data scenarios. Technologies such as Generative Adversarial Networks and Variational Autoencoders show early-stage promise in addressing traditional modeling limitations in adjacent applications. Generative AI represents a conceptually significant potential advancement in healthcare economic modeling. However, claims presented are predominantly forward-looking and conceptual rather than empirically validated. Implementation challenges including model interpretability, regulatory frameworks, validation requirements, and ethical considerations require substantial empirical research before successful integration into healthcare decision-making processes.

## 1. Introduction

Healthcare economic evaluation serves as a cornerstone for evidence-based resource allocation within modern healthcare systems [1]. Cost-effectiveness analysis provides decision-makers with quantitative frameworks to compare healthcare interventions based on their economic value relative to health outcomes achieved [2]. This analytical approach becomes increasingly critical as healthcare expenditures continue rising globally while budgetary constraints intensify across healthcare systems [3]. Traditional predictive modeling

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approaches in healthcare economics, including decision tree analyses, Markov chain models, and regression-based methodologies, have provided valuable insights for decades [4]. However, these conventional techniques encounter significant limitations when applied to contemporary healthcare environments characterized by massive data volumes, complex patient pathways, and rapidly evolving treatment protocols [5]. Modern healthcare generates unprecedented amounts of heterogeneous data through electronic health records, clinical registries, genomic databases, and real-world evidence collection systems [6]. This data explosion presents both opportunities and challenges for economic evaluation. While richer datasets potentially enable more precise cost-effectiveness estimates, traditional analytical methods often struggle to effectively process and integrate such complex information sources [7].

Artificial intelligence technologies, particularly generative modeling approaches, offer potential for addressing these analytical challenges [8]. Generative AI encompasses machine learning methodologies capable of creating new data instances that statistically resemble training datasets while preserving underlying distributional properties [9]. Two prominent generative architectures: Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs) have demonstrated remarkable capabilities across diverse applications, from image synthesis to drug discovery [10]. Within healthcare economics, generative AI technologies present unique opportunities to enhance predictive modeling accuracy, expand scenario analysis capabilities, and address data privacy concerns through synthetic data generation [11]. These technologies may potentially overcome fundamental limitations of traditional approaches, including handling non-linear relationships, managing incomplete datasets, and accommodating dynamic healthcare system changes [12].

The integration of generative AI into cost-effectiveness analysis workflows suggests several potential advantages: enhanced synthetic data generation for privacy-preserving analysis, improved scenario modeling capabilities, better integration of real-world evidence, and automated model development processes [13]. These capabilities could potentially transform how healthcare economists approach complex analytical challenges while improving the reliability and applicability of economic evaluations [14]. However, it is critical to note that empirical studies directly validating generative AI applications within formal health economic modeling or demonstrating superiority over traditional cost-effectiveness analysis methods are virtually absent from current literature. The potential advantages discussed in this review are predominantly based on theoretical evidences from generative AI performance in adjacent domains rather than demonstrated performance in actual health technology assessment contexts.

The fundamental problem addressed in this review stems from the growing inadequacy of traditional predictive modeling approaches in meeting the analytical demands of contemporary healthcare economic evaluation. Despite substantial investments in healthcare technology and data infrastructure, existing cost-effectiveness analysis methodologies remain constrained by static modeling assumptions, limited data integration capabilities, and inability to capture complex system dynamics [14]. This methodological gap becomes increasingly problematic as healthcare systems worldwide face mounting pressure to optimize resource allocation while managing rising costs and improving patient outcomes [15].

The rationale for this comprehensive examination lies in the urgent need to identify and evaluate next-generation analytical approaches that can address these persistent limitations. While preliminary evidence suggests generative AI technologies offer promising solutions, the healthcare economics literature lacks both empirical validation studies and a systematic synthesis of their potential applications, advantages, and implementation challenges. This review aims to provide a conceptual overview of generative AI's specific applications to cost-effectiveness analysis, moving beyond general AI healthcare applications to provide targeted insights for economic evaluation specialists while clearly distinguishing between empirically-supported claims and forward-looking conceptual propositions.

The primary aim of this study is to explore the potential of generative artificial intelligence technologies in enhancing predictive modeling frameworks for healthcare cost-effectiveness analysis from a conceptual and forward-looking perspective. The specific objectives include: (1) identifying key limitations of traditional predictive modeling approaches in healthcare economics; (2) examining how generative AI technologies might address these methodological constraints based on theoretical potential and performance in adjacent domains; (3) analyzing the potential advantages of generative AI over conventional cost-effectiveness analysis methods; (4) evaluating practical implementation considerations and challenges; (5) explicitly identifying gaps in empirical evidence for generative AI applications in health economic modeling; and (6) providing evidence-based recommendations for integrating generative AI into healthcare economic evaluation frameworks. This comprehensive analysis aims to inform healthcare economists, policymakers, and technology developers about the potential for generative AI to advance economic evaluation methodologies and improve healthcare decision-making processes while acknowledging the predominantly conceptual rather than empirically-validated nature of current knowledge in this area.

