Generative Large Language Models are autonomous practitioners of evidencebased medicine

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Abstract

Background

Evidence-based medicine (EBM) is fundamental to modern clinical practice, requiring clinicians to continually update their knowledge and apply the best clinical evidence in patient care. The practice of EBM faces challenges due to rapid advancements in medical research, leading to information overload for clinicians. The integration of artificial intelligence (AI), specifically Generative Large Language Models (LLMs), offers a promising solution towards managing this complexity.

Methods

This study involved the curation of real-world clinical cases across various specialties, converting them into .json files for analysis. LLMs, including proprietary models like ChatGPT 3.5 and 4, Gemini Pro, and open-source models like LLaMA v2 and Mixtral-8x7B, were employed. These models were equipped with tools to retrieve information from case files and make clinical decisions similar to how clinicians must operate in the real world. Model performance was evaluated based on correctness of final answer, judicious use of tools, conformity to guidelines, and resistance to hallucinations.

Results

GPT-4 was most capable of autonomous operation in a clinical setting – being generally more effective in ordering relevant investigations and conforming to clinical guidelines. Limitations were observed in terms of model ability to handle complex guidelines and diagnostic nuances. Retrieval Augmented Generation made recommendations more tailored to patients and healthcare systems.

Conclusions

LLMs can be made to function as autonomous practitioners of evidence-based medicine. Their ability to utilize tooling can be harnessed to interact with the infrastructure of a real-world healthcare system and perform the tasks of patient management in a guideline directed manner. Prompt engineering may help to further enhance this potential and transform healthcare for the clinician and the patient.

Introduction

Evidence-based medicine (EBM)¹ emphasizes the use of the best available clinical evidence in making decisions around patient care. It requires that clinicians update their mental models of disease and treatment to provide care proven to deliver maximal benefit.

Proper adherence to EBM defined protocols imposes a general, common-sense order to clinical tasks². Clinical encounters include a formal interview as well as a physical exam for symptoms and signs, respectively. Upon formulating differential diagnosis, clinicians must then proceed with either general, or specialty focused flowcharts of lab investigations and/or imaging studies before recommending potential therapeutic options. The practice of EBM also dictates that these actions, and the order in which they are performed are influenced by clinician experience and patient preferences or contraindications. For example, ACE inhibitors³ or radiological imaging⁴ in pregnant patients; or the side effects of drugs alongside pre-existing drug allergies. In such cases, clinicians must know and remember to check for such interactions; in addition to being aware of applicable alternatives that can be delivered to the patient.

However, owing to rapid progress in the basic sciences, changes in guidelines and standards of care, and a large ever-increasing body of peer reviewed research – practicing "pure" EBM is a daunting task. Clinicians often face the challenge of information overload^{5,6}, with the sheer number of possible interactions and treatment paths exceeding what they can feasibly manage or keep track of.

There has been major interest in artificial intelligence (AI) to aid clinicians in this set of circumstances. Currently available AI models can operate using multi-modal data⁷⁻⁹ to draw diagnostic and prognostic insights into clinical care. However, such models are usually limited in terms of how much clinical context around the patient they can consider at once – such as specific imaging studies¹⁰, or are single purpose – such as prognosticators of mortality^{11,12}. Additionally, the probability of an event occurring, however high or accurate, does not always translate into knowledge of the "next-best-step" for a patient. As an example, a person predicted to have a high risk of mortality by a binary classification model may deteriorate in a variety of ways that may not be easily apparent, with each factor requiring different investigative approaches and treatment.

While implementation of simpler models is growing, this increase also signals a potential increase in complexity. An increase in the number of sources that a clinicians must parse may counterintuitively add to the information overload a clinician must contend with – manifesting as clinicians ignoring models due because of alarm fatigue¹³ or loss of faith in predictions secondary to limited or confusing explanations of model behavior¹⁴. No model is perfect, and multiple models operating in the same space may further contradict and confound each other¹⁵ – paradoxically distracting from the point of EBM.

Generative Large Language Models¹⁶⁻¹⁸ (LLMs), with their billions of tunable parameters, have emerged as a comprehensive solution for language-based tasks. At their core, these models perform *next-word-prediction*, in that they choose the most likely next word given all preceding

words. The largest of these models are trained on web-scale data, meaning that they have been exposed to nearly all text to ever exist. LLMs have also been shown to encode clinical knowledge¹⁹, and being able to accurately answer questions from clinical licensing exams²⁰. However, such demonstrations of their utility are limited by several factors.

The ability of large language models to perform well at medical QA tasks may not be representative of their performance in real-world settings. The presence of specific symptomatology in relation to specific lab investigations may be considered a source of mild data leakage wherein the model is biased towards the right answer due to the construction of the question or prompt. However, in real-world settings, a clinician must choose from a huge menu of possible next steps, and therefore has considerably more degrees-of-freedom available. Additionally, at time of writing, commercially available LLMs (such as ChatGPT) have a training cutoff in 2021²¹, and are unaware of any new information since that time unless supplemented by information from online sources. While it is possible to inject knowledge into LLMs with supervised fine-tuning²², the costs associated with training, updating, and verifying these models at large enough scale render continuous updates unfeasible. This set of circumstances is especially challenging for learning healthcare systems wherein paradigms of clinical care may change quickly, or for smaller institutions with specific concerns around logistics – such as availability of specialists²³ or indicated drugs²⁴ and investigations²⁵. Similarly, population level data such as antibiotic resistance²⁶ or cultural concerns²⁷ may escape the model's sphere of knowledge entirely. Finally, directing a model to generate text around a subject it is not aware of increases the risk of hallucinations 21,28 – or generation of correct sounding fabricated text.

However, many of these limitations may also be overcome through the use of *Retrieval Augmented Generation* (RAG)^{29,30} – which involves the injection of verified, task-specific information to a model during the process of generating a response. In this work, we leverage novel techniques to demonstrate that LLMs should not be seen only as medical databases, and that there is profound utility in utilizing their ability to reason. Through piecemeal construction of text input to an LLM, next-word-prediction can be extended towards the creation of agents that can autonomously execute the tasks and responsibilities of evidence based clinical care. To enable this, we create a framework that equips LLMs with the ability to interface with the physical world using custom tools that each attend to one aspect of clinical responsibility. We demonstrate the utility of this framework against real-world clinical scenarios and discuss the potential benefits of navigating clinical care within the ambit of language instead of numbers.

Methods

Data sources

We curated real-world clinical cases across multiple specialties. An expert faculty specialist from each discipline converted the case to a structured .json file containing discrete categories of clinically relevant information paired to associated values (Supplementary Figure 1). Curated cases were representative of patients encountered in a tertiary care center at varying levels of diagnostic complexity.

In addition, each such file contained links to prevailing diagnostic and treatment guidelines relevant to the case. Where relevant, this documentation was also supplemented with imitation institutional guidelines for certain cases to simulate how a clinician must alter their recommendations in special circumstances.

