Title. AI Agents in Clinical Medicine: A Systematic Review

Short Title. Agents in Medicine

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ABSTRACT

Background: AI agents built on large language models (LLMs) can plan tasks, use external tools, and coordinate with other agents. Unlike standard LLMs, agents can execute multi-step processes, access real-time clinical information, and integrate multiple data sources. There has been interest in using such agents for clinical and administrative tasks, however, there is limited knowledge on their performance and whether multi-agent systems function better than a single agent for healthcare tasks.

Purpose: To evaluate the performance of AI agents in healthcare, compare AI agent systems vs. standard LLMs and catalog the tools used for task completion

Data Sources: PubMed, Web of Science, and Scopus from October 1, 2022, through August 5, 2025.

Study Selection: Peer-reviewed studies implementing AI agents for clinical tasks with quantitative performance comparisons.

Data Extraction: Two reviewers (A.G., M.O.) independently extracted data on architectures, performance metrics, and clinical applications. Discrepancies were resolved by discussion, with a third reviewer (E.K.) consulted when consensus could not be reached.

Data Synthesis Twenty studies met inclusion criteria. Across studies, all agent systems outperformed their baseline LLMs in accuracy performance. Improvements ranged from small gains to increases of over 60 percentage points, with a median improvement of 53 percentage points in single-agent tool-calling studies. These systems were particularly effective for discrete tasks such as medication dosing and evidence retrieval. Multi-agent systems showed optimal performance with up to 5 agents, and their effectiveness was particularly pronounced when dealing with highly complex tasks. The highest performance boost occurred when the complexity of the AI agent framework aligned with that of the task.

Limitations: Heterogeneous outcomes precluded quantitative meta-analysis. Several studies relied on synthetic data, limiting generalizability.

Conclusions: AI agents consistently improve clinical task performance of Base-LLMs when architecture matches task complexity. Our analysis indicates a step-change over base-LLMs, with AI agents opening previously inaccessible domains. Future efforts should be based on prospective, multi-center trials using real-world data to determine safety, task matched and cost-effectiveness.

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INTRODUCTION

Large language models (LLMs) have demonstrated expert performance on medical examinations[1,2,3]. Recent studies have begun to implement these LLMs in clinical settings, showing improvements in performance.[4,5] However, clinical deployment faces critical safety challenges[6,7,8,9] LLMs can generate plausible but incorrect information, known as hallucinations.[10,11] In up to 22% of clinical interactions, LLM showed misinformation errors most common in medication dosing, symptom recognition, and diagnostic reasoning.[12,13] These models also may lack access to current medical literature and patient-specific data from electronic health records, limiting their ability to provide evidence-based care.[14,15]

To overcome these limitations, researchers have developed AI agents, LLM systems augmented with tools that can access external information, perform calculations, and complete multi-step clinical tasks autonomously.[16–20,21,22] Unlike standard LLMs that provide single responses to questions, AI agents can search medical databases, extract data from patient records, calculate medication doses, and coordinate multiple information sources to answer complex clinical questions.[23,24,25]

Multi-agent systems (Agentic AI)[26] take this further, using teams of specialized AI agents[27] with an orchestration layer that collaborate like multidisciplinary care teams to tackle complex interdisciplinary diagnostic and treatment planning challenges.[28,29,30,31] Despite their theoretical advantages over base LLMs, systematic evidence on the use of AI agents in clinical tasks is lacking.

This systematic review evaluates the current state of AI agents in clinical medicine, quantifies their performance compared with base LLMs, and identifies applications suited for research and near-term integration. We also outline safeguards and design principles needed to ensure safe and effective implementation.

METHODS

Protocol and Registration

This study used an established methodological framework, consistent with the extended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[32] The study protocol was pre-registered on the International Prospective Register Reviews (PROSPERO; CRD420251120318).

Data Sources and Searches

We conducted a comprehensive literature search across three bibliographic databases: PubMed, Web of science, and Scopus, from October 1, 2022 (corresponding to the rise of agentic frameworks) through August 5, 2025. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords across three conceptual domains: (1) agentic systems ("multi-agent" OR "tool-calling" OR "agentic AI" OR "autonomous agent" OR "ReAct" OR "LangChain" OR "AutoGen"); (2) large language models ("GPT" OR "Claude" OR "Gemini" OR "LLaMA" OR "large language model" OR "foundation model"); and (3) clinical applications ("clinical" OR "medical" OR "healthcare" OR "diagnosis" OR "treatment" OR "patient care"). The full search strategy for each database is provided in Supplementary Methods. We additionally performed forward and backward citation searching of included studies and reviewed preprint servers (arXiv, medRxiv, bioRxiv) to identify articles in press. For articles that have not yet undergone peer review, we present a narrative analysis outside the rigorous systematic review criteria.

Study Selection

Studies were included if they met all of the following criteria: (1) described an AI agent system, defined as an LLM that autonomously determines when to call external tools, coordinates multiple specialized agents, or both; (2) applied this system to a human health-related task with clinical relevance; (3) reported quantitative performance metrics comparing the agentic approach to a baseline (single-pass LLM, human performance, or established clinical standard); (4) were published as peer-reviewed articles in English.

We excluded: (1) studies using single-pass LLMs without agentic capabilities; (2) purely technical papers without clinical applications; (3) simulation or benchmark studies lacking real-world validation or clinical tasks; (4) review articles, editorials, conference abstracts, and preprints not yet accepted for publication.

Two reviewers (A.G, M.O) independently screened all titles and abstracts using Covidence systematic review software. Articles marked for potential inclusion by either reviewer underwent full-text assessment. Disagreements were resolved through discussion, with a third reviewer (E.K) providing arbitration when consensus could not be reached.

Data Extraction and Quality Assessment

We developed a standardized data extraction form, piloted on five randomly selected studies, and refined based on extractor feedback. Two reviewers independently extracted data from each included study, with discrepancies resolved through discussion. Extracted variables included:

1. Study characteristics: First author, publication year, country, clinical domain, study design, sample size, data source (real-world vs. synthetic), external validation (yes/no), code availability.

Technical specifications: Base-LLM(s) used, AI agent framework (e.g., AutoGen, LangChain, CrewAI and custom)[33], agent architecture type (multi-agent only, tool-calling only, or combined), number of agents, number and types of tools, and consensus mechanism for multi-agent systems.

Performance metrics: Primary outcome measure, baseline comparator, absolute and relative performance improvement, secondary outcomes, and subgroup analyses where available.

Implementation details: Computational requirements, runtime, and cost estimates were reported, and human oversight requirements were reported.

Risk of Bias Assessment

We adapted the QUADAS-AI tool[34] (Quality Assessment of Diagnostic Accuracy Studies for AI) to assess risk of bias and applicability concerns. This modified instrument evaluated four domains: (1) Patient/Data Selection, (2) Index Test (AI system), (3) Reference Standard, and (4) Flow and Timing. Each domain was rated as low risk, high risk, or unclear risk of bias.[34] Additionally, we assessed concerns regarding applicability for the first three domains.

Specific high-risk indicators included: use of synthetic/simulated data only, single-center validation, sample size <100, lack of external validation, unclear ground truth establishment, and selective outcome reporting. Two reviewers independently assessed each study, with disagreements resolved through consensus discussion.

Data Synthesis and Analysis

Given the heterogeneity in clinical domains, outcomes, and architectures, we did not conduct a meta-analysis; instead, we performed a narrative synthesis structured around our pre-specified research questions. We stratified analyses by:

1) Architecture type: Studies were categorized as single AI agent using tool-calling only, multi-agent only, or combined (multi-agent plus tools) based on their primary implementation.
2) Clinical domain: We grouped studies into diagnosis/prognosis, evidence synthesis, treatment planning, clinical operations, genomics, and other specialized applications.
3) Complexity metrics: We analyzed relationships between performance and system complexity, defined by number of agents (for multi-agent systems) and number of tools (for tool-calling systems).

For studies reporting comparable outcomes, we calculated median performance improvements with interquartile ranges (IQR).