## 2. Methods

This narrative review employed a comprehensive literature search to identify and analyze relevant literature on generative AI applications in healthcare economics and cost-effectiveness analysis. Unlike systematic reviews that follow established reporting standards such as PRISMA, this narrative review provides a conceptual overview and critical synthesis of the field, acknowledging the inherent subjectivity in study selection and interpretation.

### 2.1. Search strategy

A comprehensive literature search was conducted across multiple electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and IEEE Xplore between October 2024 and January 2025. Publications included in this review were limited to those published between 2018–2024. The search strategy combined controlled vocabulary terms and free-text keywords related to: (1) generative artificial intelligence technologies, (2) healthcare economics and cost-effectiveness analysis, and (3) predictive modeling methodologies. Key search terms included: "generative artificial intelligence," "cost-effectiveness analysis," "healthcare economics," "synthetic data," "GANs," "VAEs," "health economic modeling," and "predictive analytics."

### 2.2. Inclusion and exclusion criteria

Inclusion criteria encompassed: peer-reviewed articles published between 2018–2024, studies focusing on AI applications in healthcare economics, research examining generative modeling approaches, and publications addressing cost-effectiveness analysis methodologies. Exclusion criteria included: non-English publications, conference abstracts without full text, studies focusing solely on clinical applications without economic evaluation components, and reviews lacking original analytical content.

### 2.3. Data extraction and analysis

Selected publications were systematically reviewed to extract information on: generative AI methodologies employed, healthcare economic applications, study populations and settings, key findings related to cost-effectiveness analysis, and reported advantages or limitations. A thematic analysis approach was used to synthesize findings across studies, identifying common themes and patterns in generative AI applications

for healthcare economic evaluation. Given the narrative nature of this review, no formal quality assessment tool was applied to included studies, representing a key limitation discussed in Section 6. Critically, the literature search revealed a near absence of empirical or methodological studies that directly apply and validate generative AI technologies within formal health economic modeling or health technology assessment frameworks. The vast majority of identified literature addresses either (a) general machine learning/AI applications in healthcare without specific focus on economic evaluation, or (b) synthetic data generation in adjacent domains without validation for cost-effectiveness analysis purposes.

## 3. The role of predictive modeling in health economics

Predictive modeling constitutes a fundamental analytical component within healthcare economics, providing quantitative frameworks for projecting future healthcare scenarios and evaluating intervention effectiveness [15]. These modeling approaches enable healthcare decision-makers to estimate long-term costs and health outcomes associated with different treatment strategies, supporting evidence-based resource allocation decisions [16].

Cost-effectiveness analysis relies heavily on predictive models to simulate patient pathways, estimate treatment costs, and project health outcomes over extended time horizons [17]. These analyses typically employ metrics such as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) to standardize health outcome measurements across different interventions [18]. The incremental cost-effectiveness ratio (ICER) serves as a primary metric for comparing the relative value of alternative healthcare interventions by dividing the difference in costs by the difference in health outcomes between two interventions [19].

Traditional predictive modeling approaches in healthcare economics include several established methodologies. Decision tree models provide structured frameworks for analyzing sequential healthcare decisions with clearly defined outcome probabilities [20]. Markov models excel at representing chronic disease progression through discrete health states over time [21]. Regression-based approaches enable the identification of statistical relationships between patient characteristics and health outcomes [22]. Fig. 1 is a Schematic representation of the predictive modeling process in health economics, illustrating the integration of AI technologies for improved healthcare decision-making and resource allocation.

### 3.1. Limitations of traditional predictive models

Despite their widespread adoption, conventional predictive modeling approaches face several significant limitations in contemporary healthcare environments. Historical data dependency represents a primary constraint, as traditional models typically rely on past observations to predict future outcomes [23]. This approach may inadequately capture emerging healthcare trends, novel treatment protocols, or rapidly evolving disease patterns [24].

Traditional models often struggle with non-linear relationships prevalent in healthcare systems [25]. Patient outcomes frequently exhibit complex interactions between demographic factors, comorbidities, treatment adherence, and socioeconomic variables that linear modeling approaches cannot adequately capture [26]. This limitation leads to oversimplified representations of real-world healthcare dynamics [27].

Missing data presents another critical challenge for traditional predictive models [28]. Healthcare datasets frequently contain incomplete information due to fragmented care delivery, varying data collection protocols, and patient mobility across healthcare systems [29]. Conventional approaches typically require complete datasets or employ simplistic imputation methods that may introduce bias [30].