Finally, each file contained one or more questions for the LLM to answer given provided clinical context. For the purposes of this study, this question was always "*What is the next best step in management?*" since an appropriate answer to this question would attend to most of clinical protocol – knowing which investigations to order, how to interpret results, generation of a diagnosis, and next best steps on top.

Tools

We created tools that allowed LLMs to retrieve information from case specific .json files; and models were required to explicitly ask for the results from a tool in a manner similar to a clinician ordering an investigation within a hospital setting. These tools were dedicated to retrieval of either of the patient's symptoms, signs (physical examination), past medical history, electrocardiogram (ECG), results from other machine learning models, lab studies, and imaging studies. (Figure 1, Table 1)

Tools consisted of a name, and a descriptive text informing the model of its function/functionality. Tools for symptoms and signs worked without any input data, and returned long-form patient history, symptomatology, and physical exam findings respectively from the relevant .json file. In contrast, either of the lab study and imaging study tools required the LLM to provide a contextual input selected from a pre-defined list of investigations. For example, a "Serum direct bilirubin", or a "Chest X-Ray". The list of investigations was created by pooling investigations from all available cases to more closely replicate a real hospital setting, and not bias the model in any direction.

Finally, a tool was created for querying case-specific clinical guidelines for the purpose of *Retrieval Augmented Generation*^{29,30} (RAG), wherein the LLM was allowed to look up information regarding its current belief in the most likely diagnosis and generate its final recommendation accordingly. However, in order to be shown case-specific guidelines, the LLM had to provide the RAG tool with the correct diagnosis for the case.

If the LLM asked for a lab or imaging study not mentioned in the case, it was instead provided with a "*Not available*" text. Similarly, if there were no specific guidelines associated with the case or the LLM provided an incorrect diagnosis to the RAG tool, it was provided with a text stating "*No updated guidelines available. Use your best clinical judgment*". Finally, if the LLM made an error in selecting a tool, it was provided with feedback stating "*selection> is not a valid tool. Please try with one of <tool names>*".

Prompting

LLMs accept plain text as input and provide plain text as output. In this context, the term *prompt*³¹ refers both to any directions and context supplied to the model. A key differentiator between LLMs and other kinds of machine learning models is that LLM behavior cannot be fully directed and isn't fully deterministic. Thus, *prompt engineering*³² refers to the (often subjective) process of formulating and modifying prompts such that the downstream LLM generates text according to specification.

We formulated an initial system prompt structured as a set of instructions giving the LLM an identity (*"You are a professor of medicine"*), as well as a general set of instructions about how to utilize the tools it was provided with. These instructions recommended judicious use of tools in a logical, directed manner. (Figure 2, Supplementary Table 1).

Importantly, the prompt also contained instructions to treat the output of a tool as the starting point for an *observation* that would act as an internal monologue and recommend an *action* that would be the next tool in line that it would utilize. Finally, the LLM was directed to stop using tools and provide a *final answer* once confident of it, or when it thought that the tooling would no longer provide any useful information. This method of iteratively building the overall input to the model is described as *chain-of-thought*^{33,34} prompting, and it allowed us to establish a context for the model to operate off and keep generated text on guardrails. At each step, the overall output of the model was parsed using a rule-based approach to see if the model had reached the final answer – and if so, the execution of the process was halted, and the overall chain of responses logged for evaluation.

Model selection

We utilized and evaluated the utility and functionality of both proprietary and open-source models as autonomous operators. Proprietary models included both offerings by OpenAI (ChatGPT 3.5, and ChatGPT 4), and one by Google (Gemini Pro).

We also utilized the current state-of-the-art open-source models. These included the LLaMA v2 70-Billion³⁵ chat model, and the Mixtral-8x7B (56 Billion parameter) model – a *Mixture of Experts*³⁶ model that utilizes a combination of multiple smaller models to generate text. Both these models are publicly available and associated synthetic benchmarks put their performance at or above ChatGPT-3.5 for several tasks.

Open-source models have the limitation of only being able to operate on relatively smaller amounts of text. A token is the smallest piece of semantic context a model may utilize, generate,

or manipulate, and corresponds approximately to 3/4th of a word. (4096 tokens, or around 3100 words). Of these, the preamble text required for setting up the model's functionality took a little under 2000 tokens. While this limitation did not affect the ability of open-source models to utilize provided tools, it precluded the utilization of RAG for generating final answers since guidelines would far exceed what could fit inside the prompt.

Performance evaluation

Models were permitted a maximum of three tries to generate coherent text related to a case. A run was only restarted if the model generated nonsensical text in the first response to the initial prompt. All subsequent text was logged and manually evaluated by the same clinician who curated the case.

We evaluated model responses on a three-point scale (0: Poor, 1: Fair, 2: Good) for correctness of final answer; judicious use of tools; conformity to guidelines; and resistance to hallucinations. Conformity to guidelines was evaluated in terms of the model's agreement with provided, and prevailing guidelines. In case the model was incorrect in its diagnosis, it was automatically marked 0 for the remaining tooling and guidelines as well.

Case difficulty and the amount of information needed to make useful decisions may vary from clinician to clinician, and we elected to include a secondary appraisal of difficulty into the evaluation process as well. Cases were graded for difficulty on a scale of 0-2 as before. All cases are available for review within the linked online repository, and a full overview of the evaluation algorithm is provided within **Supplementary Table 2**.

Software and hardware

We utilized the transformers³⁷, PyTorch³⁸, and LangChain libraries to create this framework. These libraries were called from within the Python³⁹ programming language (3.11.x).

Proprietary models are accessible over the internet through APIs and do not require specialized hardware. For these models, response generation was done on the lead author's laptop. The open-source models were run at 16-bit precision within the Minerva computing cluster at Mount Sinai.

Results

We curated five cases each from the specialties of Cardiology, Critical care, Emergency medicine, Genetics, and Internal medicine. Each case was also ascribed a difficulty of either easy, medium, or hard by the evaluating clinician. In this way, we gathered 12 easy, 7 medium, and 6 hard difficulty cases (Supplementary Table 3). Models evaluated each case by building up their knowledge about the patient through the utilization of available tooling and investigations (Supplementary Table 4). A sample run for GPT-4 solving a case of Acute MI is as shown in Table 2 with the corresponding .json file in Supplementary Figure 1.

Performance trends across specialties and case difficulty are as reported below, and tabulated across **Figures 3 / 4**, and **Tables 3 / 4**.

Correctness of final answer

GPT-4 outperformed the next best model in Cardiology (80% vs 50%), Critical care (100% vs 90%), Genetics (100% vs 60%), and Internal medicine (60% vs 40%). GPT-4 and GPT-3.5 were tied at 70% for Emergency medicine. Performance was generally worse for more difficult cases, with Gemini Pro getting no correct responses for any of the hard difficulty cases. GPT-4 outperformed GPT-3.5 across all levels of difficulty.

Errors mostly issued from models ordering irrelevant investigations, getting a "not available" in return, and not having sufficient resilience to errors to go back and re-establish differentials despite having instructions and the freedom to do so.