Results

Study Selection

Our search strategy across PubMed, Web of Science, and Scopus identified 6,023 records after removal of duplicates. Following title and abstract screening, 254 articles underwent full-text assessment for eligibility. After applying inclusion criteria requiring peer-reviewed AI agent LLM implementations for clinical tasks, 20 studies met all criteria and were included in the final analysis.[35–53,54] Reasons for exclusion included: non-AI agent single-pass LLM implementations (n=184), simulation or benchmark-only studies without clinical validation (n=31), and studies lacking comparative performance metrics (n=22) (Supplementary **Figure 1.**).

Overview of the included studies

The 20 included studies, published between 2024-2025, encompassed many clinical applications with different evaluation datasets: clinical cases (n=5, ranging from 16-302 cases), clinical reports/EMG interpretations (n=2, totaling 419 reports), multiple-choice questions (n=2, totaling 5,120 MCQs), evidence synthesis queries (n=4, ranging from 50-500 queries), actual patient data (n=2, 117 patients), computational vignettes (n=1, 10,000 calculations), biological/genomic datasets (n=4, including 8 biomarker datasets, 92 nanobodies, 1,106 gene sets, and 272 articles) (**Supplementary Table 1**). Sample sizes varied from 8 to 10,000 items. Studies were predominantly comparative designs (n=16, 80%), with two simulation studies validated through prospective laboratory experiments (10%), one retrospective case-control study (5%), and one randomized controlled trial (5%). Clinical domains clustered around decision-support tasks: diagnosis and prognosis applications dominated (n=8, 40%), particularly for rare disease diagnosis, followed by evidence synthesis (n=5, 25%), treatment planning (n=3, 15%), clinical operations (n=2, 10%), genomics applications (n=2, 10%), and medical education (n=1, 5%). Agent architectures revealed three implementation patterns: single-agent tool-calling frameworks (n=8, 40%), multi-agent systems without tool integration (n=5, 25%), and hybrid multi-agent plus tool-calling architectures (n=7, 35%). The predominant LLM backbone was the GPT-4 family (n=15, 75%), followed by Llama-3 variants (n=4, 20%), Claude-3 Opus (n=4, 20%), and Gemini-1.5 (n=4, 20%), with multiple studies testing several models. Notably, only one study employed prospective randomized controlled trial methodology.

Risk of Bias

Quality assessment using QUADAS-AI criteria revealed some methodological concerns. Only 30% (6/20) of studies achieved low risk of bias across all domains. The remaining 70% demonstrated high risk in at least one domain, with patient selection representing the most problematic area (60% high risk). Other sources of bias stemmed from: synthetic data dependence (n=13, 65%), single-center designs (n=20, 100%), spectrum bias, reference standard concerns (n=5, 25%) (**Supplementary Table 1**).

Performance Synthesis

Overall Performance Improvements

Aggregate performance improvements demonstrated substantial heterogeneity, with median gains of +36% over baseline LLM (range: +3.5% to +76%).

Single AI Agent Tool-Calling Performance

Single-agent implementations were typically deployed for narrow clinical domains to address specific LLM limitations. These architectures achieved the highest median improvement (+53.0%, IQR: 36.0-56.9%) (**Table 2**). Our analysis identifies two primary reasons for this performance increase: one focuses on enhancement through tools (independent of the AI agent framework), while the other pertains to the AI agent framework itself. Goodell et al., Xu et al., and Low et al. primarily achieved performance gains through the tools they employed. Goodell et al.'s calculation tool, which is crucial for LLMs given their inherent challenges with computations[55] improved performance by +59.1% in comparison to the base-LLM (Gpt-4o). Woo et al., Low et al., and Xu et al. showed improved evidence gathering using domain-specific web search for oncology, orthopedics, and genomics. Web search in the studies we found was the most common tool implementation (n=8). In contrast, Ferber et al. observed that clinical decision-making in oncology necessitates capabilities beyond standard LLMs and tools, including multi-modal interpretation of pathological biopsies, radiographic imaging, and complex calculations, which led to the development of their AI agent. The AI agent surpassed baseline LLM (GPT-4) performance by 56.9%. Similarly, Pickard et al. developed an AI agent for biomarker discovery, yielding improved results compared to both the base-LLM and tool augmentation LLM.

Multi Agents performance

Our systematic review identified two distinct multi-agent approaches. Pure multi-agent systems without tools showed modest gains (+14.05%, IQR: 8.95-45.15%). Multi-agent systems with tools demonstrated slightly better performance (+17.17%, IQR: 4.12-39.3%) with high variance (**Table 2**). The reason for the high variance may be as these multi-agent frameworks were often applied to tasks that could have been efficiently managed by either a single agent or tool-augmented LLMs (non-AI agent framework). Nevertheless, for the studies who showed high increased performance was particularly noteworthy in more complex tasks, indicating that multi-agent systems may be more beneficial in such scenarios.

Qu et al. developed a multi-agent team incorporating a fine-tuned CRISPR-Llama3 model, completing 22 gene-editing tasks on 288 benchmark test cases and achieving external validation through AI-guided knockout of four genes (TGFβR1, SNAI1, BAX, BCL2L1). Swanson et al. created a "virtual laboratory" comprising specialized agents (PI, immunologist, machine learning specialist, etc.), successfully developing antibodies validated through wet-lab experiments. Wang 2025 developed a multi-agent system for oncology treatment planning, achieving +4.75% improvement over standard ECHO auto-planning methods for lung cancer. Moreover, Ke et al. demonstrated that multi-agent systems can mitigate clinical decision biases, improving accuracy from 0% to 76% on bias-containing complex cases, surpassing human physicians by 21%. Chen et al. similarly showed that multi-agent improved reasoning for rare disease diagnosis.

Mejia et al. demonstrated managing separately different tools by advanced custom multi-agent frameworks that can automate appointment scheduling by efficiently matching patients with resources. However, the benefits of multi-agent systems tend to be limited for tasks that are already suited for single AI agents. Gorenshtein 2025a, Chen et al., and Altermatt et al., who utilized multi-agent systems for evidence synthesis and answering multiple-choice questions, showed that the improvements are primarily linked to the tools implemented rather than the collaborative efforts of the agents. As mentioned by Altermatt et al. that simpler single-agent strategies are sufficient to address most of the questions in the study.[48]

Agent Number and Tool Scaling Effects

Our analysis revealed an inverted-U relationship between agent number and performance, with optimal results at 4-5 agents before declining performance ($\beta = -8.815$, $R^2 = 0.162$). Tool number showed a weak positive correlation with performance ($\beta = 8.869$, $R^2 = 0.377$). It's important to consider that our analysis is highly limited by task heterogeneity and varying comparison baselines (**Supplementary Figure 2**).

Multi agent Consensus Method

Multi-agent implementations employed various consensus mechanisms: supervisor agent coordination (36.36%, n=4/11), sequential processing (45.45%, n=5/11), majority voting (9.09%, n=1/11), and custom approaches (9.09%, n=1/11).

Base-LLM vs AI agent *deployment and backbone suitability*

We analyzed models with paired baselines and AI agent variants to determine which LLM might be most beneficial for implementing AI agent workflows. We did not find any specific LLM that would benefit significantly more from the AI agent workflow. However, we observed that older models with lower performance might have greater improvement potential.

When inspecting backbone suitability for an AI agent framework, Ferber et al. noted that smaller parameter models, such as Llama-3-70B and Mixtral-8×7B, struggle to provide accurate timing for tool calling compared to higher preforming models like GPT-4 (87.5% for GPT-4 vs. 39.1% for Llama and 7.8% for Mixtral). Similarly, Goodell et al. demonstrated lower performance from Llama-3-70B compared to GPT-4 as backbones of AI agent systems. In examining larger parameter models, Omar et al. did not observe any significant differences regarding the backbone of the LLM itself. Conversely, Woo et al. and Mejia presented conflicting findings; however, Woo et al. study was simple enough that the tool itself was enough to solve it, and Meija study utilized different outcomes, making it challenging to relate their results to this comparison (**Figure 1.**).

