

A Survey of Large Language Models for Healthcare: from Data, Technology, and Applications to Accountability and Ethics

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Abstract—The utilization of large language models (LLMs) in the Healthcare domain has generated both excitement and concern due to their ability to effectively respond to free-text queries with certain professional knowledge. This survey outlines the capabilities of the currently developed LLMs for Healthcare and explicates their development process, to provide an overview of the development roadmap from traditional Pretrained Language Models (PLMs) to LLMs. Specifically, we first explore the potential of LLMs to enhance the efficiency and effectiveness of various Healthcare applications highlighting both the strengths and limitations. Secondly, we conduct a comparison between the previous PLMs and the latest LLMs, as well as comparing various LLMs with each other. Then we summarize related Healthcare training data, training methods, and usage. Finally, the unique concerns associated with deploying LLMs in Healthcare settings are investigated, particularly regarding fairness, accountability, transparency, and ethics. Our survey provides a comprehensive investigation from perspectives of both computer science and Healthcare specialties. Besides the discussion about Healthcare concerns, we support the computer science community by compiling a collection of open-source resources, such as accessible datasets, the latest methodologies, code implementations, and evaluation benchmarks in the Github¹. Summarily, we contend that a significant paradigm shift is underway, transitioning from PLMs to LLMs. This shift encompasses a move from discriminative AI approaches to generative AI approaches, as well as a shift from model-centered methodologies to data-centered methodologies. Also, we determine that the biggest obstacle of using LLMs in Healthcare are fairness, accountability, transparency and ethics.

Index Terms—Large Language Model, Medicine, Healthcare Application

I. INTRODUCTION

Recently, Large Language Models (LLMs) have emerged as a driving force in Artificial Intelligence (AI) due to their impressive abilities in understanding, generating, and even reasoning. The integration of such LLMs into Healthcare represents a significant shift in the application of AI towards

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¹<https://github.com/KaiHe-better/LLM-for-Healthcare>

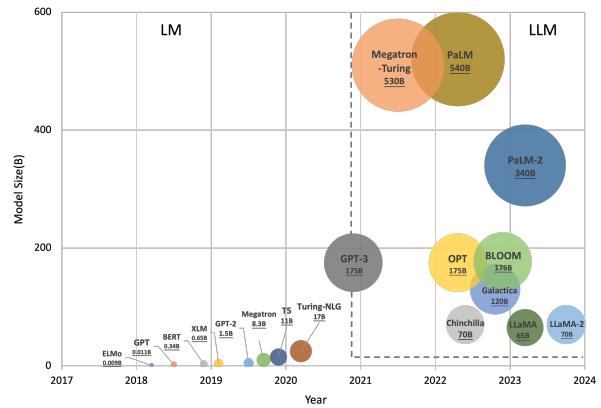


Fig. 1. The development from PLMs to LLMs. GPT-3 [15] marks a significant milestone in the transition from PLMs to LLMs, signaling the beginning of a new era.

improving clinical outcomes, conserving resources, and enhancing patient care. For example, healthcare researchers are constantly grappling with complex challenges such as diagnosing rare diseases [1], understanding patient narratives [2], and personalized treatment planning [3]. By employing LLMs like Med-PaLM 2 [4], which demonstrates expert-level accuracy on the US Medical Licensing Examination (USMLE), these models provide advanced capabilities in processing and understanding medical language, directly contributing to more precise diagnostics and tailored treatment plans [5]. In addition to specialized models like Med-PaLM 2, more general models such as ChatGPT and GPT-4 have also demonstrated superior performance in a variety of healthcare-related tasks [6]. These advancements not only broaden the scope of LLM applications in the field but also ensure better patient outcomes through enhanced accuracy and efficiency in healthcare services.

Initially, Pretrained Language Models (PLMs) such as BERT [7] and RoBERTa [8] were developed for many general NLP tasks [9]–[13] and further adapted to Healthcare tasks. However, their application in Healthcare field was limited as they typically functioned as single-task systems lacking the ability to interact dynamically with complex medical data [2], [14]. Consequently, their use was predominantly confined to theoretical research rather than real-world medical scenarios.

However, the development of LLMs like GPT-3 represents a transformative evolution from PLMs to LLMs, as illustrated in Figure 1. With over 100 billion parameters, GPT-3 demon-

strates exceptional understanding and generating capabilities, which significantly enhance its functionality across various applications, including Healthcare [15]–[17]. These capabilities allow LLMs to process and analyze a broader array of data types, such as patient records, clinical notes, and research papers, to identify patterns and suggest potential diagnoses that might be overlooked by human clinicians [18]. Additionally, the integration of LLMs into Healthcare is further supported by their enhanced explainability and adaptability. The introduction of Chain-of-Thought (CoT) processing in newer LLMs contributes to a more transparent AI decision-making process. This transparency is crucial in Healthcare settings, where understanding the rationale behind AI-generated decisions can foster greater trust and reliability among medical professionals in employing AI-powered tools [16]. Thus, the leap in model capacity and sophistication not only broadens the scope of LLM applications but also deepens their impact, particularly in specialized fields like Healthcare.

Besides the above mentioned general abilities, many studies start to improve LLMs by tailoring them to the unique Healthcare application characteristics. Understanding such trend will be helpful for further deepening and broadening Healthcare applications. For example, considering Healthcare field inherently contains multimodal data, the studies [19]–[21] explore LLM's ability to understand and recognise diverse medical images. More detail, HuatuoGPT [22] have the ability to actively ask questions for the patients rather than respond passively, which can help to mine more potential medical information. BenTsao [23] focus on introducing traditional medical knowledge. In addition, some disease-specific LLMs have been proposed, including OphGLM [24] for ophthalmology and SoulChat [25] for mental health. Besides the above limited example, there are immense potential of LLMs for Healthcare waiting to be explored. Beyond the specific instances mentioned, the potential for LLMs in healthcare is vast and ripe for exploration. We are convinced that dedicating resources to develop effective, ethical, and bespoke LLMs for healthcare is not only essential but also holds great promise and practical benefits.

This paper aims to update readers on the latest developments in this field and provide comprehensive information for those who want to use or develop a Healthcare LLM. Our survey represents a comprehensive examination of LLMs specifically within the Healthcare domain, not only including various Healthcare applications, but also contains detailed technology summarization. We aims to provide insights about how different technologies affect different Healthcare-related tasks. More importantly, as the capabilities of LLMs increase, the challenge of applying AI for Healthcare due to performance limitations is decreasing. Consequently, issues of fairness, accountability, transparency, and ethics are becoming more significant impediments to practical implementation. For this reason, we discuss these four critical issues in the context of employing LLMs and emphasise their importance.