Judicious use of tools

GPT-4 outperformed the next best model in Cardiology (80% vs 60%), Emergency medicine (70% vs 40%), and Genetics (75% vs 35%). GPT-4 and GPT-3.5 were tied at 60% each for Critical care and Internal medicine. We found that GPT-4 was generally more precise about which investigations to order and got to the correct differentials quicker as seen in the "Observations" following the use of each tool. In contrast, other models often ordered largely unnecessary investigations in smaller quantities, or in some cases – the whole list of investigations were ordered together.

Interestingly, for both GPT models, changing the system prompt to redefine the identity of the model led to slightly different behavior. For Genetics Case 1 (Down Syndrome) in the pre-natal setting, we performed an additional run for these models wherein they were given the identity of a "Clinical Geneticist" instead of the usual "Professor of Medicine". Upon doing this, GPT-3.5 shifted from consideration of *hyperemesis gravidarum* to tending towards the more correct "Prenatal screening and diagnostic testing". Similarly, while GPT-4 was correct in its diagnosis with both identities, its recommendations with the same set of guidelines as a geneticist was more tailored to the patient and available resources.

Conformity to guidelines

With RAG enabled, GPT-4 outperformed the next best model in Critical Care (90% vs 70%), Genetics (75% vs 37.5%), and Internal medicine (75% vs 35%). While GPT-3.5 outperformed GPT-4 for Cardiology (80% vs 70%), and Emergency medicine (90% vs 65%), the overall average performance for GPT-4 exceeded that of GPT-3.5 by ~10%. This was the same overall performance difference across all cases between GPT-4 with RAG enabled (74%), and with RAG disabled (63.5%) (**Supplementary Figure 2**). The extent of conformity was also seen to drop dramatically for more difficult cases when utilizing GPT-4, while GPT-3.5 actually improved in the harder cases.

We also found that LLMs can pick and choose if provided text is relevant to their thinking. In case 5 for Emergency Medicine (Cellulitis), institutional guidelines for Opioid overdose were shown to the model in addition to the usual clinical guidelines for Cellulitis. Despite the instructions contained within the system prompt, we found that none of the commercial models utilized the (irrelevant) information within provided text.

Resistance to hallucinations

All tested models suffered from relatively minimal hallucinations while acting autonomously. GPT-3.5 was most resilient getting perfect scores in all specialties except for Critical Care (90%). GPT-4 performed slightly worse in scoring 100% for Cardiology, Genetics, and Internal Medicine – while losing on Critical care (90%), and Emergency Medicine (80%). Hallucinations were mostly restricted to incorrect naming of investigations (For example, "ARTERIAL BLOOD GAS" vs the provided "ABG") in the case of the commercial models.

Both open-source models were also found to be moderately resistant to hallucinations except for the specialty of Emergency medicine wherein LLaMa-70B scored only 10%. As before, open-source models are restricted to 4096 tokens, and generating text in excess of this limit led to behavior wherein tools were often utilized repeatedly and endlessly unless the run was manually terminated.

In Cardiology Case 2 (Cardiogenic shock), the .json file had an erroneous interpretation of the value of SERUM CREATININE. Models were shown "3.2mg/dL (Normal)" if they ordered this test. However, GPT-4 correctly interpreted this value as elevated in the subsequent observation.

Overall performance and steerability

Commercial models generally performed better than open-source models across all metrics. However, the commercial models themselves displayed very different suitability for utilization as autonomous practitioners. Gemini Pro had to be restarted an average of 3.6 times per specialty, and GPT-3.5 had to be restarted an average of 1.2 times per specialty due to an immediate divergence from the instructions laid out to them. In comparison, GPT-4 did not require any restarts and reported metrics come from the first run for each case. All models were found to be resilient to the slightly different syntaxes used by clinicians to record history, and utilization of domain specific jargon and abbreviations (for example, "hep C" vs. "hepatitis C", and "h/o" vs "history of") did not meaningfully affect model understanding of context.

Discussion

In this work, we enable LLMs to act as autonomous practitioners of evidence-based clinical practice by utilizing a combination of LLM reasoning ability, inherent clinical knowledge, prompt engineering, diagnostic tooling, as well as real-time information lookup and contextualization. We demonstrate that the capacity of LLMs to reason is a profound ability that can have implications far beyond treating such models as databases that can be queried using natural language.

LLMs are versatile tools capable of understanding clinical context and generating possible downstream actions. Given the current state of machine learning, such models represent a seachange in terms of how to approach the patient. Of all clinical decision support systems currently available, they represent the best way to get to the all-important next-best-step of management, especially in resource or experience limited settings. This is evidenced by the more complex models tested within this framework being able to achieve not just excellent diagnostic performance, but also being able to generate the basis of future personalized care for each patient. Performance trends, especially for GPT-4 were maintained even across the cases considered difficult by human clinicians. Notably, the framework allows for switching out the underlying model through one-line of code, and such implementations will allow for instantaneous performance uplifts as even better models become available.

As such, this work opens the door to many downstream real-world applications. Properly vetted models may assume the role of triage specialists – wherein after the initial presentation of the patient is catalogued, the model can take over all responsibilities in terms of ordering and interpreting investigations, or issuing alarms while the clinician in the emergency setting may focus on interventions. For less acute presentations and in outpatient settings – the model may even be the first point of contact with the patient for establishing a baseline history of presenting illness, which can then be forwarded to an upstream clinician as a first-pass assessment including lab results. Existing work⁴⁰ has already shown the utility of LLMs to save the clinician from information overload by condensing voluminous patient histories into more easily understood summaries. In all these cases, such a manner of operation represents a reduction in clinical workload, and faster care for the patient.

The immense costs of training LLMs ensures that new knowledge cannot be easily injected into such models. This is an especially important concern for applications which rely on domain specific knowledge or where such knowledge changes often. A very relevant example in the healthcare space is antibiotic resistance^{26,41}. Microbial populations and susceptibilities change both from region-to-region and from time-to-time. It stands to reason that such knowledge cannot be made part of a model, or it will quickly start to issue stale or incorrect recommendations. However, institutions already maintain records of antibiotic resistance which LLMs can parse for the purpose of issuing very specific recommendations. As we demonstrate, even for the best available model (GPT-4), the addition of RAG increased performance at generating text that conformed to the best available clinical knowledge. **(Supplementary Figure 2)**

Fully autonomous models also represent other accessory workflow advantages. As above, minor prompt engineering enables the model to output all differential diagnoses it is considering at each step of the process, and the reasoning behind them. Such directions may be immensely useful for clinical education⁴² since they represent step-by-step considerations of the next-best-step specific to the patient and pathology – something that may be difficult to glean from mainstream textbooks. Additionally, as human supervisors / clinicians have access to the entire thought-process of the model – the manner of operation described in this work is entirely transparent and, by definition, is in keeping with easily verified clinical guidelines. In contrast, the vast majority of clinical decision support systems must still provide complex saliency maps⁴², or statistical measures of importance that do not support any claims of causality⁴³. Further, LLMs operating in this manner may also largely circumvent the concerns that issue with the use of predictive models in healthcare settings¹⁵.