Preprint AI agents' frameworks

Notable preprint studies not included in the formal analysis demonstrated advancing capabilities of multi-agent frameworks. [24,30,56,57] The Microsoft MAI-DxO framework achieved 85.5% diagnostic accuracy while reducing costs by 69% compared to baseline models (from $7,850 to $2,397 for comparable accuracy). [21] Li et al. reported progressive performance improvements in a simulated hospital environment across 32 departments, with agents learning from sequential patient interactions. [49] Integration with electronic health records was demonstrated by Shi et al., showing 29.6% improvement over baseline in multi-tabular reasoning tasks.[48] For radiological applications, Chen et al. implemented a modular multi-agent system achieving 79.9% overall diagnostic accuracy in chest X-ray interpretation (**Supplementary Table 2**).[58]

Discussion

This systematic review demonstrates that AI agents consistently improve clinical task performance when architecture matches task complexity. Shown by the heterogeneity in performance improvements, ranging from +3.5% to +76%, with greater enhancements and narrow range observed when the architecture corresponded to task complexity. Our analysis indicates a step-change over base-LLMs, with AI agents opening previously inaccessible domains **(Figure 2.**).

Defining AI agents in Healthcare

The inconsistent use of "AI agent" terminology in medical literature[59,60] necessitates clear definitions. Based on the literature[16–20,27] and our analysis, we identified the following definitions. A true AI agent requires a minimum two of three core capabilities with the first core being mandatory, while for Agentic AI (multi-agent) both the first and the third core are mandatory: 1-Iterative reasoning processes (e.g., ReACT prompting[61])-mandatory, 2-Tool selection, 3-Multi-agent collaboration. By adopting this terminology, we believe future clinical studies can be more accurately categorized into LLM, LLM utilizing tools, AI agents, and multi-agent systems (Agentic AI) (**Figure 2.**).

Practical Considerations for Implementation

Our analysis reveals several critical factors that institutions should consider when implementing AI agent systems in clinical practice.

Choosing the Right Model Architecture

While no single LLM emerged as universally superior for AI agent applications, model size significantly impacts performance. Lower performance models struggled with the complex reasoning required for tool selection. For example, Ferber et al. found that GPT-4 achieved 87.5% accuracy in tool-calling decisions compared to only 39.1% for Llama-3-70B and 7.8% for Mixtral-8B. This finding contradicts recent enthusiasm for small language models (SLMs)[62] in healthcare and suggests institutions should prioritize higher performance, well-validated models for initial implementations.

However, a promising hybrid approach may reconcile cost concerns with performance needs: using a high performance "orchestrator" model to interpret findings and coordinate tasks (deciding which tool and which agent to use), while deploying smaller, specialized models (SLMs) as "workers" for specific functions (using the tool themselves without thinking).[63] In this architecture, the orchestrator handles complex reasoning and tool calling, while SLMs execute defined tasks like data extraction or calculation. This approach could reduce computational costs while maintaining the sophisticated reasoning necessary for clinical decision-making.

Optimal Team Size for Multi-Agent Systems

For institutions considering multi-agent implementations, our analysis identified a highest performance for team of 4-5 agents, beyond which performance plateaus or even declines (**Supplementary Figure 2A**). This finding aligns with established organizational theory on optimal team sizes[64] and challenges the assumption that adding more agents inevitably improves outcomes.[65]

Tool Calling and Integration

The number of tools showed a modest positive correlation with performance (Figure 2B), with web search emerging as the most consistently valuable addition (40% of the studies). For clinical deployment, we found that most framework have the following core set of validated tools: medical literature search (RAG or web-search domains e.g. PubMed) for evidence-based recommendations, calculator functions for dosing and risk scores if needed, structured data extraction from clinical notes and current clinical guideline access. Additional tools can be added incrementally based on specific workflow needs rather than implemented all at once.

Consensus Mechanisms: Matching Method to Task

When implementing multi-agent systems, the choice of consensus mechanism matters. Our analysis identified three primary approaches with different strengths: Supervisor coordination (36.4% of studies): Best for hierarchical clinical decisions where one agent needs final authority, Sequential processing (45.5%): Optimal for stepwise workflows like diagnostic workups, Democratic voting (9.1%): Most effective for consensus-building in ambiguous cases. Recent evidence suggests task-specific optimization: voting protocols excel in diagnostic reasoning tasks (13.2% improvement over consensus) by exploring multiple diagnostic pathways, while consensus methods perform better for factual queries (+2.8%) through cross-verification.[66] Institutions should match the consensus mechanism to their specific use case rather than defaulting to one approach.

Implementation Recommendations

Based on our findings, we provide a structured approach to implementing AI agents. Initially, it is advisable to utilize high-performing models as the primary reasoning model, acting as the "orchestrator." Additionally, it is important to limit the use of multi-agent systems to no more than five specialized agents to maintain clarity and efficiency. Institutions should start with essential tools, such as search functionalities, calculations, and data extraction capabilities and expand their toolkit as demonstrated needs arise. Furthermore, aligning consensus mechanisms with clinical workflows is crucial, as a tailored approach will be more effective than a one-size-fits-all solution. Lastly, considering hybrid architectures that strike a balance between sophisticated reasoning and computational efficiency, such as employing "workers" and SLM for tool-using agents, can enhance overall performance. These practical considerations, derived from our systematic analysis, provide early roadmap that will require further research to validate this approach. Institutions and researchers following this roadmap may begin their journey with AI agents while avoiding common pitfalls as identified in early implementations studies.

Architecture-Task Alignment

In our analysis, we observed a pattern indicating that more complex frameworks tend to yield better performance for intricate tasks. Based on this finding and clinical readiness indicators, we built upon the results a practical three-tier framework for clinicians considering the implementation of AI agents. These tiers based on three criteria: (1) consistency of performance improvement across studies, (2) quality of validation data (real-world vs. synthetic), and (3) implementation complexity and risk. This framework will help clinicians avoid both under-utilization of beneficial tools and over-engineering of simple problems.

Tier 1 - Ready for Clinical Pilot Programs: Tool-augmented LLMs for discrete, auditable micro-tasks (medication calculations, Hounsfield unit extraction).[67,68] These showed +53% median improvement and address specific limitations of standard LLMs, with low bias in the way the tool is being implemented. They primarily rely on Base-LLM without significant modifications, suggesting a safe application in clinical practice.[69,70] Woo et al. illustrated that sometimes, the solution lies simply in utilizing tool-augmented LLMs. They compared LLMs integrated with RAG to a single AI agent utilizing RAG (Tier-2), revealing only a 2% performance increase (+34% compared to the baseline of ChatGPT-4) when responding to questions concerning orthopedic guidelines.

Tier 2 - Supervised Clinical Research: Single AI agents are well suited to manage complete clinical workflows (e.g., report generation, treatment recommendations, differential diagnosis development)[58,71]. The single AI agent show promise but require careful human oversight. These systems achieved strong performance gains (Ferber et al. +57%, Gao et al. +17%) but rely heavily on synthetic data and lack real-world validation. We recommend these be tested in supervised research settings with "human-in-the-loop" mechanisms, allowing clinicians to review and modify outputs before implementation.[72,67] This is particularly important given the ethical considerations of autonomous clinical decision-making.[75,76] Instead, clinicians should explore, using real clinical data, how iterative reasoning processes can enhance the performance of tool-augmented LLMs in tasks that demand more than simple tool usage

Tier 3 - Research Only: Multi-agent systems, despite theoretical appeal, showed high variability, modest improvements over single agents, and in one randomized trial, performed worse than physicians. Our analysis found diminishing returns beyond 4-5 agents and suggests these systems are often over-engineered for problems solvable with simpler approaches. Reserve these for genuine interdisciplinary challenges in controlled research environments.

This hierarchical framework function as a three-layer framework where the clinicians should always try implement their choice of model from the lower tier and move to the next tier if the results aren't sufficient (**Figure 3.**). By this logic the physicians will benefit by having a well fitted model, avoiding unnecessary computational cost or high amount of errors. Additionally, researchers will benefit from knowing at which clinical stage they should implement the three framework provided (tool-augmented LLMs, Single AI agent, Multi AI agents) (**Table 3**, **Supplementary table 3,4**).

Limitations

This systematic review has several limitations. First, the substantial heterogeneity in clinical domains, outcome metrics, and baseline comparators precluded meaningful quantitative meta-analysis, limiting our ability to provide precise effect estimates. Second, we restricted peer-reviewed publications, though this decision enhanced quality assurance. Third, the analysis of scaling effects (agent and tool number) is confounded by task heterogeneity and varying comparison baselines. Further, no study provides a comparison of multi-agent to single-agent. Finally, the absence of standardized evaluation frameworks for AI agent systems means performance metrics vary widely across studies, complicating direct comparisons.