Compared with existing studies about LLMs for Healthcare [6], [18], [26], [27], they primarily concentrate on Healthcare applications and often discuss the impacts without delving into the technical aspects of development and usage

methods. The surveys [28] only focus on medical or Healthcare applications of LLMs. The study [28] mainly focus on highlighting the potentials and pitfalls of LLMs for Healthcare. However, they are not provided with any detailed technological insights and some core problems like accountability and ethics. Some former studies [29], [30] involved part of technological content, but they focus on general LLM developments and assessments [5] without specific adaptations and discussions for Healthcare. The studies of [27], [31] have focused on Healthcare PLMs rather than LLMs.

Besides our comprehensive investigation, the survey further analyzes and summarizes some development trends, including the current transition from PLMs to LLMs in Healthcare field. We provide a brief introduction to Healthcare PLMs as background information and then delve into the details of Healthcare LLMs. Additionally, we analyze non-technological concerns towards Healthcare LLMs, such as fairness, accountability, transparency, and ethics. Finally, we outline the distinct challenges that emerge when employing LLMs within Healthcare field. These challenges encompass augmenting medical knowledge, seamless integration of LLMs within Healthcare procedures, interactions between patients and medical practitioners, and inherent issues associated with LLMs. Our contributions can be summarized as:

- We propose a comprehensive survey about LLMs for Healthcare. Our paper provides an overview of the development roadmap from PLMs to LLMs, which updates readers on the latest advancements in this field.
- We have compiled an extensive list of publicly available data, training techniques, and evaluation systems for LLMs in Healthcare, which can be useful for those who plan to create their private Healthcare LLMs.
- We analyze numerous ethical considerations about the utilization of LLMs for Healthcare. These considerations encompass aspects such as robustness, toxicity, bias, fairness, accountability, transparency, ethics, as well as other constraints and prospective research areas. Our comprehensive analysis is anticipated to guide medical researchers in making informed choices when selecting LLMs suitable for their specific needs.

The overall structure of this paper is illustrated in Figure 2. Besides this Introduction section, Section II presents the applications of PLMs and LLMs in the Healthcare domain. Section III introduces and discusses the existing studies on PLMs and LLMs, highlighting their differences. The training and utilization of LLMs are described in Section IV. Evaluation methods for LLMs are discussed in Section V. Section VI focuses on the topics of fairness, accountability, transparency, and ethics specifically related to Healthcare LLMs. Lastly, Section VII provides the conclusion of the paper.

II. WHAT LLMs CAN DO FOR HEALTHCARE? FROM FUNDAMENTAL TASKS TO ADVANCED APPLICATIONS

Numerous endeavors have been made to apply PLMs or LLMs to Healthcare. In the early stages, the studies primarily focused on fundamental tasks, including medical Named

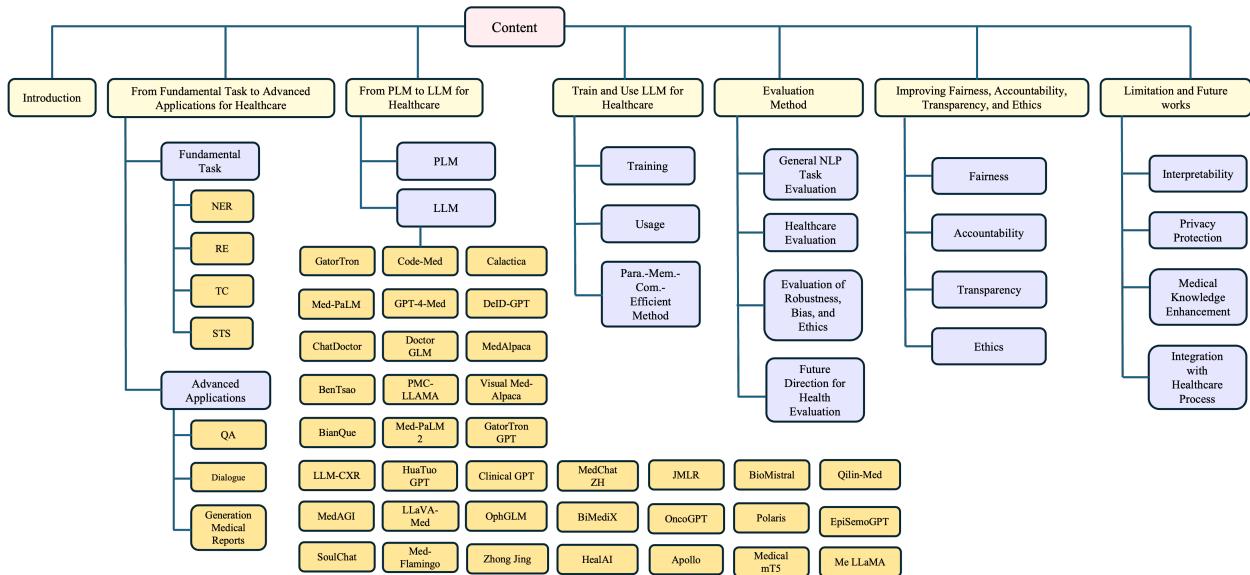


Fig. 2. The organizational framework for the content. Section III, Section IV, Section V are technology details, while Section II, Section VI and Section VI are more valued for Healthcare professionals.

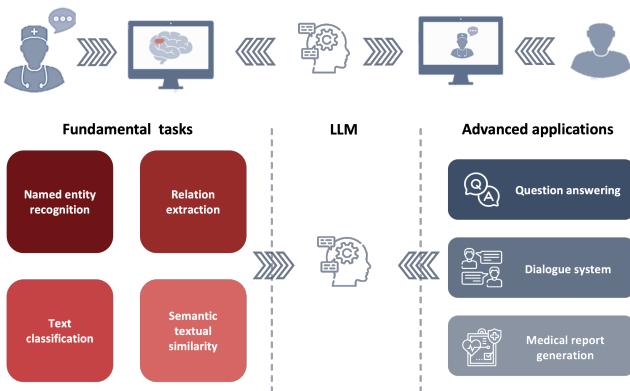


Fig. 3. LLMs for Healthcare: from fundamental task to advanced applications.

Entity Recognition (NER), Relation Extraction (RE), Text Classification (TC), and Semantic Textual Similarity (STS), due to the challenges of accessing diverse medical datasets, the complexity of the medical domain, and limitations of the models' capabilities [31]. Based LLMs, the concept of Artificial General Intelligence (AGI) with Healthcare adaptation has been proposed [32], [33], which has led to more practical applications in various aspects of the Healthcare field. For instance, some online medical consultation systems [34], [35] have been deployed, which can answer professional medical questions for patients and serve as guides in hospitals. Furthermore, some researchers explore the automatic generation of multimodal medical reports [36], [37]. The overall application framework of LLMs for Healthcare is shown in Figure 3. In the following sections, we analyze what LLMs can do for Healthcare in detail, and compare the strengths and weaknesses of LLMs and PLMs on different tasks.