Prompt engineering also dramatically shortens the time required to program new behavior into models when errors are found. For example, in the case of the example quoted in **Table 2**, the model (GPT-4) did not fully take clinical circumstances into account and ordered results from both the machine learning model, and serum troponins. While these tests added to the certainty of the diagnosis, they may also be considered unnecessary given the acuity of the presentation and the contributing clinical signs. Prompt engineering allows for remedying situations like these simply by telling the model to only "perform absolutely necessary investigations", or by making the model aware of how long results may take to arrive. Similar considerations may be applied to clinical guidelines as well. We believe the best way to engineer these prompts will vary from facility-to-facility and consider this an avenue for future work.

Finally, iterative construction of the prompt for the model as demonstrated also reduces the potential⁴⁴ for hallucinations. By utilizing *chain-of-thought* prompting coupled to stepwise injection of verified correct information into the model's thoughts, we encourage the model to think in a specific direction and possibly discard incorrect assumptions that can cause significant dissimilarities between desired and observed output. This is an especially pertinent approach over utilizing models are pure Question-Answering tools since LLM hallucinations may snowball⁴⁵, and the response may diverge more from reality with each generated word. Autonomous operation of LLMs also reduces or removes the input required from humans for operation, and largely reduces the potential for model misuse or *jailbreaking*⁴⁶ – a fact that is especially useful for information-controlled hospital settings.

Our work must be considered in light of some limitations. While we present real-world cases in this work, the data was deposited into .json files. Any extension of this work into an actual clinical setting will involve setting up adapters and timers which will bridge the tools available to the LLM with the infrastructure of the clinical setting. However, this is more of an engineering problem than a research question. Similarly, multi-modal models that can accept images, video and audio in addition to text are largely in their infancy in the context of clinical work. Therefore, we restricted our evaluations to the results of the investigations rather than the raw imaging data. Finally, clinical guidelines for certain conditions were especially voluminous, and we were restricted to GPT-4 generated summaries of these guidelines in order to fit them into reasonably sized prompts. We attempted to circumvent this limitation by asking models to generate their final recommendations using a combination of their own clinical knowledge and provided text;

but we stipulate the larger models may be able to generate bespoke recommendations to individual patients either with more context to look through, or more sophisticated guideline retrieval.

Remaining limitations issue from the LLMs themselves. One, while we test with both commercial and open-source models, the actual model that interacts with this framework as well as the patient must be properly vetted – especially in the context of biases that propagate within healthcare and healthcare systems. We found that smaller models were often more temperamental, and they required frequent restarts, and often ignored directions despite being explicitly asked to perform in a specific manner. The largest of the tested models (ChatGPT-4) did not have this problem, and we believe special purpose training may ameliorate the issue for smaller models - which we consider another avenue for future work. Two, data privacy is a concern for any sensitive information. Open-source models are largely immune to this concern since the data stays local to the health system - but as before, they perform worse than the commercial models. Three, the amount of text a model can accommodate limits its overall utility. Open-source models that cannot go over 4096 tokens also cannot be made to ingest complex clinical guidelines and make patient-specific decisions. Such models may require institution specific finetuning to enhance their utility or may otherwise benefit from recent work⁴⁷ that allows for increased context length. Finally, there's the cost of running such models. Larger models perform better, but they require commensurately more computational resources. However, these costs may be amortized by the cost saving measures indicated above, and once hardware catches up to the software, continued operation may be a smaller concern.

In conclusion, LLMs are profound tools that bring us closer to the promise of Artificial General Intelligence. Giving them access to tools which form their eyes, ears, and hands allows them to integrate with the moving parts of a modern healthcare system; an integration that could lead to significant changes in medical practice. Our work represents an initial step in this direction, potentially altering how medicine is practiced by clinicians and experienced by patients.

Figures

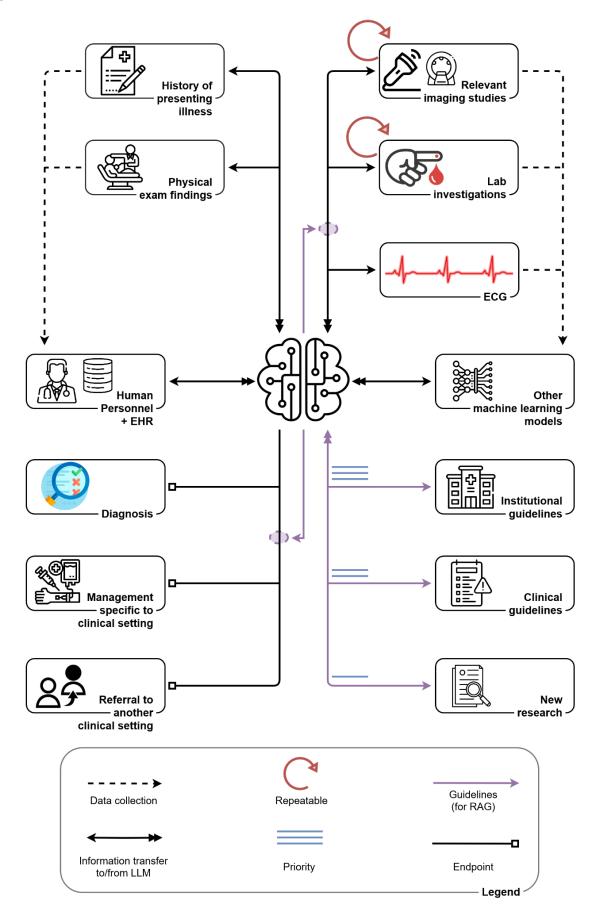


Figure 1. Workflow

The executor LLM relies on human personnel to generate the history of presenting illness, and the physical exam findings. Following this, it autonomously chooses which lab investigations or imaging studies to order, and how to interpret them. These interpretations form the basis of the model's next step or order. During this process, it may also query the output of existing machine learning systems.

Following this, the model queries all available literature on the most likely differential diagnosis it is considering. In this figure, blue horizontal lines indicate the degree of importance given by the model to any one source of information. This is an important consideration since we want institutional knowledge to override general purpose guidelines which may not be entirely appropriate for any one patient population.