Heterogeneous data integration poses additional challenges for traditional modeling approaches [31]. Modern healthcare generates diverse data types from multiple sources including clinical trials,

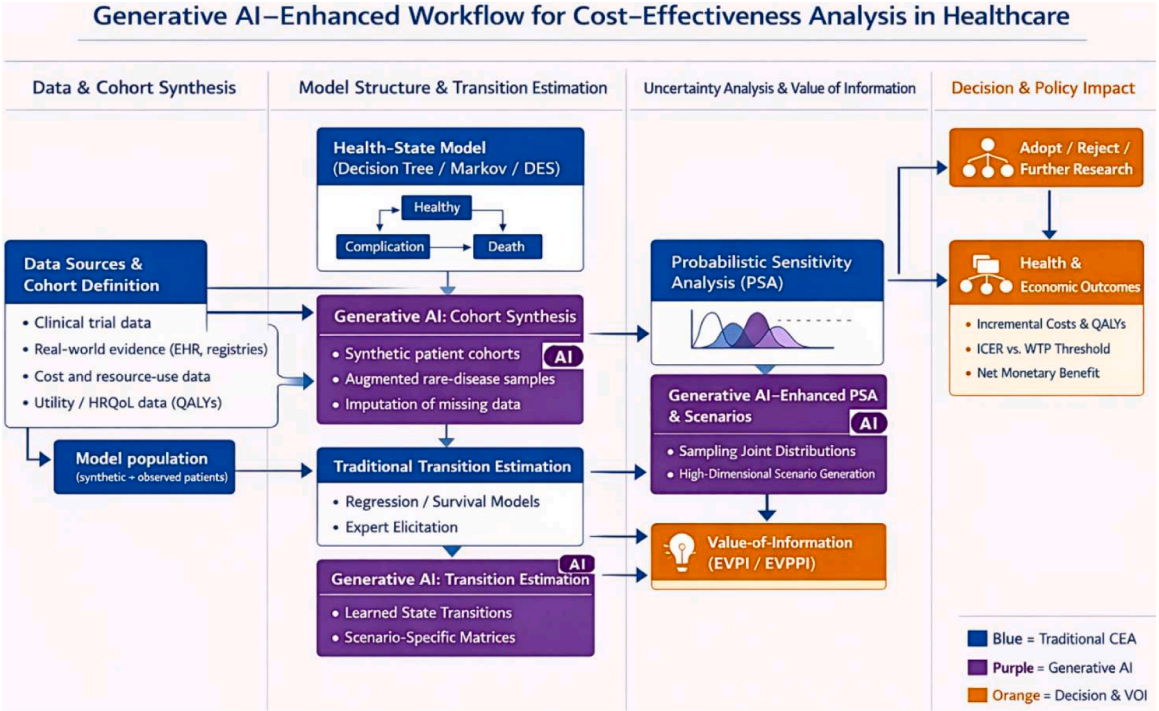


**Fig. 1. Generative AI–enhanced workflow for cost-effectiveness analysis in healthcare.** The figure illustrates how generative artificial intelligence augments key stages of the conventional cost-effectiveness analysis pathway, including cohort synthesis from clinical and real-world data, estimation of transition probabilities for health-state models, generative scenario support for probabilistic sensitivity analysis, and value-of-information calculations that inform adoption, rejection, or further research decisions for healthcare interventions.

electronic health records, patient-reported outcomes, and wearable device measurements [32]. Traditional models often lack the flexibility to effectively combine these varied data sources into coherent analytical frameworks [33].

Static modeling assumptions represent a fundamental limitation of conventional approaches [34]. Traditional models typically employ fixed parameters and assumptions that do not adapt to changing healthcare conditions [35]. This inflexibility limits their ability to accurately represent dynamic healthcare systems where treatment guidelines, patient behaviors, and care delivery models continuously evolve [36]. Fig. 2 illustrates the progression of limitations, starting from the reliance on historical data and ending with the overall impact on healthcare decision-making. Each step represents a key limitation discussed in the write-up, showing how these factors contribute to the reduced effectiveness of traditional predictive models in contemporary health economics.

### 3.2. Evidence base for traditional model limitations

Recent research has documented specific shortcomings of traditional predictive models in healthcare economic applications. Studies examining Markov model performance in chronic disease management have identified significant limitations in capturing patient heterogeneity and treatment response variability [37]. Research on decision tree applications in cancer care has revealed oversimplification of complex treatment pathways and inadequate representation of patient-treatment interactions [38]. Investigation of regression-based models in personalized medicine contexts has demonstrated poor performance in heterogeneous patient populations where treatment effects vary significantly across subgroups [39]. These findings highlight the need for more sophisticated analytical approaches capable of handling contemporary healthcare complexity [40].