A. NER and RE for Healthcare

The initial step towards unlocking valuable information in unstructured Healthcare text data mainly involves performing NER and RE. By extracting medical entities such as drugs, adverse drug reactions, proteins, and chemicals, as well as predicting the relations between them, a multitude of useful functions can be achieved, including but not limited to Adverse Drug Event [38], Drug Drug Interaction [39], [40], and Chemistry Protein Reaction [41]. Information Extraction also provide fundamental information for a range of other Healthcare applications, such as medical entity normalization and coreference [42], [43], medical knowledge base and knowledge graph construction [44], [45], and entity-enhanced dialogue [46], [47]. For example, by employing NER and RE tasks, the Healthcare knowledge databases Drugbank² [48] and UMLS [49] are constructed, which facilitate various applications in Intellectual Healthcare³ [50].

In the early stages of research on NER with PLMs, a significant portion of studies focused on sequence labeling tasks, as highlighted in previous research [51]. To accomplish this, PLMs-based approaches were employed to generate contextualized representations for individual tokens, coupled with a classification header such as a linear layer, BiLSTM, or CRF [52]–[54]. In the case of RE tasks, the extracted entity pairs' representations were typically fed into a classification header to determine the existence of relations between the given entities [11], [55], [56].

²Drugbank is a free and comprehensive online database that provides information on drugs and drug targets. The most recent version (5.0) includes 9591 drug entries, such as 2037 FDA-approved small molecule drugs, 241 FDA-approved biotech drugs, 96 nutraceuticals, and over 6000 experimental drugs.

³UMLS is a collection of controlled vocabularies used in biomedical sciences and Healthcare. It features a mapping structure that enables easy translation among different terminology systems, and serves as an extensive thesaurus and ontology of biomedical concepts.

In the era of LLMs, NER and RE have been improved to work under more complex conditions and more convenient usages. One example is LLM-NERRE [57], which combines NER and RE to handle hierarchical information in scientific text. This approach has demonstrated the ability to effectively extract intricate scientific knowledge for tasks that require the use of LLMs. These tasks often involve complexities that cannot be effectively handled by typical PLMs such as BERT. Meanwhile, LLMs can finish medical NER and RE well even without further training. The study [58] employed InstructGPT [59] to perform zero- and few-shot information extraction from clinical text, despite not being trained specifically for the clinical domain. The results illustrated that InstructGPT can perform very well on biomedical evidence extraction [60], medication status extraction [61], and medication attribute extraction [61]. This observation supports the notion that LLMs can be applied with flexibility and efficiency.

Despite their capabilities, they still perform comparably to specially trained state-of-the-art (SOTA) PLMs, particularly in domains that involve professional terms and symbols in very detailed fields [62]. When training LLMs in highly specialized areas, the quantity of collected data is often insufficient and lacks diversity. Consequently, LLMs frequently experience catastrophic forgetting, which can detrimentally impact their ability to adapt to these specialized fields. In contrast, PLMs do not require as much data [63], making them better suited for tasks within very detailed domains. Overall, we maintain that both PLMs and LLMs have distinct advantages in the field of Information Extraction.

B. Text Classification for Healthcare

TC aims to assign labels to text of different lengths, such as phrases, sentences, paragraphs, or documents. In Healthcare research, a large amount of patient data is collected in the electronic format, including disease status, medication history, lab tests, and treatment outcomes, which is a valuable source of information for analysis. However, these data can only be used with appropriate labels, while TC is one of the most commonly used technology. For example, a research study [64] proposed several methods, based on hybrid Long Short-Term Memory (LSTM) and bidirectional gated recurrent units(Bi-GRU) to achieve medical TC. These methods were demonstrated effective in the Hallmarks dataset and AIM dataset [65] (Both these two datasets were sourced from biomedical publication abstracts). The study [66] used text classification to identify prescription medication mentioned in tweets and achieved good results using PLMs. Also, some studies employ TC-based Sentiment Analysis (SA) to understand patient emotion or mental healthcare, aiming to provide more humanized treatments [67], [68].

However, PLMs-based TC usually cannot satisfy explainable and reliable requirements in the Healthcare field, while LLMs-based TC mitigates these issues to some extent. For example, CARP [69] takes advantage of LLMs by introducing Clue And Reasoning Prompting to achieve better TC tasks. This study adopts a progressive reasoning strategy tailored to address the complex linguistic phenomena involved in TC.

First, LLMs were prompted to find superficial clues like keywords, tones, and references in Healthcare data. Then, a diagnostic reasoning process was induced for final decision-making. AMuLaP [70] is another example, which proposed Automatic Multi-Label Prompting for few-shot TC. By exploring automatic label selection, their method surpasses the GPT-3-style in-context learning method, showing significant improvements compared with previous PLMs-based results [71].

Unlike in general domains where LLMs and SOTA PLMs exhibit similar performance in TC, LLMs demonstrate a clear advantage in healthcare. This advantage is primarily due to the inherent complexity of healthcare data, which make tasks are more challenging. Healthcare texts are laden with specialized language, including technical terms, abbreviations, and jargon that are unique to the field. Moreover, the context in which these terms are used can significantly alter their meanings. For instance, the abbreviation "MI" might mean "mitral insufficiency" or "myocardial infarction," depending on the surrounding context. Given these conditions, text classification tasks in healthcare often require the integration of various types of data and an understanding of their interplay. This necessitates models that are not only capable of summarizing information but also adept at reasoning based on the context. LLMs are particularly well-suited for these tasks due to their deeper contextual understanding and ability to handle complex interactions within the text, making them more effective for healthcare applications than PLMs.

C. Semantic Textual Similarity for Healthcare

STS is a way to measure how much two sentences mean the same thing or two documents are similar. In Healthcare, STS is often used to combine information from different sources, especially used for Electronic Health Records (EHR). The 2018 BioCreative/Open Health NLP (OHNLP) challenge [72] and the National NLP Clinical Challenges (n2c2) 2019 Track 1 show that STS can help reduce mistakes and disorganization in EHRs caused by copying and pasting or using templates. This means that STS can be used to check the quality of medical notes and make them more efficient for other NLP tasks [73]. The study [74] proposed a new method using ClinicalBERT, which was a fine-tuned BERT-based method. The proposed iterative multitask learning technique helps the model learn from related datasets and select the best ones for fine-tuning. Besides, STS can be used for Healthcare information retrieval. For examples, if a patient ask question like "I was diagnosed with non-clear cell renal cell carcinoma, what are the chances of recurrence after cure? Give me evidence from relevant scientific literature", Our AI systems may need retrieval related database to find papers which contain similar semantic sentences. For doctor, when face patients who are difficult to diagnose, this technology can identify similar patients for doctors' reference.