Finally, the model issues its recommendations based entirely on the question it is tasked to answer. This may be generating the final diagnosis, the management specific to the clinical setting it finds itself in, or referral to another facility.

ldentity I	Answer the provided question as best you can as a professor of medicine . Your responses must be as detailed as possible, and use medical terminology. Your patient is an inpatient in all cases. You are in charge of the patient, and your decisions are final. Referrals are only possible as part of your final answer. You are able to utilize tools to answer questions related to medical practice, from finding diagnoses to suggesting recommended investigations and treatments. You must use the most relevant tools first, and then use the output of those tools to determine which tools to use next. You must use these tools in the order a clinician is likely to in real life. You must stop using tools and provide a final answer when confident that remaining tools will not provide any additional information. Your final answer must be informed by available guidelines AND your clinical judgment.
Tooling I	<text></text>
Operation	Question: the input question you must answer Thought: you should always think about what to do Action: the action to take, should only be one of [{tool_names}] Action Input: the input to the action Observation: the result of the action (this Thought/Action/Action Input/Observation can repeat N times) Thought: I now know the final answer Final Answer: the final answer to the original input question Begin! Remember to answer as a professor of medicine when giving your final answer. Do not make any recommendations or discuss next steps unless explicity asked for.
Task	Question: {input}

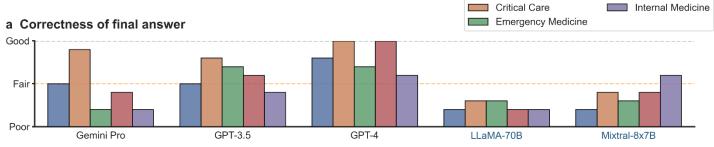
Figure 2. System / Initial prompt

Preamble text that establishes the framework for the LLM. Overall text may be separated into 4 parts each with their own function:

- (1) Identity: Tells the model who it is and how it's expected to respond. The model was asked to assume the identity of a "professor of medicine" for most of our testing.
- (2) Tooling: Provides the model with a general sense of directions regarding when to use tools. Actual choice and order of tool use is up to the model. Also establishes a stop condition for the model i.e. when it reaches a final answer.
- (3) Operation: Establishes "chain-of-thought" prompting structure. The narrative the model uses to generate the next word is built up piecemeal through repeated iterations of thoughts, actions, and observations in that order until the final answer is reached.
- (4) Task: What the model is supposed to provide a solution for "*What is the next best step in management*"?

Text in curly brackets is replaced by names of tools, and the question at runtime. The full prompt is available in **Supplementary Table 3**.

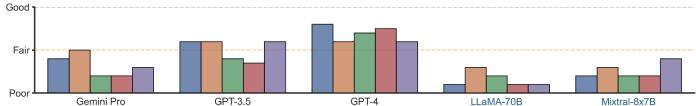
Performance by specialty



Cardiology

Genetics

b Judicious use of tools



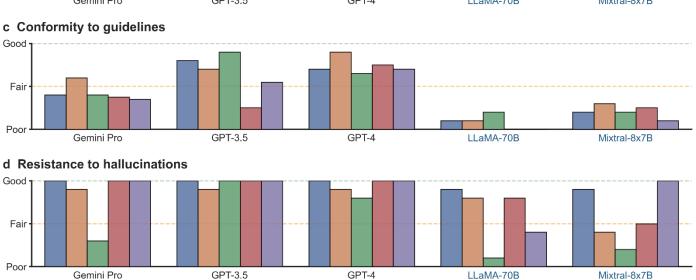


Figure 3. Model performance within framework by specialty

Fair = 50%, Good = 100% accuracy. Open-source models are highlighted in dark blue. All API models (Gemini Pro, GPT-3.5, and GPT-4) had Retrieval Augmented Generation enabled and were shown guidelines for each case. Both open-source models (LLaMA-70B and Mixtral-8x7B) did not have sufficient context length to accommodate guidelines. Number of questions by specialty: 5 each (25 total).

Performance by difficulty

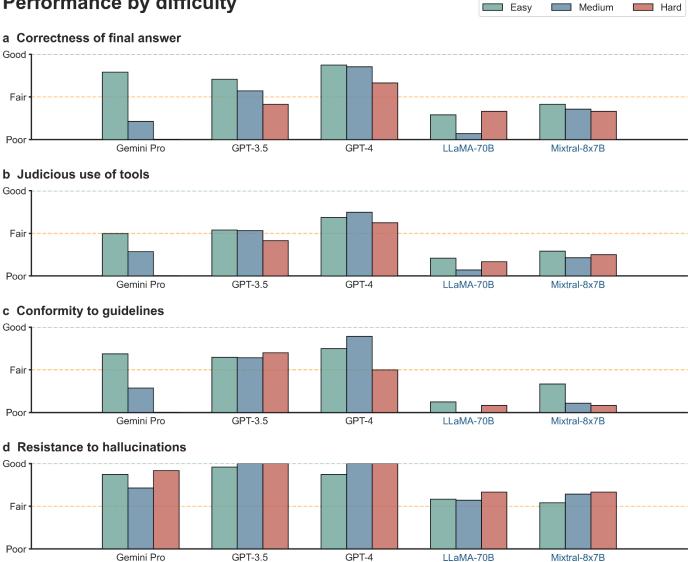


Figure 4. Model performance within framework by case difficulty

Fair = 50%, Good = 100% accuracy. Open-source models are highlighted in dark blue. All API models (Gemini Pro, GPT-3.5, and GPT-4) had Retrieval Augmented Generation enabled and were shown guidelines for each case. Both open-source models (LLaMA-70B and Mixtral-8x7B) did not have sufficient context length to accommodate guidelines. Number of questions by specialty: 5 each (25 total).

Tables

Tool name	Tool description	Notes		
Symptom tool	Use this tool when you need to know about the patient's symptoms. The tool may be used only once . The tool does not accept any input.	Patient's history of presenting illness and physical exam. Would ordinarily be gathered at point of		
Past medical history tool	Use this tool when you need to know about the patient's past medical history. The tool may be used only once. The tool does not accept any input.	contact.		
Sign tool	Use this tool when you need to know about the patient's physical exam. The tool may be used only once. The tool does not accept any input.			
Lab investigation tool	Use this tool when you need to know about lab investigations. The tool is recommended if the diagnosis is inconclusive. The tool accepts a list of names of lab investigations as a string. It is very important to only order lab investigations if they are relevant.	Names of lab investigations are pooled from all cases.		
	The tool must be called again with a different lab investigation if earlier results are inconclusive, not	Multiple labs can be ordered at once.		
	available, or insufficient. Repeating this tool is preferred before moving on to imaging studies.	Outputs the absolute value of the lab investigation		
	Lab investigations cannot be repeated. You must specify the exact name of the lab investigation. E.g. SERUM ALBUMIN instead of just ALBUMIN. Lab investigations must only be ordered from the list of available investigations provided to you.	alongside an interpretation in parenthesis. E.g. SERUM CREATININE:		
	Only the following lab investigations are available: {names of lab investigations}	1.1mg/dL (Elevated)		
Imaging study tool	Use this tool when you need to know about radiological or sonographic studies. The tool is recommended if the diagnosis is inconclusive.	Names of imaging studies are pooled from all cases.		
	The tool accepts a list of names of imaging studies as a string. Only one imaging study can be ordered at a time. Start with the most relevant one. The tool must be called again with a different imaging study	Only one imaging study be ordered at a time.		
	if earlier results are inconclusive or not available. Imaging studies must only be ordered from the list of available studies. Only the following imaging studies are available:	Outputs the diagnosis statement from the imaging study.		