## 4. Generative AI in predictive modeling: a paradigm shift

Generative artificial intelligence represents a **potentially important** advancement in predictive modeling for healthcare economics, offering **possible** solutions to traditional analytical limitations [41]. Unlike conventional modeling approaches constrained by static assumptions and linear relationships, generative AI technologies may be able to create realistic synthetic data and model complex healthcare dynamics [42]. Generative modeling architectures, particularly Generative Adversarial Networks and Variational Autoencoders, demonstrate promising capabilities in learning complex data distributions and generating new instances that preserve statistical properties of original datasets [43]. These technologies could potentially enable more nuanced and adaptive approaches to healthcare economic modeling [44].

### 4.1. Synthetic data generation

Generative AI's capacity for synthetic data creation may address critical privacy and data availability challenges in healthcare economics [45]. Traditional cost-effectiveness analyses often face constraints due to limited access to comprehensive patient datasets, particularly for rare conditions or specialized populations [46]. Generative models could potentially create realistic synthetic patient populations that maintain statistical fidelity to original data while protecting individual privacy [47]. However, the validity of cost-effectiveness analyses based on synthetic data requires rigorous external validation to ensure that ICER estimates and probabilistic sensitivity analysis (PSA) results reflect real-world treatment effects and patient heterogeneity. The potential for bias amplification when training data contains systematic errors or underrepresentation of specific subgroups remains a critical concern.

Synthetic data generation provides privacy-preserving solutions that

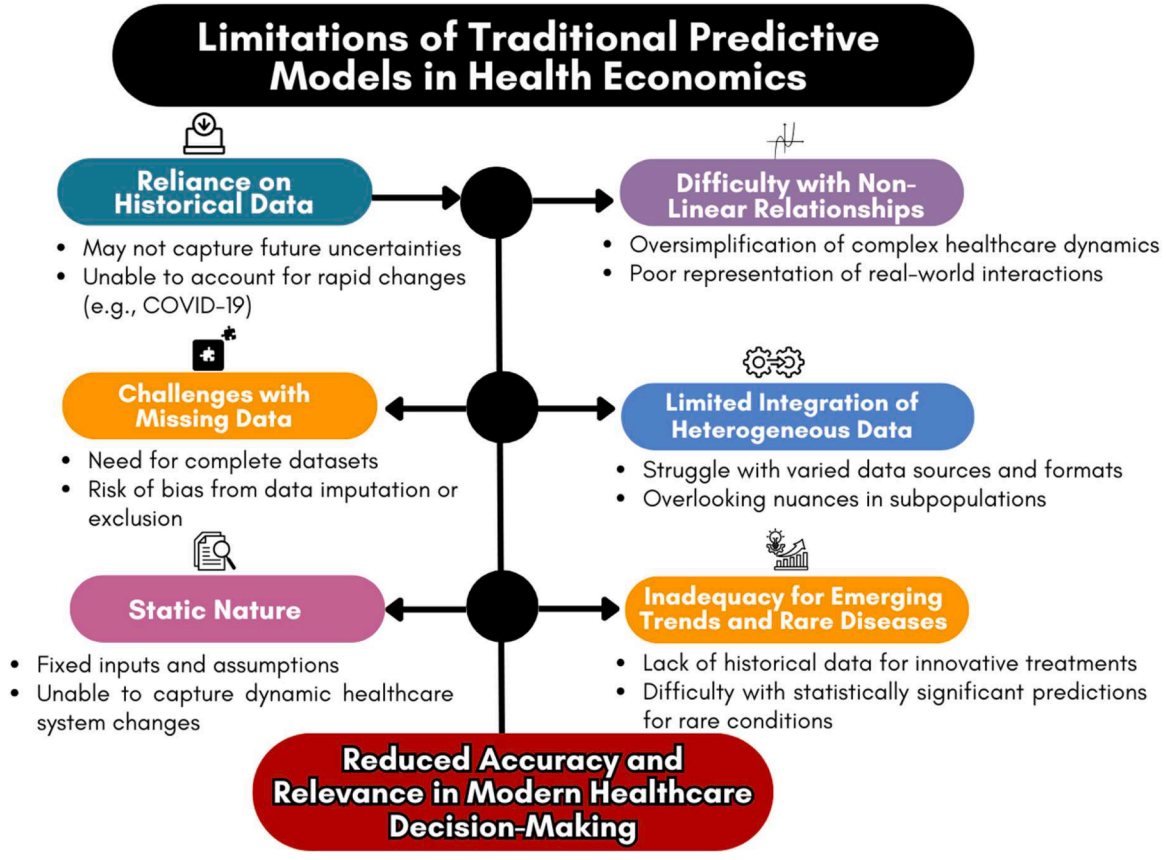


**Fig. 2.** Limitations of traditional predictive models in health economics.

enable broader collaboration among researchers and healthcare organizations [48]. By creating datasets that do not correspond to actual patients, generative AI facilitates data sharing without violating privacy regulations such as HIPAA or GDPR [49]. This capability opens new opportunities for collaborative research and more comprehensive cost-effectiveness analyses [50]. Nevertheless, synthetic datasets must undergo comprehensive validation against independent real-world data to verify that they maintain clinically meaningful relationships and do not introduce artificial patterns that could mislead economic evaluations.