When comes to compare PLMs and LLMs, we need to break down the situation to start some discussion. For short text semantic classification, SOTA PLMs and LLMs are comparable. The reason is typically such tasks contain less contextual

information, which means the advantage of LLMs in handling large context windows and understanding complex narrative structures is less pronounced. In such cases, the fundamental ability of both PLMs and LLMs to understand and interpret language at a basic level plays a more significant role, leading to similar levels of performance. On the other hand, for tasks like information retrieval, LLMs tend to be overly complex and resource-intensive for the role of a simple retriever. Typically, LLMs excel in directly generating responses or completing texts based on given inputs. In contrast, PLMs, which are generally more lightweight, are better suited for retrieving external knowledge. This distinction makes PLMs more practical for applications where quick, efficient retrieval of information is required without the additional overhead of generating new text content.

D. Question Answering for Healthcare

Traditionally, QA is a separate task that involves generating or retrieving answers for given questions. In Healthcare, QA can be very beneficial for medical professionals to find necessary information in clinical notes or literature, as well as providing basic Healthcare knowledge for patients. According to a report by the Pew Research Center [75], over one-third of American adults have searched online for medical conditions they may have. A strong QA system for Healthcare can significantly fulfill the consultation needs of patients.

Many studies [27], [31], [76] explored how to adapt general PLMs to answer Healthcare questions, including designing special pertaining task [77], fine-tuning on Healthcare data [78], and introducing external Healthcare knowledge base [79]. However, due to their limited language understanding and generation abilities [80], PLMs-based QA systems struggle to play a significant role in real-world Healthcare scenarios.

With the advent of powerful LLMs, prompt-based methods have been introduced to solve various tasks by formulating them as QA tasks, including NER [81], RE [11], and SA [82]–[85]. In addition to these tasks, LLMs have significantly improved typical QA tasks in professional fields, such as Healthcare. For instance, Med-PaLM 2 [4], a medical domain LLM, achieved a score of up to 86.5% on the USMLE dataset, outperforming Med-PaLM [86] by over 19% and setting a new state-of-the-art. This LLM also approached or exceeded state-of-the-art performance across MedMCQA [87], PubMedQA [88], and MMLU clinical topics datasets [89]. In the study [90], the use of ChatGPT, Google Bard, and Claude for patient-specific QA from clinical notes was investigated. The accuracy, relevance, comprehensiveness, and coherence of the answers generated by each model were evaluated using a 5-point Likert scale on a set of patient-specific questions. Another study [91] proposed a retrieval-based medical QA system that leverages LLMs in combination with knowledge graphs to address the challenge. As one of the most outstanding ability, LLMs are obviously superior to PLMs on QA tasks.

E. Dialogue System for Healthcare

Chatbots have demonstrated promising potential to assist both patients and health professionals [92]–[94]. The imple-

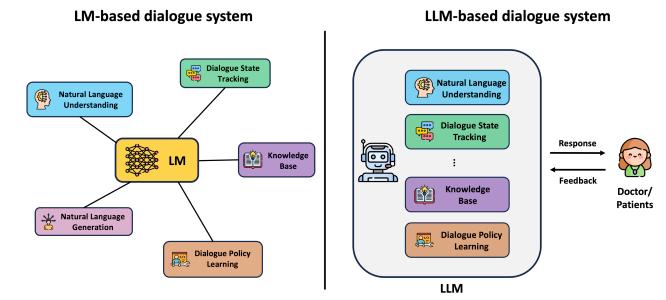


Fig. 4. The comparison between PLMs-based with LLMs-based dialogue system.

mentation of Healthcare Dialogue Systems can decrease the administrative workload of medical personnel and mitigate the negative consequences resulting from a shortage of physicians [95]. Apart from the QA component, dialogue systems are generally classified into two categories: task-oriented and open-domain dialogue systems [96]. Task-oriented dialogue systems are designed to address specific issues for Healthcare, such as hospital guides or medication consultations. In contrast, open-domain dialogue systems prioritize conversing with patients without any specific tasks. These systems are usually used as chatbots to provide emotional support, or mental health-related applications [97], [98]. For example, the study of [99] shows that patients who participated in a telehealth project had lower scores for depression, anxiety, and stress, and experienced 38% fewer hospital admissions. However, this project adds to the workload of physicians who are already occupied with face-to-face medical practice. In addition to their existing responsibilities, they are required to provide remote telemedicine consultations, further increasing their workload. To maintain good results without overburdening physicians, automated dialogue systems are a promising technology for Healthcare.

In the early stages, the study of [100] proposed an ontology-based dialogue system that supports electronic referrals for breast cancer. This system can handle the informative responses of users based on the medical domain ontology. Another study KR-DS [101] is an end-to-end knowledge-routed relational dialogue system that seamlessly incorporates a rich medical knowledge graph into topic transitions in dialogue management. KR-DS includes a novel Knowledge-routed Deep Q-network (KR-DQN) to manage topic transitions, which integrates a relational refinement branch for encoding relations among different symptoms and symptom-disease pairs and a knowledge-routed graph branch for topic decision-making. In general, PLMs-based dialogue systems often comprise multiple sub-modules, like Nature Language Understanding, Dialogue Management, Nature Language Understanding, or Knowledge Introduction modules [96]. Each individual sub-module within the overall system has the potential to become a bottleneck, thereby restricting the system's practical applications.

In the case of LLM-based dialogue systems, the original pipeline system can be transformed into an end-to-end system leveraging the capabilities of a powerful LLM [29], as shown

in Figure 4. By utilizing an LLM, the remaining task involves aligning the system with human preferences and fine-tuning it for specific fields, without the need for many extra sub-modules, and achieving some advanced abilities that PLMs can hardly do. For example, a new approach [102] was proposed to detect depression, which involves an interpretable and interactive system based on LLMs. The proposed system not only provides a diagnosis, but also offers diagnostic evidence that is grounded in established diagnostic criteria. Additionally, users can engage in natural language dialogue with the system, which allows for a more personalized understanding of their mental state based on their social media content. Chatdoctor [103] is a specialized language model designed to overcome the limitations observed in the medical knowledge of prevalent LLMs like ChatGPT, by providing enhanced accuracy in medical advice. Chatdoctor adapted and refined LLaMA [104] using a large Healthcare dialogues dataset and incorporating a self-directed information retrieval mechanism. This allows Chatdoctor to utilize real-time information from online sources to engage in conversations with patients. More LLMs for Healthcare can be seen in Section III-B.