	{names of imaging studies}	
ECG tool	Use this tool when you need to know about the ECG (electrocardiogram). The tool is recommended regardless of how certain the diagnosis is. The tool does not accept any input.	The ECG is a commonly performed, low-cost, non-invasive investigation. Therefore, the model is encouraged to utilize it.
Machine learning tool	Use this tool when you need to know about predictions issued by machine learning models relevant to this patient. The tool is recommended to guide further testing. The tool accepts a list of names of machine learning models as a string and returns a probability value. Only one machine learning model can be used at a time. Only the following machine learning models are available: {names of available outcome specific machine learning models}	The model is only made aware of this tool in case there are relevant machine learning models available. Requires interpretation of probability.
Guidelines tool	Use this tool when you need to know about established guidelines. Use this tool when you have a top differential diagnosis and need to know if there are any tests that can help you confirm or refute the diagnosis. This tool must not be used more than once. If the guidelines suggest a test you haven't ordered yet, you must order that test if it is available. If the guidelines suggest a test that is not available, you must add the recommendation to your final answer. You must not order tests which have already been ordered. After using this tool, you must proceed to consider available treatment guidelines before giving your final answer. You may not use existing knowledge to recommend a treatment unless no treatment guidelines are available. Your recommendation must be as relevant to the patient's condition as per the treatment guidelines as possible. This tool must be used to personalize your final answer for the patient in front of you. Do not quote recommendations from guidelines verbatim. The use of this tool is compulsory before issuing your final answer. The tool accepts your most likely differential diagnosis as a string. Institutional guidelines take precedence over other guidelines.	Guidelines are taken from reputable sources and distilled into two subheadings: INITIAL ASSESSMENT, and INITIAL TREATMENT. Guidelines are only shown to the model if the diagnosis provided by the model is correct.

Table 1. Tools

Tool names and descriptions as they are inserted into the initial prompt for the LLM. For tools that expect an input, italicized text is replaced by names of investigations that are pooled from all available cases at runtime. These investigations represent the degrees-offreedom within which the model may act.

Text in bold represents safety measures to prevent the model from getting stuck in place, or specialized directions for the model that direct the model to modify its downstream output. Lines of text in the description are separated for clarity.

Question	What is the next best step in management?		
Observation	To determine the next best step in management, I first need to understand the patient's symptoms and clinical presentation.		
Action + Action Input	Symptom tool (No input)		
Tool response	Patient reported 1 hour ago with left sided chest pain, sweating, nausea, vomiting, shortness of breath.		
Observation	The symptoms suggest a possible cardiac event, such as a myocardial infarction. I need to gather more information about the patient's past medical history and physical exam findings to further narrow down the differential diagnosis.		
Action + Action Input	Past medical history tool (No input)		
Tool response	No past medical history available.		
Observation	The lack of past medical history makes it difficult to assess the patient's risk factors for cardiac disease. However, given the patient's symptoms, I should proceed with a physical exam to gather more information.		
Action + Action Input	Sign tool <i>(No input)</i>		
Tool response	S3 gallop		
Observation	An S3 gallop is often associated with conditions that cause rapid ventricular filling, such as congestive heart failure. This finding, in combination with the patient's symptoms, further supports the possibility of a cardiac event. I should use the machine learning tool to predict the likelihood of a low ejection fraction, which is often seen in heart failure.		
Action + Action Input	Machine learning tool (Low ejection fraction (<40%) model)		
Tool response	Low ejection fraction (<40%): 0.9		
Observation	The high probability of a low ejection fraction suggests that the patient may be experiencing heart failure. However, to confirm this diagnosis, I need to order relevant lab investigations and an ECG.		
Action + Action Input	Lab investigation tool (SERUM TROPONINS)		
Tool response	SERUM TROPONINS: 0.1 ng/mL (Elevated)		
Observation	The elevated troponin levels are indicative of myocardial injury, which is consistent with a myocardial infarction. This, in combination with the patient's symptoms and the S3 gallop, strongly suggests a cardiac event. I should now order an ECG to further confirm this diagnosis.		
Action +	ECG tool		

Action Input				
Tool response	ST elevation in leads V1-V4			
Observation	The ST elevation in leads V1-V4 is consistent with an anterior wall myocardial infarction. This, along with the patient's symptoms, elevated troponins, and the S3 gallop, confirms the diagnosis of a myocardial infarction. I should now use the guidelines tool to determine the most appropriate next steps in management.			
Action + Action Input	Treatment guidelines tool (Acute myocardial infarction)			
Tool response <guidelines about="" acute="" general="" management="" mi="" of=""></guidelines>				
	According to institutional (Institutional guidelines): The institution does not accept STEMI patients beyond initial evaluation. Patient must be immediately transferred to another facility.			
Observation	Given the patient's symptoms, physical exam findings, elevated troponins, ST elevation on ECG, and the high probability of a low ejection fraction, the diagnosis of ST-elevation myocardial infarction (STEMI) is confirmed. The guidelines suggest that the primary goal of STEMI management is to rapidly restore blood flow to the occluded coronary artery. This can be achieved through reperfusion therapy, such as percutaneous coronary intervention (PCI) or fibrinolysis.			
	As per the guidelines, the patient should be given aspirin as soon as possible and continued indefinitely. P2Y12 inhibitors such as clopidogrel, prasugrel, or ticagrelor should be given in addition to aspirin. An anticoagulant, such as unfractionated heparin, low molecular weight heparin, or bivalirudin, should also be administered.			
	In addition to reperfusion and antithrombotic therapy, the patient should be started on oral beta blockers within the first 24 hours, unless there are contraindications. ACE inhibitors should be given within the first 24 hours to STEMI patients with left ventricular systolic dysfunction, heart failure, or hypertension. High-intensity statin therapy should be initiated in all patients with STEMI without contraindications. Pain relief with opioids, such as morphine, can be given if required.			
	However, according to institutional guidelines, this institution does not accept STEMI patients beyond initial evaluation. Therefore, the patient must be immediately transferred to another facility for further management.			
Final answer	The next best step in management is to immediately start the patient on aspirin, a P2Y12 inhibitor, and an anticoagulant. The patient should also be started on a beta blocker, an ACE inhibitor, and high-intensity statin therapy within the first 24 hours, unless there are contraindications. Pain relief with opioids can be given if required. <i>However, given the institutional guidelines, the patient must be immediately transferred to another facility for further management, including reperfusion therapy.</i>			

Table 2. Sample run for a case of acute myocardial infarction (Internal Medicine Case 4)with GPT-4

Question posed: What is the next best step in management?

Each row of the table indicates an interaction with the model in order. "*Observations*" correspond to the inner monologue of the model in interpreting the output or response from the last tool utilized. "*Action + Action Input*" correspond to the model calling the actual tool (Italicized text corresponds to the input given by the LLM to the tool). "*Tool response*" is the information recorded within the .json file that is retrieved by using the tool. "*Final answer*" is the LLM's actual response to the question asked, and the termination point of the run.