### 4.2. Enhanced scenario simulations

Generative AI enables sophisticated scenario modeling capabilities that surpass traditional analytical approaches [51]. While conventional models rely on fixed assumptions and predetermined parameters, generative technologies can simulate diverse healthcare futures by dynamically varying multiple input variables [52]. This flexibility allows policymakers to explore a broader range of potential outcomes and evaluate intervention robustness under different conditions [53]. However, the practical operationalization of generative scenario generation within formal health technology assessment processes, including requirements for documentation, reproducibility, and regulatory acceptance by payer organizations and HTA bodies, requires further development and standardization.

Advanced scenario simulation capabilities prove particularly valuable for long-term cost-effectiveness projections [54]. Generative models can incorporate evolving factors such as demographic changes, technological advances, and policy modifications to provide more realistic long-term projections [55]. This dynamic modeling approach supports more informed strategic planning and resource allocation decisions [56]. Yet, the interaction between generative scenario generation and fundamental economic modeling challenges, such as structural uncertainty, model calibration to observed data, and appropriate discount rates, requires careful methodological consideration.

### 4.3. Handling complex datasets

Modern healthcare generates vast amounts of complex, multidimensional data that traditional models struggle to process effectively [57]. Generative AI technologies excel at identifying patterns and relationships within high-dimensional datasets, enabling more comprehensive analysis of healthcare interventions [58]. Deep learning architectures underlying generative models can capture subtle interactions between variables that conventional approaches might overlook [59]. However, the "black box" nature of these models poses challenges for health economic evaluation, where transparency, explainability, and causal inference are essential for decision-maker acceptance.

Generative AI's ability to process heterogeneous data types represents a potential advancement for healthcare economic modeling [60]. These technologies can simultaneously analyze structured clinical data, unstructured text from medical records, and continuous measurements from monitoring devices [61]. This comprehensive data integration capability enables more accurate and holistic cost-effectiveness evaluations [62]. Nonetheless, integrating diverse data sources through generative AI requires careful attention to data quality, measurement error, and the risk of incorporating spurious correlations that do not reflect causal treatment effects.

## 5. Advantages of generative AI over traditional methods

Generative AI technologies offer potential improvements over conventional cost-effectiveness analysis approaches across multiple dimensions [63]. These possible advantages encompass enhanced analytical accuracy, improved flexibility, better data utilization, and increased efficiency in model development and deployment [64]. However, it is essential to emphasize that these advantages are predominantly theoretical rather than empirically demonstrated within formal health economic evaluation contexts. The extent to which these theoretical benefits translate into improved health economic decision-making depends on rigorous validation, appropriate regulatory frameworks, and careful attention to methodological limitations, areas where empirical research is critically lacking.

### 5.1. Improved accuracy and flexibility

Generative AI models demonstrate potential for capturing non-linear relationships common in healthcare systems [65]. Traditional linear modeling approaches often inadequately represent complex interactions between patient characteristics, treatment protocols, and health outcomes [66]. Generative technologies may model these intricate relationships more accurately, **potentially** leading to improved cost-effectiveness predictions [67]. Nevertheless, improved statistical fit to training data does not automatically ensure better predictive performance for future populations or settings, emphasizing the critical importance of external validation studies.

The adaptive nature of generative AI models enables continuous learning and refinement as new data becomes available [68]. Unlike static traditional models, generative approaches can update their understanding of healthcare dynamics based on emerging evidence [69]. This adaptability may prove valuable in rapidly evolving healthcare environments where treatment protocols and patient populations change frequently [70]. However, model updating and recalibration introduce challenges related to version control, reproducibility, and ensuring consistency with previous economic evaluations submitted to regulatory bodies.

### 5.2. Privacy-preserving synthetic data

Generative AI's synthetic data capabilities address fundamental privacy challenges in healthcare research [71]. Traditional cost-effectiveness analyses often face constraints due to data sharing restrictions and privacy concerns [72]. Synthetic data generation enables researchers to create realistic datasets that preserve statistical properties while eliminating privacy risks [73]. While promising, synthetic data validation requires demonstrating not only statistical similarity to original data but also preservation of clinically meaningful relationships, treatment effect heterogeneity, and rare but important events that influence cost-effectiveness estimates.

Research demonstrates that high-quality synthetic datasets generated through generative models may produce reliable cost-effectiveness analyses while maintaining complete patient anonymity [74]. These capabilities facilitate broader collaboration and data sharing among research institutions, potentially improving the quality and scope of healthcare economic evaluations [75]. However, the potential for privacy leakage through inference attacks and the regulatory acceptability of synthetic data for formal health technology assessment submissions remain areas requiring further investigation.