F. Generation of Medical Reports from Images

Medical reports are of significant clinical value to radiologists and specialists, but the process of writing them can be tedious and time-consuming for experienced radiologists, and error-prone for inexperienced ones. Therefore, the automatic generation of medical reports has emerged as a promising research direction in the field of Healthcare combined with AI. This capability can assist radiologists in clinical decision-making and reduce the burden of report writing by automatically drafting reports that describe both abnormalities and relevant normal findings, while also taking into account the patient's history. Additionally, related models are expected to assist clinicians by pairing text reports with interactive visualizations, such as highlighting the region described by each phrase.

In an early stage, the study [105] proposed a data-driven neural network that combines a convolutional neural network with an LSTM to predict medical tags and generate a single sentence report, by employing a co-attention mechanism over visual and textual features. However, a single-sentence report is limited to real medical scenes. To generate multi-sentence reports, the study [106] proposed a multi-level recurrent generation model consisting of a topic-level LSTM and a word-level LSTM, and they also fused multiple image modalities by focusing on the front and later views.

Most recently proposed models for automated report generation rely on multimodal technology implemented by LLMs, which can support more advanced applications. For example, VisualGPT [107] utilizes linguistic knowledge from large language models and adapts it to new domains of image captioning in an efficient manner, even with small amounts of multimodal data. To balance the visual input and prior linguistic knowledge, VisualGPT employs a novel self-resurrecting encoder-decoder attention mechanism that enables the used PLM to quickly adapt to a small amount of in-domain image-text data. ChatCAD [108] introduced LLMs

into medical-image Computer Aided Diagnosis (CAD) networks. Their proposed framework leverages the capabilities of LLMs to enhance the output of multiple CAD networks, including diagnosis networks, lesion segmentation networks, and report generation networks, by summarizing and reorganizing information presented in natural language text format. Their results show that ChatCAD achieved significant improvements under various measures compared with the other two report-generation methods (R2GenCMN [109] and CvT2DistilGPT2 [110]). ChatCAD+ [111] is a multimodal system that addresses the writing style mismatch between radiologists and LLMs. The system is designed to be universal and reliable, capable of handling medical images from diverse domains and providing trustworthy medical advice by leveraging up-to-date information from reputable medical websites. ChatCAD+ also incorporates a template retrieval system that enhances report generation performance by utilizing exemplar reports, resulting in greater consistency with the expertise of human professionals. It should be noted that ChatCAD and ChatCAD+ are both integrated systems that utilize existing LLMs, rather than being LLMs themselves.

G. Summary

Based on the information provided, we can deduce that currently, LLMs perform on par with SOTA PLMs. For simpler fundamental tasks, the distinct advantages of LLMs are less apparent. However, as the complexity of advanced tasks increases—particularly those involving complex data conditions and requiring advanced semantic understanding and comprehensive generative capabilities—LLMs begin to demonstrate their strengths.

Besides, LLMs play an integral role in specific sub-fields of Healthcare with enough further training. One notable example is the application of LLMs in advancing oncology research, where they contribute to scientific advancements and improve research efficiency. The studies [112]–[114] have emerged as the predominant learning paradigm in histopathology image analysis, offering valuable support for various tumor diagnosis tasks, including tumor detection, sub-typing, staging, and grading. It is worth mentioning that these applications place significant emphasis on the multimodal capability of LLMs, as Healthcare data inherently consists of text, images, and time series data. By leveraging the strengths of LLMs, researchers, and Healthcare professionals can harness the power of multiple modalities to improve diagnostic accuracy and patient care.

Apart from the aforementioned achievements, there are also several challenges that need to be addressed. One of the primary hurdles is the complexity of medical decision-making, which demands consideration of a patient's multifaceted information spanning medical, psychological, and social factors. Although AI excels in data analysis, it significantly lacks the ability to understand complex human emotions and cultural backgrounds. This limitation becomes particularly apparent in scenarios requiring emotional and psychological support, such as long-term cancer treatments, where the empathetic care provided by doctors and nurses is irreplaceable by AI due to its inability to empathize and resonate emotionally.

TABLE I

SUMMARIZATION OF TRAINING DATA AND EVALUATION TASKS FOR EXISTING PLMs FOR HEALTHCARE. THE DIFFERENT TRAINING METHODS ARE DELINEATED WITH A SOLID LINE AND THE TRAINING DATA ARE FURTHER DELINEATED WITH A DASHED LINE.