It is seen that the model chooses to go for an ejection fraction prediction model and SERUM TROPONINS before proceeding forward. This may not be the best choice given the acuity of the presentation (please see discussion).

Treatment for an acute myocardial infarction is usually a primary Percutaneous Coronary Intervention (PCI) procedure performed within 90 minutes of patient presentation (as alluded to by the model in the final observation). However, in this case, institutional level guidelines (underlined) alongside general treatment guidelines provided to the model inform it that "*The institution does not accept STEMI patients beyond initial evaluation. Patient must be immediately transferred to another facility.*" Retrieval Augmented Generation pushes the model into the direction of transferring the patient to another facility which manifests in the final answer.

The .json file corresponding to this case is available as **Supplementary Figure 1**.

Metric	Correctness of final answer	Judicious use of tools	Conformity to guidelines	Resistance to hallucinations	
		Gemini Pro			
Cardiology	50%	40%	40%	100%	
Critical Care	90%	50%	60%	90%	
Emergency Medicine	20%	20%	40%	30%	
Genetics	40%	20%	37.5%	100%	
Internal Medicine	20%	30%	35%	100%	
		GPT-3.5			
Cardiology	50%	60%	80%	100%	
Critical Care	80%	60%	70%	90%	
Emergency Medicine	70%	40%	90%	100%	
Genetics	60%	35%	25%	100%	
Internal Medicine	40%	60%	55%	100%	
		GPT-4			
Cardiology	80%	80%	70%	100%	
Critical Care	100%	60%	90%	90%	
Emergency Medicine	70%	70%	65%	80%	
Genetics	100%	75%	75%	100%	
Internal Medicine	60%	60%	70%	100%	
	LL	aMA-70B Chat			
Cardiology	20%	10%	10%	90%	
Critical Care	30%	30%	10%	80%	
Emergency Medicine	30%	20%	20%	10%	
Genetics	20%	10%	0%	80%	
Internal Medicine	20%	20%	0%	40%	
Mixtral-7x8B					
Cardiology	20%	20%	20%	90%	
Critical Care	40%	30%	30%	40%	
Emergency Medicine	30%	20%	20%	20%	
Genetics	40%	20%	25%	50%	
Internal Medicine	60%	40%	10%	100%	

Table 3. Model performance within framework by specialty

Scores are presented as percentage values for clarity. (50%: Fair, 100%: Good) All API models (Gemini Pro, GPT-3.5, and GPT-4) had Retrieval Augmented Generation enabled and were shown guidelines for each case. Both open-source models (LLaMA-70B and Mixtral-8x7B) did not have sufficient context length to accommodate guidelines. Number of questions by specialty: 5 each (25 total).

Metric	Correctness of final answer	Judicious use of tools	Conformity to guidelines	Resistance to hallucinations	
		Gemini Pro	<u>, -</u>		
Easy	79.2%	50%	68.8%	87.5%	
Medium	21.4%	28.6%	28.6%	71.4%	
Hard	0%	0%	0%	91.7%	
	GPT-3.5				
Easy	70.8%	54.2%	64.6%	95.8%	
Medium	57.1%	53.6%	64.3%	100%	
Hard	41.7%	41.7%	70%	100%	
		GPT-4			
Easy	87.5%	68.8%	75%	87.5%	
Medium	85.7%	75%	89.3%	100%	
Hard	66.7%	62.5%	50%	100%	
	LL	aMA-70B Chat			
Easy	29.2%	20.8%	12.5%	58.3%	
Medium	7.1%	7.1%	0%	57.1%	
Hard	33.3%	16.7%	8.3%	66.7%	
Mixtral-7x8B					
Easy	41.7%	29.2%	33.3%	54.2%	
Medium	35.7%	21.4%	10.7%	64.3%	
Hard	33.3%	25%	8.3%	66.7%	

Table 4. Model performance within framework by case difficulty

Scores are presented as percentage values for clarity. (50%: Fair, 100%: Good) All API models (Gemini Pro, GPT-3.5, and GPT-4) had Retrieval Augmented Generation enabled and were shown guidelines for each case. Both open-source models (LLaMA-70B and Mixtral-8x7B) did not have sufficient context length to accommodate guidelines. Number of questions by difficulty - Easy: 12, Medium: 7, Hard: 6

Contributions

The study was conceived and designed by A.V.; Code was written by A.V.; Underlying data were analyzed and visualized by A.V.; Cases were collected and evaluated by J.Lampert, J.Lee, A.Sawant, D.A, A.Sakhuja; The first draft of the manuscript was written by A.V.; G.N.N. supervised the project. A.V. and G.N.N. had access to and verified the data. All authors provided feedback and approved the final draft for publication.

Disclosures

Dr. Nadkarni reports consultancy agreements with AstraZeneca, BioVie, GLG Consulting, Pensieve Health, Reata, Renalytix, Siemens Healthineers, and Variant Bio; research funding from Goldfinch Bio and Renalytix; honoraria from AstraZeneca, BioVie, Lexicon, Daiichi Sankyo, Meanrini Health and Reata; patents or royalties with Renalytix; owns equity and stock options in Pensieve Health and Renalytix as a scientific cofounder; owns equity in Verici Dx; has received financial compensation as a scientific board member and advisor to Renalytix; serves on the advisory board of Neurona Health; and serves in an advisory or leadership role for Pensieve Health and Renalytix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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References