Future Directions-Emerging Evidence from non-peer review Literature

When looking at the preprint analysis we identified further exploration beyond AI agents' performance. Microsoft AI study who showed the cost-effectiveness of reducing unnecessary medical tests through a multi-agent framework (MAI-DxO)[24]. Additionally the integration of AI agents into hospitals and EHR.[56,57,77] With Tsinghua University taking the simulated AI-hospital transforming it into real-time evaluations of a hospital operating entirely on AI agents.[78] Such advancements could significantly ease the documentation burden on physicians[79,80] and reducing costs and time.[81] Future studies should explore prospective validations, create standardized clinical evaluation framework, explore secondary outcome, consensus, task task-architecture matching and ethics in AI agent[82]

Conclusions

AI agents improve clinical task performance compared with base LLMs, particularly when architecture is matched to task complexity. Tool-augmented and single-agent systems are ready for near-term deployment, while multi-agent frameworks should be limited to high-complexity problems under research conditions. We define AI agents as systems combining iterative reasoning with tool use and/or multi-agent collaboration to guide consistent study and reporting. Future work should emphasize prospective, multi-center trials with real-world data, standardized evaluation, and integration with electronic health records within clear regulatory frameworks.

Reference

1. Health C for D and R. Artificial Intelligence-Enabled Medical Devices. *FDA*. Published online July 10, 2025. Accessed August 8, 2025. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-enabled-medical-devices

2. Singhal K, Tu T, Gottweis J, et al. Toward expert-level medical question answering with large language models. *Nat Med*. 2025;31(3):943-950. doi:10.1038/s41591-024-03423-7

3. Katz U, Cohen E, Shachar E, et al. GPT versus Resident Physicians — A Benchmark Based on Official Board Scores. *NEJM AI*. 2024;1(5):AIdbp2300192. doi:10.1056/AIdbp2300192

4. Goh E, Gallo RJ, Strong E, et al. GPT-4 assistance for improvement of physician performance on patient care tasks: a randomized controlled trial. *Nat Med*. 2025;31(4):1233-1238. doi:10.1038/s41591-024-03456-y

5. Goh E, Gallo R, Hom J, et al. Large Language Model Influence on Diagnostic Reasoning: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(10):e2440969. doi:10.1001/jamanetworkopen.2024.40969

6. Omar M, Soffer S, Agbareia R, et al. Sociodemographic biases in medical decision making by large language models. *Nat Med*. 2025;31(6):1873-1881. doi:10.1038/s41591-025-03626-6

7. Hager P, Jungmann F, Holland R, et al. Evaluation and mitigation of the limitations of large language models in clinical decision-making. *Nat Med*. Published online July 4, 2024:1-10. doi:10.1038/s41591-024-03097-1

8. Zhao YF, Bove A, Thompson D, et al. Generative AI Is Not Ready for Clinical Use in Patient Education for Lower Back Pain Patients, Even With Retrieval-Augmented Generation. *AMIA Summits Transl Sci Proc*. 2025;2025:644-653.

9. Au Yeung J, Kraljevic Z, Luintel A, et al. AI chatbots not yet ready for clinical use. *Front Digit Health*. 2023;5:1161098. doi:10.3389/fdgth.2023.1161098

10. Roustan D, Bastardot F. The Clinicians' Guide to Large Language Models: A General Perspective With a Focus on Hallucinations. *Interact J Med Res*. 2025;14:e59823. doi:10.2196/59823

11. Omar M, Sorin V, Collins JD, et al. Multi-model assurance analysis showing large language models are highly vulnerable to adversarial hallucination attacks during clinical decision support. *Commun Med*. 2025;5(1):330. doi:10.1038/s43856-025-01021-3

12. Asgari E, Montaña-Brown N, Dubois M, et al. A framework to assess clinical safety and hallucination rates of LLMs for medical text summarisation. *Npj Digit Med*. 2025;8(1):274. doi:10.1038/s41746-025-01670-7

13. Kim Y, Jeong H, Chen S, et al. Medical Hallucinations in Foundation Models and Their Impact on Healthcare. Published online February 26, 2025. doi:10.48550/arXiv.2503.05777

14. Alber DA, Yang Z, Alyakin A, et al. Medical large language models are vulnerable to data-poisoning attacks. *Nat Med*. 2025;31(2):618-626. doi:10.1038/s41591-024-03445-1

15. Clusmann J, Kolbinger FR, Muti HS, et al. The future landscape of large language models in medicine. *Commun Med*. 2023;3:141. doi:10.1038/s43856-023-00370-1

16. Krishnan N. AI Agents: Evolution, Architecture, and Real-World Applications. Published online March 16, 2025. doi:10.48550/arXiv.2503.12687

17. AI agents — what they are, and how they'll change the way we work. Source. Accessed August 10, 2025. https://news.microsoft.com/source/features/ai/ai-agents-what-they-are-and-how-theyll-change-the-way-we-work/

18. Yang Y, Chai H, Song Y, et al. A Survey of AI Agent Protocols. Published online June 21, 2025. doi:10.48550/arXiv.2504.16736

19. What Are AI Agents? | IBM. July 3, 2024. Accessed August 10, 2025. https://www.ibm.com/think/topics/ai-agents

20. What are AI Agents?- Agents in Artificial Intelligence Explained - AWS. Amazon Web Services, Inc. Accessed August 10, 2025. https://aws.amazon.com/what-is/ai-agents/

21. Gao Y, Xiong Y, Gao X, et al. Retrieval-Augmented Generation for Large Language Models: A Survey. Published online March 27, 2024. doi:10.48550/arXiv.2312.10997

22. Amugongo LM, Mascheroni P, Brooks S, Doering S, Seidel J. Retrieval augmented generation for large language models in healthcare: A systematic review. *PLOS Digit Health*. 2025;4(6):e0000877. doi:10.1371/journal.pdig.0000877

23. Park CR, Heo H, Suh CH, Shim WH. Uncover This Tech Term: Application Programming Interface for Large Language Models. *Korean J Radiol*. 2025;26(8):793-796. doi:10.3348/kjr.2025.0360

24. Nori H, Daswani M, Kelly C, et al. Sequential Diagnosis with Language Models. Published online June 27, 2025. doi:10.48550/arXiv.2506.22405

25. Barra FL, Rodella G, Costa A, et al. From prompt to platform: an agentic AI workflow for healthcare simulation scenario design. *Adv Simul Lond Engl*. 2025;10(1):29. doi:10.1186/s41077-025-00357-z

26. Guo T, Chen X, Wang Y, et al. Large Language Model based Multi-Agents: A Survey of Progress and Challenges. Published online April 19, 2024. doi:10.48550/arXiv.2402.01680

27. Sapkota R, Roumeliotis KI, Karkee M. AI Agents vs. Agentic AI: A Conceptual Taxonomy, Applications and Challenges. Published online May 28, 2025. doi:10.48550/arXiv.2505.10468

28. Tsiotras P, Gombolay M, Foerster J. Editorial: Decision-making and planning for multi-agent systems. *Front Robot AI*. 2024;11:1422344. doi:10.3389/frobt.2024.1422344

29. Zou J, Topol EJ. The rise of agentic AI teammates in medicine. *Lancet Lond Engl*. 2025;405(10477):457. doi:10.1016/S0140-6736(25)00202-8

30. Zuo K, Jiang Y, Mo F, Lio P. KG4Diagnosis: A Hierarchical Multi-Agent LLM Framework with Knowledge Graph Enhancement for Medical Diagnosis. Published online March 28, 2025. doi:10.48550/arXiv.2412.16833

31. Wang W, Ma Z, Wang Z, et al. A Survey of LLM-based Agents in Medicine: How far are we from Baymax? Published online May 26, 2025. doi:10.48550/arXiv.2502.11211

32. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

33. Derouiche H, Brahmi Z, Mazeni H. Agentic AI Frameworks: Architectures, Protocols, and Design Challenges. Published online August 13, 2025. doi:10.48550/arXiv.2508.10146