Model Name	Base	Para. (B)	Training Data	Eval task	Date	Link
BEHRT [115]	Transformer	-	CPRD, HES	Disease Prediction	04/2020	Github
BioMegatron [116]	Megatron	1.2	PubMed	biomedical NER, RE, QA	10/2020	Github
PubMedBERT [117]	BERT	0.11	PubMed	BLURB	01/2021	Huggingface
Bio-ELECTRA-small [118]	ELECTRA	0.03	PubMed	Biomedical NER	03/2020	-
BioELECTRA [119]	ELECTRA	0.03	PubMed, PMC	BLURB, BLUE	06/2021	Github
AraBERT [120]	BERT	0.11	Arabic Wikipedia, OSIAN	Arabic SA, NER, QA	03/2021	Github
FS-/RAD-/GER-BERT [121]	BERT	0.11	Unstructured radiology reports	Chest Radiograph Reports Classification	07/2020	Github
VP [11]	BART	0.14	PubMed	Biomedical NER	03/2023	Github
BioBART [122]	BART	0.14	PubMed	Biomedical EL, NER, QA, Dialogue, Summarization	04/2022	Github
BioLinkBERT [123]	BERT	0.34	PubMed	BLURB, USMLE	03/2022	Github
ELECTRAMed [124]	ELECTRA	0.11	PubMed	Biomedical NER, RE, and QA	04/2021	Github
KeBioLM [125]	PubMedBERT	0.11	PubMed	BLURB	04/2021	Github
BioFLAIR [126]	BERT	0.34	PubMed	Bio NER	08/2019	Github
ouBioBERT [127]	BERT	0.11	PubMed, Wikipedia	BLUE	02/2021	Github
SCIFIVE [128]	T5	0.77	PubMed, PMC	Biomedical NER, RE, NIL, QA	05/2021	Github
BioBERT [78]	BERT	0.11	PubMed, PMC	Biomedical NER, RE, QA	05/2019	Github
BioALBERT-ner [129]	ALBERT	0.18	PubMed, PMC	Biomedical NER	09/2020	Github
GreenCovidSQuADBERT [130]	BERT	0.34	PubMed, PMC, CORD19	NER, QA	04/2020	Github
Bio-LM [131]	RoBERTa	0.34	PubMed, PMC, MIMIC-III	18 Biomedical NLP Tasks	11/2020	Github
BioALBERT [132]	ALBERT	0.03	PubMed, PMC, MIMIC-III	6 BioNLP Tasks	04/2022	Github
BlueBERT [133]	BERT	0.34	PubMed, MIMIC-III	BLUE	06/2019	Github
ClinicalBERT [134]	BERT	0.11	MIMIC-III	Hospital Readmission Prediction	11/2020	Github
Clinical XLNet [135]	XLNet	0.11	MIMIC-III	PMV, Mortality	11/2020	Github
MIMIC-BERT [136]	BERT	0.34	MIMIC-III	Biomedical NER	08/2019	-
UmlsBERT [137]	BERT	0.11	MIMIC-III	MedNLI, i2b2 2006, 2010, 2012, 2014	06/2021	Github
CharacterBERT [136]	BERT	0.11	MIMIC-III, OpenWebText, PMC	Medical NER, NLI, RE, SS	10/2020	Github
Clinical KB-ALBERT [137]	ALBERT	0.03	MIMIC-III, UMLS	MedNLI, i2b2 2010, 2012	12/2020	Github
MedGPT [136]	GPT-2	1.5	MIMIC-III, private EHRs	Disorder Prediction	07/2021	-
KAD [138]	BERT	-	MIMIC-CXR	PadChest, ChestXRay14, CheXpert and ChestX-Det10	03/2023	Github
Japanese-BERT [139]	BERT	10.11	Japanese EHR	Symptoms Classification	07/2020	Github
MC-BERT [140]	BERT	0.11	Chinese EHR	Chinese Biomedical Evaluation benchmark	08/2020	Github
BERT-EHR [141]	BERT	-	General EHR	Myocardial Infarction, Breast Cancer, Liver Cirrhosis	03/2021	Github
Med-BERT [142]	BERT	0.11	General EHR	Disease prediction	05/2021	Github
SAPBERT [143]	BERT	0.11	UMLS	MEL	10/2022	Github
CODER [144]	mBERT	0.34	UMLS	MCSM, Medical RE	02/2022	Github
AlphaBERT [145]	BERT	0.11	Discharge diagnoses	Extractive Summarization Task	04/2020	Github
BioMed-RoBERTa [146]	RoBERTa	0.11	BIOMED	CHEMPROT, RCT	05/2020	Github
RadBERT [147]	BERT	-	Radiology Report Corpus	Report Coding, Summarization	05/2020	-
BioBERTpt [148]	BERT	0.11	Private clinical notes, WMT16	SemClinBr	11/2020	Github
RoBERTa-MIMIC [149]	RoBERTa	0.11	i2b2 2010, 2012, n2c2 2018	i2b2 2010, 2012, N2C2 2018	12/2020	Github
CHMBERT [150]	BERT	0.11	Medical text data	Disease Prediction	01/2021	-
Galén [151]	RoBERTa	0.11	Private clinical cases	CodiEsp-D, CodiEsp-P, Cantemist-Coding tasks	05/2021	Github
Spanish-BERT [152]	BERT	-	Spanish data	Spanish Clinical Case Corpus	04/2020	-
French-BERT [153]	BERT	0.11	French clinical documents	DEFT challenge	06/2020	-
ABioNER [154]	BERT	0.11	Arabic scientific literature	Arabic NER	03/2021	-
SINA-BERT [155]	BERT	0.11	Online Persian source	Persian QA, SA	04/2021	-
CT-BERT [156]	BERT	0.11	Tweet	COVID-19 Text Classification	05/2020	Github
MentalBERT [98]	BERT	0.11	Reddit	Depression Stress, Suicide Detection	10/2021	huggingface

* PMV means prolonged mechanical ventilation prediction. NER means Named Entity Recognition, NLI means Natural Language Inference, RE means Relation Extraction, SS means Sentence Similarity. MCSM means medical conceptual similarity measure [157]. MEL means medical entity linking. EL means Entity Linking. For clarity, we only list parts of representative evaluation tasks. For the column of Para. (B), only the largest size is listed.

Moreover, ethical and privacy concerns escalate as AI applications deepen in healthcare. Questions about how patient data is handled, safeguarding privacy, and securing information are paramount. Additionally, determining liability in cases of diagnostic errors requires clear legal and ethical guidelines. Another issue is the uneven global distribution of technology, which creates a "digital divide" where developing countries and low-income regions might not benefit from AI advancements, potentially exacerbating health inequalities. More related discussion can be seen in Section VI.

Finally, AI struggles with diseases that have unclear causes or complex pathological mechanisms. The effectiveness of AI models largely depends on existing medical knowledge, and their capability remains limited in areas that are not yet fully understood. These challenges underscore the necessity for a collaborative effort among healthcare, technology, legal, and ethical experts worldwide to ensure that the advancement of technology benefits all, respecting and protecting individual rights.

III. FROM PLMs TO LLMs FOR HEALTHCARE

Apart from the increasing model sizes, two significant developments from PLMs to LLMs are the transition from Discriminative AI to Generative AI and from model-centered to data-centered approaches.

During the PLMs period, published PLMs were primarily evaluated on Natural Language Understanding (NLU) tasks, such as mentioned NER, RE, and TC. These studies are grouped as discriminative AI, which concentrates on classification or regression tasks instead of generation tasks. In contrast, generative AI generates new content, often requiring the model to understand existing data (e.g., textual instructions) before generating new content. The evaluation tasks of generative AI are usually QA and conversation tasks.

The second perspective is the change from model-centered to data-centered. Before the rise of LLMs, previous research focused on improving neural architecture to enhance the encoding abilities of proposed models. As neural models became increasingly larger, the over-parameterization strategy [158]

demonstrated promising abilities in learning potential patterns reserved in annotated datasets. Under such conditions, high-quality data played a more significant role in further enhancing various Healthcare applications [159], [160], namely, the transition from model-centered to data-centered direction. On the other hand, recent related developments present a multimodal trend, providing significant support to the data of EHRs, medical images, and medical sequence signals. Based on powerful LLMs, more existing and promising research and applications for Healthcare can be explored. Addressing the challenge of systematically collecting matched multimodal data holds significant importance. For such reason, we list detailed data usages and access links of each LLM in section III-B.

In the following sections, we first briefly introduce the focus of previous PLM studies. Then more details about existing LLMs in the Healthcare field are provided. Table I - IV summarize related PLMs and LLMs. Among these four Tables, Table II are organized in chronological order, which aims to show a development road map for all PLMs and LLMs. Table I and Table IV are grouped by employed training method, aiming to compare and discuss different LMs and LLMs.

A. PLMs for Healthcare

While our survey primarily concentrates on LLMs for Healthcare, it is important to acknowledge that previous studies on PLMs have played a foundational role in the development of LLMs. In this section, we sum up the key research focus at a high level for PLMs, namely 1) enhancing neural architectures, and 2) utilizing more efficient pre-training tasks. These two points will be compared with the distinct study focus of LLMs in section III-B, to further support the transition from discriminative AI to generative AI and from model-centered to data-centered.