### 5.3. Enhanced scenario exploration

Generative AI enables comprehensive scenario analysis that traditional models may struggle to achieve [76]. While conventional approaches typically evaluate limited sets of predetermined scenarios, generative technologies can explore vast ranges of potential healthcare futures [77]. This expanded analytical capability provides decision-makers with more comprehensive understanding of intervention performance under diverse conditions [78]. Yet, the practical utility of extensive scenario exploration depends on appropriate prioritization of clinically and economically relevant scenarios, clear communication of uncertainty to decision-makers, and integration with established

health economic modeling best practices.

Dynamic scenario modeling appears particularly valuable for evaluating healthcare interventions under uncertainty [79]. Generative models can incorporate probabilistic distributions for key variables, enabling robust sensitivity analyses and risk assessments [80]. This analytical depth supports more informed decision-making in complex healthcare environments [81]. However, how generative scenario generation interacts with established probabilistic sensitivity analysis methods, value of information analysis, and structural uncertainty assessment requires methodological clarification and empirical validation.

### 5.4. Integration with real-world data

Generative AI shows potential for integrating real-world evidence into cost-effectiveness analyses [82]. Traditional models often struggle to incorporate diverse data sources such as electronic health records, patient registries, and administrative databases [83]. Generative technologies can potentially combine these varied data types to create more comprehensive and realistic economic models [84]. However, real-world data integration through generative AI must address fundamental challenges of confounding, selection bias, and missing data mechanisms to ensure that resulting cost-effectiveness estimates reflect causal treatment effects rather than artifacts of observational data limitations.

The ability to integrate real-world evidence may enhance the external validity and applicability of cost-effectiveness analyses [85]. By incorporating actual patient experiences and healthcare system performance data, generative models can provide more accurate predictions of intervention effectiveness in real-world settings [86]. Nonetheless, bridging the gap between real-world data analysis and the counterfactual reasoning required for economic evaluation necessitates careful methodological development and validation against randomized controlled trial evidence where available.

### 5.5. Automation and efficiency

Generative AI may significantly reduce the time and effort required for cost-effectiveness analysis development [87]. Traditional modeling approaches often involve labor-intensive processes including manual data preparation, feature engineering, and model calibration [88]. Generative technologies can potentially automate many of these tasks, enabling more efficient analysis development and deployment [89]. However, claims that generative AI can fully "automate model development" for cost-effectiveness analysis require substantial qualification, as health economic models fundamentally require structural assumptions, causal reasoning, expert clinical and economic judgment, and transparent parameterization that cannot be fully automated in a robust manner. The role of generative AI is better characterized as augmenting and supporting human expertise rather than replacing the analytical reasoning essential to credible economic evaluation.

Automated support capabilities may prove valuable for routine economic evaluations and repeated analyses [90]. Healthcare organizations might leverage generative AI to rapidly evaluate new interventions or update existing analyses as new evidence emerges [91]. This efficiency improvement supports more timely and responsive healthcare decision-making [92]. Nevertheless, efficiency gains must be balanced against the need for thorough validation, peer review, and the inherent complexity of translating automated model outputs into actionable health policy recommendations.

Table 1 provides a comprehensive mapping of specific generative AI methods to cost-effectiveness analysis tasks, detailing appropriate validation approaches and associated risks with mitigation strategies. This table systematically maps specific generative AI methods to potential cost-effectiveness analysis tasks, outlining appropriate validation approaches and associated risks with mitigation strategies. Details in the table should be interpreted as a forward-looking framework proposing how generative AI technologies could theoretically be applied to health economic evaluation, recognizing that empirical validation of these use cases in real-world health technology assessment contexts remains largely absent from current literature. The validation approaches and risk mitigation strategies represent recommended best practices that would need to be implemented and tested in future empirical research.

## 6. Limitations of the review

This narrative review acknowledges several important limitations that should be considered when interpreting the findings and conclusions presented.

### 6.1. Methodological limitations

The narrative review approach, while comprehensive in scope, lacks the systematic methodology and meta-analytical rigor of systematic reviews. The selection and interpretation of literature may introduce subjective bias, and the absence of formal quality assessment tools limits the evaluation of individual study methodologies. This review did not follow PRISMA guidelines for systematic reviews; consequently, there is