34. Guni A, Sounderajah V, Whiting P, Bossuyt P, Darzi A, Ashrafian H. Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies Using AI (QUADAS-AI): Protocol for a Qualitative Study. *JMIR Res Protoc*. 2024;13:e58202. doi:10.2196/58202

35. Gorenshtein A, Sorka M, Khateb M, Aran D, Shelly S. Agent-guided AI-powered interpretation and reporting of nerve conduction studies and EMG (INSPIRE). *Clin Neurophysiol*. 2025;177:2110792. doi:10.1016/j.clinph.2025.2110792

36. Gorenshtein A, Shihada K, Sorka M, Aran D, Shelly S. LITERAS: Biomedical literature review and citation retrieval agents. *Comput Biol Med*. 2025;192:110363. doi:10.1016/j.compbiomed.2025.110363

37. Omar M, Glicksberg BS, Nadkarni GN, Klang E. Refining LLMs outputs with iterative consensus ensemble (ICE). *Comput Biol Med*. 2025;196:110731. doi:10.1016/j.compbiomed.2025.110731

38. Chen X, Yi H, You M, et al. Enhancing diagnostic capability with multi-agents conversational large language models. *Npj Digit Med*. 2025;8(1):159. doi:10.1038/s41746-025-01550-0

39. Goodell AJ, Chu SN, Rouholiman D, Chu LF. Large language model agents can use tools to perform clinical calculations. *Npj Digit Med*. 2025;8(1):163. doi:10.1038/s41746-025-01475-8

40. Ferber D, El Nahhas OSM, Wölflein G, et al. Development and validation of an autonomous artificial intelligence agent for clinical decision-making in oncology. *Nat Cancer*. Published online June 6, 2025:1-13. doi:10.1038/s43018-025-00991-6

41. Qu Y, Huang K, Yin M, et al. CRISPR-GPT for agentic automation of gene-editing experiments. *Nat Biomed Eng*. Published online July 30, 2025:1-14. doi:10.1038/s41551-025-01463-z

42. Automatic biomarker discovery and enrichment with BRAD | Bioinformatics | Oxford Academic. Accessed August 8, 2025. https://academic.oup.com/bioinformatics/article/41/5/btaf159/8125018

43. Woo JJ, Yang AJ, Olsen RJ, et al. Custom Large Language Models Improve Accuracy: Comparing Retrieval Augmented Generation and Artificial Intelligence Agents to Noncustom Models for Evidence-Based Medicine. *Arthroscopy*. 2025;41(3):565-573.e6. doi:10.1016/j.arthro.2024.10.042

44. Swanson K, Wu W, Bulaong NL, Pak JE, Zou J. The Virtual Lab of AI agents designs new SARS-CoV-2 nanobodies. *Nature*. Published online July 29, 2025:1-3. doi:10.1038/s41586-025-09442-9

45. Ruiz Mejia JM, Rawat DB. MedScrubCrew: A Medical Multi-Agent Framework for Automating Appointment Scheduling Based on Patient-Provider Profile Resource Matching. *Healthcare*. 2025;13(14):1649. doi:10.3390/healthcare13141649

46. Wang Z, Jin Q, Wei CH, et al. GeneAgent: self-verification language agent for gene-set analysis using domain databases. *Nat Methods*. 2025;22(8):1677-1685. doi:10.1038/s41592-025-02748-6

47. Yang EW, Velazquez-Villarreal E. AI-HOPE: an AI-driven conversational agent for enhanced clinical and genomic data integration in precision medicine research. *Bioinformatics*. 2025;41(7):btaf359. doi:10.1093/bioinformatics/btaf359

48. Altermatt FR, Neyem A, Sumonte N, Mendoza M, Villagran I, Lacassie HJ. Performance of single-agent and multi-agent language models in Spanish language medical competency exams. *BMC Med Educ*. 2025;25(1):666. doi:10.1186/s12909-025-07250-3

49. Xu W, Luo G, Meng W, et al. MRAgent: an LLM-based automated agent for causal knowledge discovery in disease via Mendelian randomization. *Brief Bioinform*. 2025;26(2):bbaf140. doi:10.1093/bib/bbaf140

50. Wang Q, Wang Z, Li M, et al. A feasibility study of automating radiotherapy planning with large language model agents. *Phys Med Biol*. 2025;70(7). doi:10.1088/1361-6560/adbff1

51. Ke Y, Yang R, Lie SA, et al. Mitigating Cognitive Biases in Clinical Decision-Making Through Multi-Agent Conversations Using Large Language Models: Simulation Study. *J Med Internet Res*. 2024;26(1):e59439. doi:10.2196/59439

52. Yang J, Shu L, Duan H, Li H. RDguru: A Conversational Intelligent Agent for Rare Diseases. *IEEE J Biomed Health Inform*. Published online 2024:1-13. doi:10.1109/JBHI.2024.3464555

53. Answering real-world clinical questions using large language model, retrieval-augmented generation, and agentic systems - Yen Sia Low, Michael L Jackson, Rebecca J Hyde, Robert E Brown, Neil M Sanghavi, Julian D Baldwin, C William Pike, Jananee Muralidharan, Gavin Hui, Natasha Alexander, Hadeel Hassan, Rahul V Nene, Morgan Pike, Courtney J Pokrzywa, Shivam Vedak, Adam Paul Yan, Dong-han Yao, Amy R Zipursky, Christina Dinh, Philip Ballentine, Dan C Derieg, Vladimir Polony, Rehan N Chawdry, Jordan Davies, Brigham B Hyde, Nigam H Shah, Saurabh Gombar, 2025. Accessed August 8, 2025. https://journals.sagepub.com/doi/10.1177/20552076251348850

54. Gorenshtein A, Weisblat Y, Khateb M, et al. AI-Based EMG Reporting: A Randomized Controlled Trial. *J Neurol*. 2025;272(9):586. doi:10.1007/s00415-025-13261-3

55. Satpute A, Giessing N, Greiner-Petter A, et al. Can LLMs Master Math? Investigating Large Language Models on Math Stack Exchange. Published online March 30, 2024. doi:10.48550/arXiv.2404.00344

56. Shi W, Xu R, Zhuang Y, et al. EHRAgent: Code Empowers Large Language Models for Few-shot Complex Tabular Reasoning on Electronic Health Records. Published online October 4, 2024. doi:10.48550/arXiv.2401.07128

57. Li J, Lai Y, Li W, et al. Agent Hospital: A Simulacrum of Hospital with Evolvable Medical Agents. Published online January 17, 2025. doi:10.48550/arXiv.2405.02957

58. Chen W, Dong Y, Ding Z, et al. RadFabric: Agentic AI System with Reasoning Capability for Radiology. Published online June 17, 2025. doi:10.48550/arXiv.2506.14142

59. Giske CG, Bressan M, Fiechter F, et al. GPT-4-based AI agents-the new expert system for detection of antimicrobial resistance mechanisms? *J Clin Microbiol*. 2024;62(11):e0068924. doi:10.1128/jcm.00689-24

60. Zhong Z, Wang Y, Wu J, et al. Vision-language model for report generation and outcome prediction in CT pulmonary angiogram. *Npj Digit Med*. 2025;8(1):432. doi:10.1038/s41746-025-01807-8

61. On the Brittle Foundations of ReAct Prompting for Agentic Large Language Models. Accessed August 9, 2025. https://arxiv.org/html/2405.13966v1

62. Shen W, Li C, Chen H, et al. Small LLMs Are Weak Tool Learners: A Multi-LLM Agent. Published online February 16, 2024. doi:10.48550/arXiv.2401.07324

63. Yang Z, Chen Y, Zhou X, et al. Agentic Robot: A Brain-Inspired Framework for Vision-Language-Action Models in Embodied Agents. Published online June 11, 2025. doi:10.48550/arXiv.2505.23450

64. Bumbuc Ş. Team Size and its Influence on the Teamwork and Communication. *Int Conf Knowl-BASED Organ*. 2024;30(2):114-119. doi:10.2478/kbo-2024-0061

65. Li J, Zhang Q, Yu Y, Fu Q, Ye D. More Agents Is All You Need. Published online October 11, 2024. doi:10.48550/arXiv.2402.05120