For Healthcare PLMs, as observed in Tables I, a majority of the models utilize the discriminative approach, predominantly built upon the BERT architecture. The rationale behind this architectural choice is evident: many typical Healthcare applications are classification tasks. These tasks range from NER in the biomedical domain to more specific challenges such as disease prediction and relation extraction. In addition, the methodology of fine-tuning (FT) stands out as the prevalent training methodology. This trend suggests a broader implication: while general pretrained models offer a foundational grasp of language, they require refinement through domain-specific data to excel in the applications of Healthcare. The choice of training datasets provides further support to the models' intent of achieving a holistic understanding of the medical domain.

Unlike recent LLMs, LLMs have the advantage of eliminating the need for FT and can directly infer at various downstream tasks. Moreover, the core research focus does not primarily revolve around improving neural architectures and developing more efficient pre-training tasks.

B. LLMs for Healthcare

With the surge in general LLM research [29], [30], there has also been a notable development of LLMs specifically tailored

for the Healthcare field. In contrast to the emphasis on neural architecture designs [161], [162], pretraining tasks [163], and training strategies [164], [165] in previous PLMs research, the studies on LLMs for Healthcare greater emphasis on the collection of diverse, precise, and professional Healthcare data, and also data security and privacy protection.

In the following sections, we present an overview and analysis of the published LLMs designed for Healthcare. For the sake of convenience, we have compiled the pertinent information in Table II and Table IV. We categorize 36 current LLMs based on their training methods, data used, and distinct features, and offer detailed comparisons among them. Table V presents a summary of the performance for the three most popular datasets used to evaluate Healthcare LLMs, aimed at enabling more straightforward comparisons.

1) Group by Training Methods, Data and Evaluate Tasks: First, the studies [167], [169], [170] concentrate on directly assessing general LLMs instead of engaging in additional training using healthcare data. This approach enables these models to be compared among themselves, as opposed to comparisons with models that have been fine-tuned using different datasets. Codex-Med [167] focused on evaluating Codex [192] and InstructGPT [59], for their proficiency in handling real-world medical questions using datasets like USMLE [193], MedMCQA [87], and PubMedQA [88]. The performance of these models was tested under various prompting scenarios including CoT, ICL, and retrieval augmentation. The Codex-Med findings revealed that Codex (code-davinci-002) 5-shot with CoT achieved 60.2%, 62.7%, and 78.2% accuracy respectively on these datasets, compared to SOTA results of 50.32%, 52.93%, and 78.20% after fine-tuning. Furthermore, InstructGPT's accuracy improved by 0.7%, 2.2%, and 3.5% on these datasets using designed CoT prompts (Table III). The error analysis indicated that the majority of errors in CoT were due to reasoning mistakes (86%) and lack of knowledge (74%), with misunderstanding of questions or context at 50%.

Similarly, GPT-4-Med [169] evaluate GPT-4 on Self-Assessment and Sample Exam of the USMLE tests, achieving an average score of 86.65% and 86.7%. This is compared to the scores of 53.61% and 58.78% obtained by GPT-3.5. DeID-GPT [170] developed a novel de-identification framework called DeID-GPT, which utilizes GPT-4 to automatically identify and remove identifying information. This study is among the first to utilize ChatGPT and GPT-4 for medical text data processing and de-identification, providing insights for further research and solution development on the use of LLMs such as ChatGPT/GPT-4 in Healthcare.

Second, for other LLMs, only GatorTron [166] and GatorTronGPT [176] are two LLMs which training from scratch. In the healthcare sector, the strategy of training LLMs from scratch is not common. The main reason is that healthcare data typically involves higher costs and is subject to strict privacy restrictions. Acquiring and properly anonymizing medical data for training involves navigating complex legal and ethical issues, which can be exceedingly expensive. Additionally, due to the specialized nature of medical data and the high demands for accuracy, training a model from scratch requires substantial computational resources and expert

TABLE II
BRIEF SUMMARIZATION OF EXISTING LLMs FOR HEALTHCARE. SORTED IN CHRONOLOGICAL ORDER OF PUBLICATION.

Model Name	Base	Para. (B)	Features	Date	Link
GatorTron [166]	Transformer	0.345, 3.9, 8.9	Training from scratch	06/2022	Github
Codex-Med [167]	GPT-3.5	175	CoT, Zero-shot	07/2022	Github
Galactica [168]	Transformer	1.3, 6.4, 30, 120	Reasoning, Multidisciplinary	11/2022	Org
Med-PaLM [86]	Flan-PaLM/PaLM	540	CoT, Self-consistency	12/2022	-
GPT-4-Med [169]	GPT-4	-	No specialized prompt crafting	03/2023	-
DeID-GPT [170]	GPT-4	-	De-identifying	03/2023	Github
ChatDoctor [103]	LLaMA	7	Retrieve online, External knowledge	03/2023	Github
DoctorGLM [171]	ChatGLM	6	Extra prompt designer	04/2023	Github
MedAlpaca [172]	LLaMA	7, 13	Adapt to Medicine	04/2023	Github
BenTsao [23]	LLaMA	7	Knowledge graph	04/2023	Github
PMC-LLaMA [173]	LLaMA	7	Adapt to Medicine	04/2023	Github
Visual Med-Alpaca [174]	LLaMA	7	Multimodal generative model, Self-Instruct	04/2023	Github
BianQue [175]	ChatGLM	6	Chain of Questioning	04/2023	Github
Med-PaLM 2 [4]	PaLM 2	340	Ensemble refinement, CoT, Self-consistency	05/2023	-
GatorTronGPT [176]	GPT-3	5, 20	Training from scratch for medicine	05/2023	Github
LLM-CXR [177]	Dolly	3	Multimodal, Chest X-rays	05/2023	Github
HuatuogPT [22]	Bloomz	7	Reinforced learning from AI feedback	05/2023	Github
ClinicalGPT [178]	BLOOM	7	Multi-round dialogue consultations	06/2023	-
MedAGI [21]	MiniGPT-4	-	Multimodal	06/2023	Github
LLaVA-Med [20]	LLaVA	13	Multimodal, Self-instruct, Curriculum learning	06/2023	Github
OphGLM [24]	ChatGLM	6	Multimodal, Ophthalmology LLM	06/2023	Github
SoulChat [25]	ChatGLM	6	Mental Healthcare	06/2023	Github
Med-Flamingo [19]	Flamingo	80	Multimodal, Few-Shot generative medical VQA	07/2023	Github
Zhongjing [179]	Ziya-LLaMA	13	Continuous pre-training, Multi-turn Chinese medical dialogue	08/2023	Github
MedChatZH [180]	Baichuan	7	Traditional Chinese Medicine, Bilingual	09/2023	Github
JMLR [181]	LLaMA	7, 13	RAG, LLM-Rank loss	02/2024	Github
BioMistral [182]	Mistral	7	Multilingual, Model merging emphasis	02/2024	Github
BiMediX [183]	Mixtral	47	English and Arabic language	02/2024	Github
OncoGPT [184]	LLaMA	7	For oncology, Real-world doctor-patient oncology dialogue	02/2024	Github
Polaris [185]	Multi-agent LLM	-	A primary agent and several specialized support agents	03/2024	-
HealAI [186]	Med-PaLM	540	RAG, Note-Writing Style, Interactive Editing	03/2024	-
Apollo [187]	Qwen	0.5, 1.8, 2, 6, 7	Multilingual, Lightweight, Proxy tuning	03/2024	Github
Medical mT5 [188]	mT5	0.7, 3	Multilingual	04/2024	Github
Qilin-Med [189]	Baichuan	7	Domain-specific continued pre-training, RAG	04/2024	-
Me LLaMA [190]	LLaMA	13, 70	Catastrophic Forgetting	04/2024	Github
EpiSemoGPT [191]	Mistral	7	Predicting epileptogenic zones	05/2024	-