**Table 1**
Use-case mapping for generative AI in cost-effectiveness analysis.

| Generative Method | CEA Task | Validation Approach | Risks and Mitigations |
|---|---|---|---|
| **Generative Adversarial Networks (GANs)** | Rare disease cohort synthesis; privacy-preserving data sharing | Statistical similarity metrics (e.g., maximum mean discrepancy); comparison of ICER distributions; clinical expert review | Risks: Mode collapse, bias amplification, privacy leakage through inference attacks. Mitigations: Differential privacy techniques, independent external validation, diverse training data |
| **Variational Autoencoders (VAEs)** | Missing data imputation in longitudinal cost studies; parameter uncertainty quantification | Imputation performance metrics; comparison with complete case analysis; sensitivity analysis across multiple imputation methods | Risks: Oversimplified distributional assumptions, failure to capture tail events. Mitigations: Comparison with multiple imputation methods, expert validation of imputed values |
| **Tabular GANs (e.g., CTGAN, TVAE)** | Synthetic patient-level data for CEA model parameterization; augmentation of real-world evidence | Utility metrics (predictive accuracy), privacy metrics (k-anonymity), fairness checks (disparities across subgroups); validation against independent RCT data | Risks: Artificial correlations, underrepresentation of minorities, regulatory non-acceptance. Mitigations: Fairness audits, comparison with original data distributions, regulatory engagement |
| **Diffusion Models** | Scenario generation for long-term disease progression; exploration of treatment pathway variations | External validation against independent cohorts; clinical plausibility assessment; comparison of cost-effectiveness planes | Risks: Computational intensity, difficulty in interpretation, deviation from established CEA methodology. Mitigations: Computational optimization, transparent documentation, parallel traditional modeling |
| **Hybrid Approaches (GAN + Traditional CEA)** | RWE augmentation for model calibration; integration of diverse data sources | Multi-level validation: synthetic data quality + CEA model structural validity + external validation of ICER estimates | Risks: Compounding uncertainties from both synthetic data and model structure, complexity in HTA submissions. Mitigations: Comprehensive uncertainty analysis, clear separation of data and model assumptions, stakeholder engagement |

no formal PRISMA flow diagram, no comprehensive documentation of the number of papers screened at each stage, and no structured quality assessment of included studies. These represent significant methodological limitations that affect the reproducibility and transparency of the review process. Language restrictions to English-only publications may have excluded relevant research published in other languages, potentially limiting the global perspective on generative AI applications in healthcare economics. Additionally, the rapidly evolving nature of AI technologies means that some recent developments may not be adequately captured in the published literature.

### 6.2. Evidence base limitations

A critical and fundamental limitation of this review is the near absence of empirical studies that directly apply and validate generative AI technologies within formal health economic modeling or health technology assessment contexts. This fundamental evidence gap means that readers must interpret all claimed advantages, improvements, and transformative potential with substantial caution. The review substantially relies on general AI/ML literature and theoretical propositions rather than demonstrated performance in actual cost-effectiveness analysis applications. This represents an important limitation and necessitates characterizing this work as forward-looking and conceptual rather than evidence-based synthesis of validated applications.

### 6.3. Technology and implementation limitations

Current generative AI technologies face several technical challenges that limit their immediate applicability to healthcare economics. Model interpretability remains a significant concern, as complex neural network architectures often function as "black boxes" with limited explainability. This lack of transparency may hinder acceptance by healthcare decision-makers and regulatory bodies. Computational requirements for training and deploying generative AI models can be substantial, potentially limiting accessibility for smaller healthcare organizations or resource-constrained settings. The need for specialized technical expertise and infrastructure may create barriers to widespread adoption.

### 6.4. Data and validation limitations

While generative AI shows promise for synthetic data generation, validation of synthetic datasets remains challenging. Ensuring that synthetic data accurately represents real-world population characteristics and treatment responses requires sophisticated validation methodologies that are still evolving. Critically, synthetic data must preserve not only statistical distributions but also clinically meaningful relationships, causal structures, and rare but important events that influence cost-effectiveness estimates. The interaction between synthetic data quality and downstream ICER uncertainty, probabilistic sensitivity analysis results, and value of information calculations requires substantial methodological development.

The quality of generative AI outputs depends heavily on the quality and representativeness of training data. Biased or incomplete training datasets may perpetuate or amplify existing healthcare disparities, raising important equity and fairness concerns. How generative models interact with fundamental challenges of health economic modeling, including structural uncertainty, model calibration to observed data, external validation, and appropriate handling of time-varying confounding, remains incompletely understood and requires rigorous investigation.

### 6.5. Operationalization and HTA integration challenges

A significant gap in current literature concerns the practical operationalization of generative AI methods within established health technology assessment processes. How generative scenario generation, synthetic data, and automated model components would be documented, validated, and presented in formal submissions to payer organizations (e.g., NICE, CADTH, IQWIG) remains unclear. Regulatory expectations for transparency, reproducibility, and appropriate use of real-world evidence versus randomized trial data are well-established for traditional CEA methods but have not been extended to generative AI approaches. The acceptability of synthetic data for regulatory decision-making, requirements for independent validation, and standards for reporting AI-augmented economic evaluations require development and consensus among HTA stakeholders.