66. Kaesberg LB, Becker J, Wahle JP, Ruas T, Gipp B. Voting or Consensus? Decision-Making in Multi-Agent Debate. In: *Findings of the Association for Computational Linguistics: ACL 2025*. ; 2025:11640-11671. doi:10.18653/v1/2025.findings-acl.606

67. CT-Agent: A Multimodal-LLM Agent for 3D CT Radiology Question Answering. Accessed August 9, 2025. https://arxiv.org/html/2505.16229v1

68. Tu T, Azizi S, Driess D, et al. Towards Generalist Biomedical AI. *NEJM AI*. 2024;1(3):AIoa2300138. doi:10.1056/AIoa2300138

69. Goh E, Gallo R, Hom J, et al. Large Language Model Influence on Diagnostic Reasoning: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(10):e2440969. doi:10.1001/jamanetworkopen.2024.40969

70. Goh E, Gallo RJ, Strong E, et al. GPT-4 assistance for improvement of physician performance on patient care tasks: a randomized controlled trial. *Nat Med*. Published online February 5, 2025:1-6. doi:10.1038/s41591-024-03456-y

71. Gao S, Zhu R, Kong Z, et al. TxAgent: An AI Agent for Therapeutic Reasoning Across a Universe of Tools. Published online March 14, 2025. doi:10.48550/arXiv.2503.10970

72. Mozannar H, Bansal G, Tan C, et al. Magentic-UI: Towards Human-in-the-loop Agentic Systems. Published online July 30, 2025. doi:10.48550/arXiv.2507.22358

73. Lee YC. Rethinking artificial intelligence in medicine: from tools to agents. *Clin Exp Emerg Med*. 2025;12(2):101-103. doi:10.15441/ceem.25.125

74. Bellos F, Li Y, Shu C, Day R, Siskind JM, Corso JJ. Towards Effective Human-in-the-Loop Assistive AI Agents. Published online July 24, 2025. doi:10.48550/arXiv.2507.18374

75. Cerqueira JAS de, Agbese M, Rousi R, Xi N, Hamari J, Abrahamsson P. Can We Trust AI Agents? A Case Study of an LLM-Based Multi-Agent System for Ethical AI. Published online May 16, 2025. doi:10.48550/arXiv.2411.08881

76. Gabriel I, Keeling G, Manzini A, Evans J. We need a new ethics for a world of AI agents. *Nature*. 2025;644(8075):38-40. doi:10.1038/d41586-025-02454-5

77. Armitage H. Clinicians can ‘chat’ with medical records through new AI software, ChatEHR. News Center. June 5, 2025. Accessed August 9, 2025. https://med.stanford.edu/news/all-news/2025/06/chatehr.html

78. Tsinghua University holds Tsinghua AI Agent Hospital Inauguration and 2025 Tsinghua Medicine Townhall Meeting-Tsinghua University. Accessed August 10, 2025. https://www.tsinghua.edu.cn/en/info/1245/14224.htm

79. Gaffney A, Woolhandler S, Cai C, et al. Medical Documentation Burden Among US Office-Based Physicians in 2019: A National Study. *JAMA Intern Med*. 2022;182(5):564-566. doi:10.1001/jamainternmed.2022.0372

80. Murad MH, Vaa Stelling BE, West CP, et al. Measuring Documentation Burden in Healthcare. *J Gen Intern Med*. 2024;39(14):2837-2848. doi:10.1007/s11606-024-08956-8

81. Sorka M, Gorenshtein A, Abramovitch H, Soontrapa P, Shelly S, Aran D. AI vs Human Performance in Conversational Hospital-Based Neurological Diagnosis. Published online August 14, 2025:2025.08.13.25333529. doi:10.1101/2025.08.13.25333529

82. Taylor RA. AI Agents, Automaticity, and Value Alignment in Health Care. *NEJM AI*. 2025;2(8):AIp2401165. doi:10.1056/AIp2401165

Tables

Table 1. Study Characteristics

Study	Study design	Clinical Domain	Sample Size	Agent Architecture	Framework	Tools Integration	Multi agent Consensus Method
Chen et al.	Compartive	Diagnosis & Prognosis (Rare disease)	302 cases	Multi Agents (n=5)	AutoGen	Web search (Orphanet database)	Hierarchical supervisor
Goodell et al.	Compartive	Clinical Operations & Triage- Clinical calculations	10,000 calculation vignettes	Single Agent+Tool Calling (n=3)	LangChain	OpenMedCalc, code executor, RAG	N/A
Omar et al.	Compartive	Diagnosis & Prognosis	4,058 MCQs	Multi Agents (n=3)	Custom	None	Sequential (Iterative consensus)
Gorenshtein 2025a	Compartive	Evidence synthesis	150 queries	Multi Agents (n=6) + Tool Calling (n=1)	AutoGen	Web search (PubMed API)	Sequential
Gorenshtein 2025b	Retrospective case control	Diagnosis & Prognosis - Neurology	219 reports	Multi Agents (n=3) + Tool Calling (n=1)	Custom	RAG	Sequential
Gorenshtein 2025c	RCT	Diagnosis & Prognosis - Neurology	200 reports	Multi Agents (n=10) + Tool Calling (n=2)	AutoGen	RAG, EHR connection	Sequential
Ferber et al.	Compartive	Treatment & Care Planning - Oncology	20 cases	Single Agent+Tool Calling (n=5)	Custom	RAG, vision, web search, code executor, transformer model	N/A
Qu et al.	Simulation+ prospective lab	Genomics (CRISPR)	288 benchmark test case	Multi Agents (n=4) + Tool Calling (n=3)	Custom	Web search, Primer3 (PCR primer designer),	Sequential

						RAG	
Pickard et al.	Simulation	Biomarker discovery	8 datasets	Single Agent+Tool Calling (n=4)	LangChain	Database APIs, web search, code executor, custom tool	N/A
Woo et al.	Comparitive	Evidence synthesis-Orthopedics	100 questions	Single Agent+Tool calling (n=2)	LangChain	RAG, quality judge LLM	N/A
Swanson et al.	Simulation+ prospective lab	Treatment & Care Planning - Immunology	92 nanobodies	Multi Agents (n=6) + Tool Calling (n=3)	Custom	ESMFold, AlphaFold, Rosetta	Hierarchical supervisor
Mejia et al.	Simulation	Clinical Operations & Triage	100 patient (MIMIC-IV)	Multi Agents (n=9) + Tool Calling (n=4)	Custom	RAG, ML model, math equations algorithm, EHR	Custom-Matching
Wang 2025a	Comparitive	Evidence synthesis-Genomics	1,106 gene sets	Single Agent+Tool Calling (n=1)	Custom	Web API domain databases	N/A
Yang 2025	Comparitive	Evidence synthesis-Oncology/genomics	500 queries	Single Agent+Tool Calling (n=1)	Custom	Code executor	N/A
Altermatt et al.	Comparitive	Medical education	1,062 MCQs	Multi Agents (n=6)	Custom	None	Majority voting
Xu et al.	Comparitive	Evidence synthesis-Genomics (MR)	272 articles	Single Agent+Tool Calling (n=1)	Custom	Web APIs (5 websites)	N/A
Wang 2025b	Comparitive	Treatment & Care Planning-Radiation oncology	17 patients	Multi Agents (n=4) + Tool Calling (n=3)	Custom	Retrieval, optimization tools	Hierarchical supervisor
Ke et al.	Comparitive	Diagnostic reasoning	16 cases	Multi Agents (n=4)	AutoGen	None	Hierarchical supervisor
Yang 2024	Comparitive	Diagnosis & Prognosis (Rare disease)	238 cases	Single Agent+Tool Calling (n=5)	LangChain	Web, RAG, ML, code, heuristic	N/A
Low et al.	Comparitive	Evidence synthesis	50 queries	Single Agent+Tool Calling (n=1)	Custom	Code executor	N/A