- 1 Davidoff, F., Haynes, B., Sackett, D. & Smith, R. Vol. 310 1085-1086 (British Medical Journal Publishing Group, 1995).
- 2 Sackett, D. L. in *Seminars in perinatology*. 3-5 (Elsevier).
- 3 Ray, J. G., Vermeulen, M. J. & Koren, G. Taking ACE inhibitors during early pregnancy: is it safe? *Can Fam Physician* **53**, 1439-1440 (2007).
- 4 Wiles, R., Hankinson, B., Benbow, E. & Sharp, A. Making decisions about radiological imaging in pregnancy. *bmj* **377** (2022).
- 5 Laker, L. F., Froehle, C. M., Windeler, J. B. & Lindsell, C. J. Quality and efficiency of the clinical decision-making process: Information overload and emphasis framing. *Production and Operations Management* **27**, 2213-2225 (2018).
- 6 Nijor, S., Rallis, G., Lad, N. & Gokcen, E. Patient safety issues from information overload in electronic medical records. *Journal of Patient Safety* **18**, e999 (2022).
- 7 Quer, G., Arnaout, R., Henne, M. & Arnaout, R. Machine Learning and the Future of Cardiovascular Care. *Journal of the American College of Cardiology* **77**, 300-313 (2021). <u>https://doi.org/doi:10.1016/j.jacc.2020.11.030</u>
- 8 Wichmann, J. L., Willemink, M. J. & De Cecco, C. N. Artificial intelligence and machine learning in radiology: current state and considerations for routine clinical implementation. *Investigative Radiology* **55**, 619-627 (2020).
- 9 Ghayvat, H., Pandya, S. & Patel, A. in *2nd International Conference on Data, Engineering and Applications (IDEA).* 1-7 (IEEE).
- 10 Çallı, E., Sogancioglu, E., van Ginneken, B., van Leeuwen, K. G. & Murphy, K. Deep learning for chest X-ray analysis: A survey. *Medical Image Analysis* **72**, 102125 (2021).
- 11 Lee, C. *et al.* Application of a novel machine learning framework for predicting non-metastatic prostate cancer-specific mortality in men using the Surveillance, Epidemiology, and End Results (SEER) database. *The Lancet Digital Health* **3**, e158-e165 (2021).
- 12 Scrutinio, D. *et al.* Machine learning to predict mortality after rehabilitation among patients with severe stroke. *Scientific reports* **10**, 20127 (2020).
- 13 Deb, S. & Claudio, D. Alarm fatigue and its influence on staff performance. *IIE Transactions on Healthcare Systems Engineering* **5**, 183-196 (2015).
- 14 Petch, J., Di, S. & Nelson, W. Opening the black box: the promise and limitations of explainable machine learning in cardiology. *Canadian Journal of Cardiology* **38**, 204-213 (2022).
- 15 Vaid, A. *et al.* Implications of the Use of Artificial Intelligence Predictive Models in Health Care Settings: A Simulation Study. *Annals of Internal Medicine* **176**, 1358-1369 (2023).
- 16 Thirunavukarasu, A. J. *et al.* Large language models in medicine. *Nature medicine* **29**, 1930-1940 (2023).
- 17 Chang, Y. *et al.* A survey on evaluation of large language models. *arXiv preprint arXiv:2307.03109* (2023).
- 18 Li, H. *et al.* Ethics of large language models in medicine and medical research. *The Lancet Digital Health* **5**, e333-e335 (2023).
- 19 Singhal, K. *et al.* Large language models encode clinical knowledge. *Nature* **620**, 172-180 (2023).
- 20 Kung, T. H. *et al.* Performance of ChatGPT on USMLE: Potential for AI-assisted medical education using large language models. *PLoS digital health* **2**, e0000198 (2023).
- 21 Bubeck, S. *et al.* Sparks of artificial general intelligence: Early experiments with gpt-4. *arXiv preprint arXiv:2303.12712* (2023).

- 22 Vaid, A., Landi, I., Nadkarni, G. & Nabeel, I. Using fine-tuned large language models to parse clinical notes in musculoskeletal pain disorders. *The Lancet Digital Health* **5**, e855-e858 (2023). https://doi.org/10.1016/S2589-7500(23)00202-9
- 23 Ferrer, R. L., Hambidge, S. J. & Maly, R. C. The essential role of generalists in health care systems. Annals of internal medicine **142**, 691-699 (2005).
- 24 Bigdeli, M. *et al.* Access to medicines from a health system perspective. *Health policy and planning* **28**, 692-704 (2013).
- 25 Agniel, D., Kohane, I. S. & Weber, G. M. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. *Bmj* **361** (2018).
- 26 Larsson, D. J. & Flach, C.-F. Antibiotic resistance in the environment. *Nature Reviews Microbiology* **20**, 257-269 (2022).
- 27 Sobo, E. J. & Loustaunau, M. O. *The cultural context of health, illness, and medicine*. (Bloomsbury Publishing USA, 2010).
- 28 Huang, L. *et al.* A survey on hallucination in large language models: Principles, taxonomy, challenges, and open questions. *arXiv preprint arXiv:2311.05232* (2023).
- 29 Lewis, P. *et al.* Retrieval-augmented generation for knowledge-intensive nlp tasks. *Advances in Neural Information Processing Systems* **33**, 9459-9474 (2020).
- 30 Cai, D., Wang, Y., Liu, L. & Shi, S. in *Proceedings of the 45th International ACM SIGIR Conference* on Research and Development in Information Retrieval. 3417-3419.
- 31 Zamfirescu-Pereira, J., Wong, R. Y., Hartmann, B. & Yang, Q. in *Proceedings of the 2023 CHI Conference on Human Factors in Computing Systems.* 1-21.
- 32 Meskó, B. Prompt engineering as an important emerging skill for medical professionals: tutorial. Journal of Medical Internet Research **25**, e50638 (2023).
- 33 Wei, J. *et al.* Chain-of-thought prompting elicits reasoning in large language models. *Advances in Neural Information Processing Systems* **35**, 24824-24837 (2022).
- ³⁴ Zhang, Z., Zhang, A., Li, M. & Smola, A. Automatic chain of thought prompting in large language models. *arXiv preprint arXiv:2210.03493* (2022).
- 35 Touvron, H. *et al.* Llama 2: Open foundation and fine-tuned chat models. *arXiv preprint arXiv:2307.09288* (2023).
- 36 Shazeer, N. *et al.* Outrageously large neural networks: The sparsely-gated mixture-of-experts layer. *arXiv preprint arXiv:1701.06538* (2017).
- 37 Wolf, T. *et al.* Huggingface's transformers: State-of-the-art natural language processing. *arXiv preprint arXiv:1910.03771* (2019).
- 38 Paszke, A. *et al.* in *Proceedings of the 33rd International Conference on Neural Information Processing Systems* Article 721 (Curran Associates Inc., 2019).
- 39 Van Rossum, G. in USENIX annual technical conference. 1-36 (Santa Clara, CA).
- 40 Van Veen, D. *et al.* Clinical Text Summarization: Adapting Large Language Models Can Outperform Human Experts. *Res Sq* (2023). <u>https://doi.org/10.21203/rs.3.rs-3483777/v1</u>
- 41 Berendonk, T. U. *et al.* Tackling antibiotic resistance: the environmental framework. *Nature reviews microbiology* **13**, 310-317 (2015).
- 42 Bösner, S., Pickert, J. & Stibane, T. Teaching differential diagnosis in primary care using an inverted classroom approach: student satisfaction and gain in skills and knowledge. *BMC medical education* **15**, 1-7 (2015).
- 43 Shin, D. The effects of explainability and causability on perception, trust, and acceptance: Implications for explainable AI. *International Journal of Human-Computer Studies* **146**, 102551 (2021).
- 44 Martino, A., Iannelli, M. & Truong, C. in *European Semantic Web Conference*. 182-185 (Springer).

- 45 Zhang, M., Press, O., Merrill, W., Liu, A. & Smith, N. A. How language model hallucinations can snowball. *arXiv preprint arXiv:2305.13534* (2023).
- 46 Wei, A., Haghtalab, N. & Steinhardt, J. Jailbroken: How does IIm safety training fail? *arXiv preprint arXiv:2307.02483* (2023).
- 47 Poli, M. *et al.* Hyena hierarchy: Towards larger convolutional language models. *arXiv preprint arXiv:2302.10866* (2023).