### 6.6. Regulatory and ethical limitations

The regulatory landscape for AI applications in healthcare remains uncertain and rapidly evolving. Current regulatory frameworks may not adequately address the unique challenges posed by generative AI technologies in healthcare economic evaluation. This uncertainty may slow adoption and implementation in clinical practice. Ethical considerations surrounding AI bias, fairness, and accountability require careful attention but are not fully resolved in current literature. The potential for generative AI to perpetuate existing healthcare inequities or create new forms of bias needs ongoing monitoring and mitigation strategies.

## 7. Conclusion

Generative artificial intelligence represents a potentially significant advancement in healthcare economic modeling, offering possible solutions to longstanding challenges in cost-effectiveness analysis. The technology's capacity to generate synthetic data, model complex nonlinear relationships, and integrate diverse data sources provides **potential** improvements over traditional analytical approaches. However, it is critical to emphasize that the field remains at an exceptionally early conceptual stage, with virtually no empirical validation of generative AI applications within formal health technology assessment processes. The majority of claims presented in this review are forward-looking propositions based on theoretical potential rather than demonstrated performance in real-world health economic evaluation contexts.

Potential advantages of generative AI include enhanced accuracy through better representation of healthcare system complexity, improved flexibility through adaptive modeling capabilities, and expanded analytical scope through comprehensive scenario exploration. Privacy-preserving synthetic data generation may address critical data sharing challenges while enabling more collaborative and comprehensive research approaches. Yet, these theoretical advantages must be balanced against current limitations in model interpretability, validation methodologies, and the fundamental absence of empirical evidence demonstrating superior performance compared to established CEA methods in actual HTA submissions or regulatory decision-making.

The potential automation capabilities of generative AI technologies could theoretically improve the efficiency and timeliness of healthcare economic evaluations. By reducing manual analytical tasks and enabling rapid model updates, these technologies might support more responsive and evidence-based healthcare decision-making processes. However, characterizing generative AI as enabling full automation of model development substantially overstates both current capabilities and appropriate application. Health economic models fundamentally require structural assumptions, causal reasoning, and expert judgment that cannot be robustly automated. The appropriate role of generative AI is as an augmentative tool supporting, rather than replacing, human expertise in economic evaluation.

Nevertheless, successful implementation of generative AI in healthcare economics requires careful attention to several critical challenges. Model interpretability and transparency concerns must be addressed to ensure acceptance by healthcare decision-makers and regulatory bodies. Robust validation methodologies need development to ensure synthetic

data quality and representativeness, including validation of ICER estimates, probabilistic sensitivity analysis results, and preservation of clinically meaningful treatment effect heterogeneity. The interaction between generative methods and fundamental CEA concepts, including structural uncertainty, model calibration, external validation, and appropriate use of real-world evidence, requires methodological clarification and substantial empirical investigation that does not currently exist.

Regulatory frameworks require evolution to accommodate generative AI technologies while maintaining appropriate oversight and quality standards. Clear guidance on the acceptability of synthetic data for HTA submissions, documentation requirements for AI-augmented models, and standards for transparency and reproducibility must be developed through stakeholder engagement. Ethical considerations including bias mitigation, fairness, and equity must remain central to implementation strategies.

Future research priorities are clear and urgent:

- Conduct rigorous empirical studies directly comparing generative AI-based cost-effectiveness analyses to traditional methods in real-world HTA contexts, including formal submissions to regulatory bodies
- Develop and validate standardized approaches for synthetic healthcare data generation specifically for health economic modeling purposes, with demonstrated preservation of clinically meaningful relationships and treatment effect heterogeneity
- Establish consensus on appropriate validation frameworks, documentation standards, and regulatory requirements for generative AI applications in health technology assessment
- Investigate model interpretability, bias mitigation, and ethical implementation through multi-stakeholder collaboration involving AI researchers, health economists, clinicians, patients, and regulatory representatives
- Create comprehensive use-case frameworks with empirical validation mapping specific generative AI technologies to appropriate CEA tasks, with clear validation requirements and risk mitigation strategies

While acknowledging current limitations and the predominantly conceptual rather than empirically-validated state of this field, the integration of generative AI into cost-effectiveness analysis represents potential progress toward more sophisticated, flexible, and data-driven approaches to healthcare economic evaluation. However, realizing this potential depends critically on substantial methodological development, rigorous empirical validation, regulatory framework adaptation, and demonstrated value in actual health technology assessment decision-making, none of which currently exists in published literature. As methodologies mature, validation evidence accumulates, and regulatory frameworks adapt, the potential benefits for improving healthcare resource allocation and patient outcomes could be substantial and warrant continued investment and development. Nevertheless, the field must transition from theoretical proposition to empirical demonstration before generative AI can be responsibly integrated into formal health economic evaluation practice.

## CRediT authorship contribution statement

**Aanuoluwapo Clement David-Olawade:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Ayodele Osunmakinde:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Folasayo I. Ayoola:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Eghosasere Egbon:** Writing – review & editing, Writing – original draft, Visualization, Methodology. **David B. Olawade:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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