Table 2. Clinical performance of agent versus baseline

Study	AI Agent Base-LLM Model(s)*	Primary Outcome	Agent vs Baseline*	Baseline comparison	External validation	Synthetic Data
Chen et al.	GPT-4	Accuracy	+14.3%	Base-LLM	No	Yes
Goodell et al.	GPT-4o, Llama-3	Accuracy	+59.1%	Base-LLM	Yes	Yes
Omar et al.	GPT-4o, Claude, Gemini-1.5-Pro	Accuracy	+13.8%	Base-LLM	No	No
Gorenshtein 2025a	GPT-4o-mini	Accuracy	+3.5%	Single LLM (Sonar-pro)	No	Yes
Gorenshtein 2025b	Gemini-1.5-Pro-002	Accuracy	+29.6%	Base-LLM	Yes- Physician review	No
Gorenshtein 2025c	GPT-4o	Quality score	-25.5%	Physicians	Yes- Comparison to Physician	No
Ferber et al.	GPT-4	Accuracy	+56.9%	Base-LLM	Yes- Physician review	Mixed
Qu et al.	GPT-4o, CRISPR-Llama3-8B (fine tuned Llama3-8b)	Design success	+49%	Base-LLM	Yes- in-vitro validation	Mixed
Pickard et al.	GPT-4	Enrichment simalirty score	+61.7%	Base-LLM	Yes	No
Woo et al.	GPT-4, Claude-3, Llama-3-70B, GPT-3.5, Mistral-8x7B	Accuracy	+36%	Base-LLM	Yes- Physician review	Yes
Swanson et al.	GPT-4o	Binding improvement	2/92 improved	Baseline wild-type nanobodies (no agent design)	Yes- in-vitro validation	Mixed
Mejia et al.	GPT-4o, GPT-4o-mini, Qwen-2.5-32B, DeepSeek-R1	Custom score	N/A	Base-LLM	No	No
Wang 2025a	GPT-4	ROUGE-L	+7.1%	Base-LLM	No	No
Yang 2025	Llama-3	None	N/A	None	No	Yes
Altermatt et al.	GPT-4o	Accuracy	+4.1%	Base-LLM+chain of thoughts	No	Yes
Xu et al.	GPT-4-Turbo, GPT-3.5-Turbo, Mixtral-	Accuracy	N/A	None	Yes	Yes

	8x22B, Llama-3 8B, Llama-3 70B, Qwen 2.5-max, Claude-3-Opus					
Wang 2025b	GPT-4o	PTV D95	+4.75%	ECHO auto-planner	Yes	Yes
Ke et al.	GPT-4-Turbo	Accuracy	+76% (Base-LLM) 28% (Physician)	Base-LLM, Physicians	Yes-Comparison to Physician	Yes
Yang 2024	GPT-3.5-Turbo	F1 score	+53%	Base-LLM	Yes	Yes
Low et al.	ChatRWD	Accuracy	+48%	Chatgpt-4	No	Yes

*The comparison to Baseline unless described otherwise is to Base-LLM. This was conducted on the best performance agentic LLM backbone (e.g. ChatGPT-4 Agentic compared to Chatgpt-4). Percentage point difference

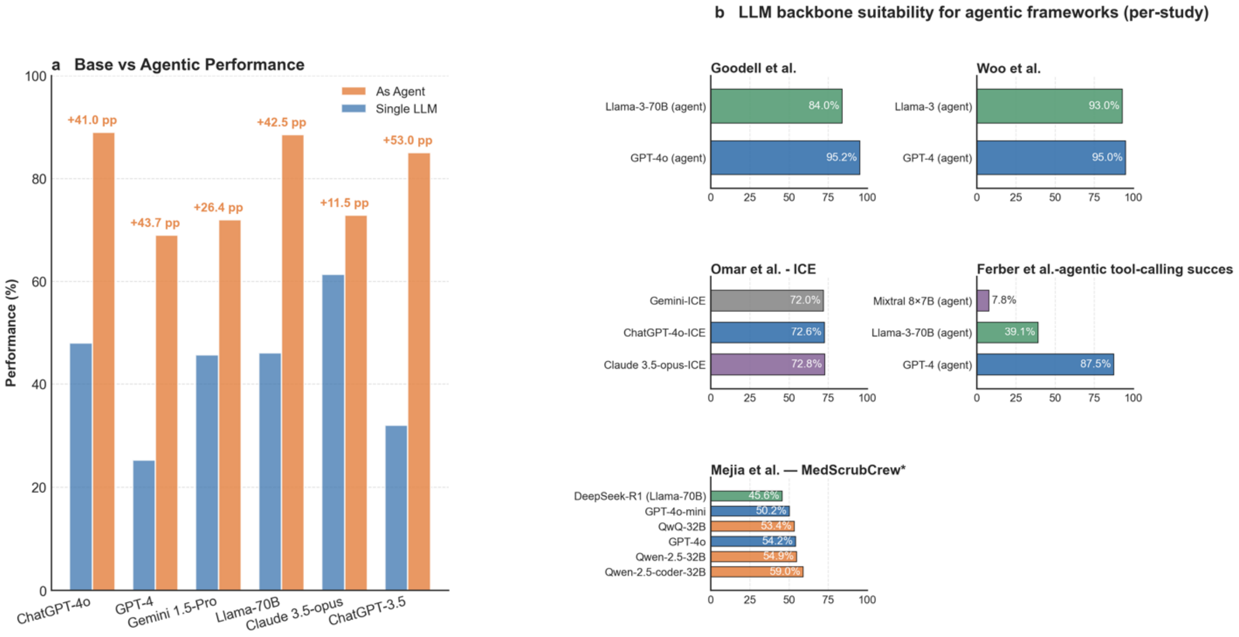
Table 3. AI Agent Architecture Selection Framework for Clinical Medicine

Architecture Type	**When to Use (Decision Criteria)**	**Clinical Applications**	Implementation Requirements	**Key Considerations & Limitations**
Simple Tool Augmentation ***Direct tool invocation without iteration***	• Single, deterministic operation • Well-defined input/output • No reasoning required • Immediate response needed • Clear success metrics	Medication Dosing Lab Value Conversion DICOM HU Extraction ICD-10 Lookup Drug Interaction Check Risk Score Calculation	**Technical:** • API integration • Minimal compute • No model fine-tuning **Clinical:** • EHR integration • Validated algorithms • Regulatory clearance for calculations	Limited to discrete tasks No complex reasoning Cannot handle ambiguity **Best for:** High-volume, repetitive tasks requiring consistent accuracy **Avoid for:** Tasks requiring clinical judgment or context
Single-Agent Systems ***Autonomous reasoning with tool orchestration***	• Multi-step workflows • Tool selection decisions • Iterative refinement needed • End-to-end task completion • Context preservation required	Radiology Reports EMG Interpretation Literature Triage Clinical Summaries Treatment Planning Discharge Notes	**Technical:** • ReAct/CoT prompting • Memory management • Tool API suite • GPT-4+ class models **Clinical:** • Workflow integration • Audit trails • Human oversight protocols	Context window limits Single perspective Tool timing critical **Best for:** Structured workflows with clear objectives **Optimal tools:** 3-5 specialized tools **Key success factor:** Well-defined task boundaries
Multi-Agent Ecosystems ***Collaborative specialized agents***	• Cross-specialty expertise • Conflicting evidence synthesis • Bias mitigation critical • Complex consensus needed • Interdisciplinary collaboration	Rare Disease Dx Tumor Board Gene Editing Virtual Lab Multi-Omics ICU Management	**Technical:** • Agent orchestration • Consensus mechanisms • Distributed compute • Optimal: 4-5 agents	Coordination overhead Conflicting outputs Error propagation **Best for:** Genuinely interdisciplinary challenges **Caution:** Diminishing returns >5 agents

			Clinical: • Multi-disciplinary protocols • Role definitions • Conflict resolution • Clinical BIases	

Figures

Figure 1. Agentic LLM backbones for clinical tasks: uplift over single-model baselines and per-study comparisons



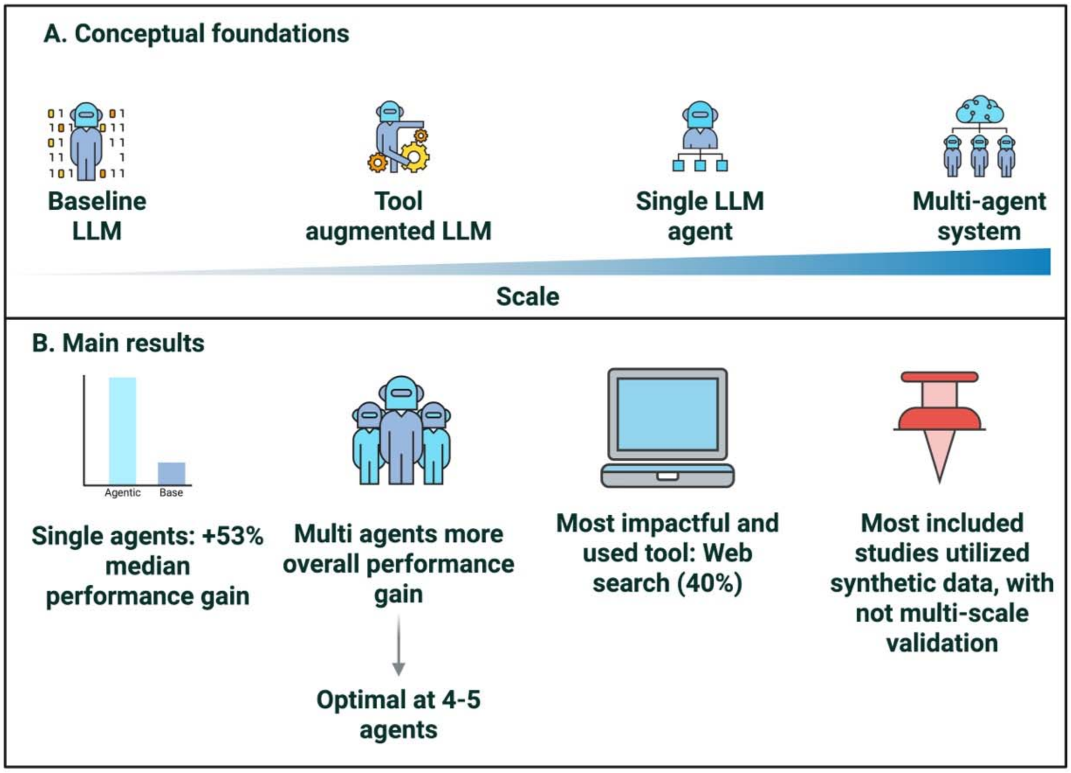
* Approximated composite using simple macro-average (sum of scores ÷ 27).

a, "Base vs agentic" performance for five backbones. Bars show accuracy/success (%) reported in the cited sources; orange = *As agent*, blue = *Single LLM*. Numbers above bars are percentage-point (pp) uplift. Values: ChatGPT-4o 88.93 vs 47.91 (+41.0 pp); GPT-4 68.97 vs 25.23 (+43.7 pp); Gemini-1.5-Pro 71.97 vs 45.58 (+26.4 pp); Llama-3-70B 88.50 vs 46.00 (+42.5 pp); Claude-3.5-opus 72.83 vs 61.34 (+11.5 pp).

b, Per-study agentic comparisons. Goodell et al. (clinical calculations): GPT-4o 95.2, Llama-3-70B 84.0. Woo et al. (orthopedic guideline QA): GPT-4 95.0, Llama-3 93.0. Omar et al. - ICE (final agentic versions): Claude-3.5-opus-ICE 72.83, ChatGPT-4o-ICE 72.59, Gemini-ICE 71.97. Ferber et al.: GPT-4 87.5, Llama-3-70B 39.1, Mixtral-8×7B 7.8. Mejia et al. - MedScrubCrew* (overall composite): Qwen-2.5-coder-32B 59.0; Qwen-2.5-32B 54.9; QwQ-32B 53.4; GPT-4o 54.2; GPT-4o-mini 50.2; DeepSeek-R1

(Llama-70B) 45.6. *Asterisk denotes an approximated composite (macro-average of 27 judged items).

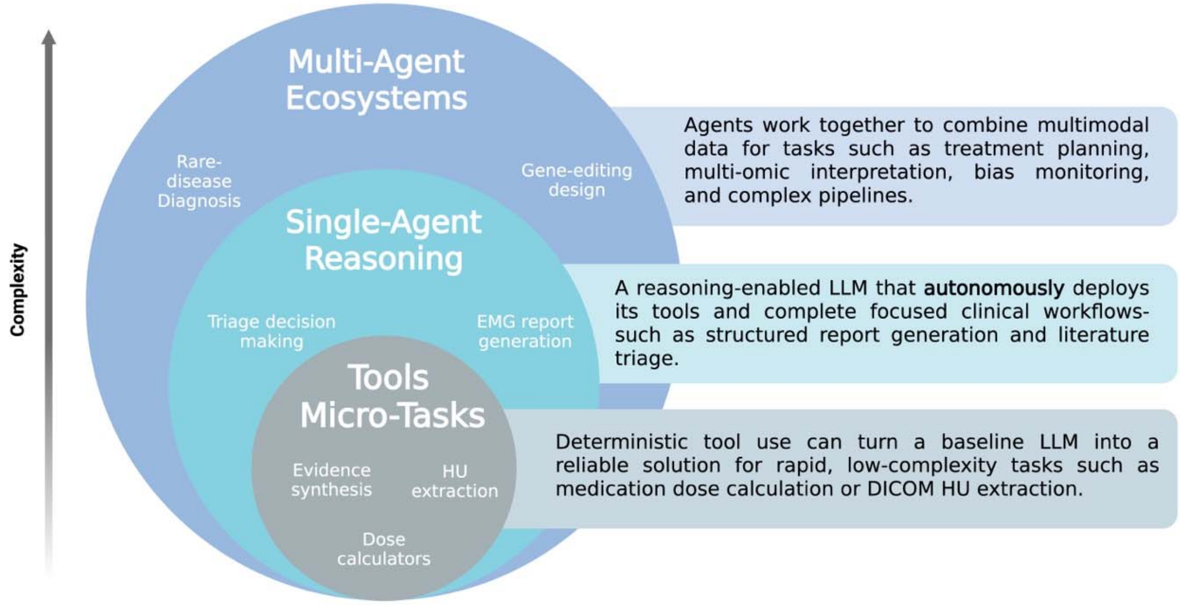
Figure 2. Conceptual foundations of LLM agent systems and a summary of the main results of the review.


A. Conceptual foundations
Baseline LLM
Tool augmented LLM
Single LLM agent
Multi-agent system
Scale
B. Main results
Agentic
Base
Single agents: +53% median performance gain
Multi agents more overall performance gain
Optimal at 4-5 agents
Most impactful and used tool: Web search (40%)
Most included studies utilized synthetic data, with not multi-scale validation

A. The top panel shows the progression in agentic scale from a baseline LLM to a tool-augmented LLM, a single LLM agent, and a multi-agent system.

B. The bottom panel summarizes findings of the review: single agents produced a median 53% performance gain over base LLMs; multi-agent systems delivered larger benefits for complex tasks with optimal teams of 4–5 agents; web search was the most commonly used and most impactful tool (about 40% of studies); many studies relied on synthetic data and lacked multi-site validation. The gradient indicates increasing agentic complexity and coordination.

Figure 3. Hierarchical taxonomy of agentic AI architectures in clinical medicine



Agents work together to combine multimodal data for tasks such as treatment planning, multi-omic interpretation, bias monitoring, and complex pipelines.

A reasoning-enabled LLM that **autonomously** deploys its tools and complete focused clinical workflows- such as structured report generation and literature triage.

Deterministic tool use can turn a baseline LLM into a reliable solution for rapid, low-complexity tasks such as medication dose calculation or DICOM HU extraction.

Concentric circles delineate the progressive complexity of agentic systems.

Inner circle: Tool-based micro-tasks**-** deterministic tool invocation by a baseline LLM for rapid, low-complexity operations (for example, evidence synthesis, dose calculators, DICOM HU extraction).

Middle circle: Single-agent reasoning**-** an autonomous, reasoning-enabled LLM that self-selects tools to complete an end-to-end clinical workflow (for example, EMG report generation, literature triage).

Outer circle: Multi-agent ecosystems**-** coordinated networks of specialised, tool-enabled agents that fuse multimodal data to tackle high-stakes, cross-disciplinary problems (for example, rare-disease diagnosis, gene-editing design, post-deployment surveillance). The schematic underpins the three-tier implementation framework proposed in this review.