TABLE III
DESIGNED COT PROMPTS FOR HEALTHCARE QA.

-
- #1 – Let's think step by step
 - #2 – Let's think step by step like a medical expert
 - #3 – Let's use step-by-step inductive reasoning
 - #4 – Let's differentiate using step-by-step reasoning like a medical expert
 - #5 – Let's derive the differential diagnosis
-

supervision. And this strategy usually need extremely large healthcare-related plain text. For example, GatorTron [166] utilizes over 90 billion tokens, including 82 billion words of de-identified clinical text to explore benefits for systems handling unstructured EHRs. The model architecture ranges from a base model with 24 transformer blocks to a large model with 8.9 billion parameters, paralleling BioMegatron [116]. GatorTronGPT [176] use a GPT-3 architecture and available in versions with 5 or 20 billion parameters, was trained from scratch using a vast corpus of 277 billion words, combining de-identified clinical text from UF Health dataset and 195 billion English words from the Pile dataset [194], [195]. Training these two LLMs are both extremely expensive.

When comes to performance, GatorTron showed it achieved F1 scores of 89.96% on i2b2 2010 [196], 80.91% on i2b2 2012 [197], and 90.00% on n2c2 2018 [198] for clinical concept extraction. Moreover, GatorTron-large registered a 96.27% F1 score on n2c2 2018 [198] for medical RE. In medical QA, performances were 74.08% and 97.19% on the emrQA Medication and emrQA Relation tasks [199]. Further,

the more powerful GatorTronGPT [176] was evaluated on biomedical RE and QA tasks, achieving F1-measure scores of 50%, 49.4%, and 41.9% on DDI [200], BC5CDR [201], and KD-DTI [202] datasets respectively, and accuracy scores of 77.6%, 45.1%, and 42.9% on PubMedQA [88], MedMCQA [87], and USMLE [193] datasets respectively.

Third, the prevalent method for adapting a general LLM to a Healthcare LLM involves the use of SFT. For such reason, 21 LLM studies in Table IV only use SFT to tuning their models. In addition, Galactica [168], Me LLaMA [190], MedChatZH [180], BioMistral [182], Visual Med-Alpaca [174], Apollo [187] employ two-step training process, name PT first and then STF. QA pairs and dialogues being the most commonly employed data types, as shown in Line 12 to 20 in Table IV. Besides, some multimodal data (Line 27 to 30) and structured Electronic Health Record (EHR) database (Line 31 to 32) are also commonly used by SFT.

Among the LLMs that employ SFT technology, Galactica [168] represents an early-stage study, which designed to handle the information overload in the scientific domain, including Healthcare. It was trained on 106 billion tokens sourced from high-quality materials to enhance the discovery of connections across various fields. This model operates on a Transformer architecture with specific features like GeLU Activation [203] and Learned Positional Embeddings [204], across different scales from 125M to 120B parameters. In Healthcare-related assessments, Galactica notably surpassed previous benchmarks with a 77.6% on PubMedQA [88] and

TABLE IV

SUMMARIZATION OF TRAINING DATA AND EVALUATION TASKS FOR EXISTING LLMs FOR HEALTHCARE. THE DIFFERENT TRAINING METHODS ARE DELINEATED WITH A SOLID LINE AND THE TRAINING DATA ARE FURTHER DELINEATED WITH A DASHED LINE. THE COLOR NAMES REPRESENT POPULAR EVALUATE DATASETS. MORE DETAIL PERFORMANCE COMPARISONS ARE SHOWN IN TABLE V.

Model Name	Method	Training Data	Evaluate datasets or tasks
Codex-Med [167]*	ICL	-	USMLE, MedMCQA, PubMedQA
GPT-4-Med [169]*	ICL	-	USMLE, MultiMedQA
DeID-GPT [170]*	ICL	-	I2b2/UTHealth de-identification task
GatorTron [166]	PT	Clinical notes	CNER, MRE, MQA
GatorTronGPT [176]	PT	Clinical and general text	PubMedQA, USMLE, MedMCQA, DDI, BC5CDR
Galactica [168]	PT+SFT	DNA, AA sequence	MedMCQA, PubMedQA, Medical Genetics
Me LLaMA [190]	PT+SFT	PubMed, MIMIC-III, MIMIC-IV, MIMIC-CXR	MIBE benchmark [190]
MedChatZH [180]	PT+SFT	Text Books, medical and general instructions	WebMedQA
BioMistral [182]	PT+SFT	PubMed central data	MMLU, USMLE, MedMCQA, PubMedQA
Visual Med-Alpaca [174]	PT+SFT	Medical QA	-
Apollo [187]	PT+SFT	Books, clinical guidelines, encyclopedias.	XMedBench
MedAlpaca [172]	SFT	Medical QA and dialogues	USMLE, Medical Meadow
BenTsao [23]	SFT	Medical QA, Medical knowledge graph	Customed medical QA
BianQue [175]	SFT	Medical QA	-
Med-PaLM 2 [4]	SFT	Medical QA	MultiMedQA, Long-form QA
SoulChat [25]	SFT	Empathetic dialogue, Long text	-
ChatDoctor [103]	SFT	Patient-doctor dialogues	iCliniq
DoctorGLM [171]	SFT	Chinese medical dialogues	-
OncoGPT [184]	SFT	Oncology conversations	Oncology Question Answering
HuatuoGPT [22]	SFT	Conversation data and instruction	CmedQA, webmedQA, and Huatuo-26M
Med-PaLM [86]	SFT	Medical data	MultiMedQA, HealthSearchQA
PMC-LLaMA [173]	SFT	Biomedical academic papers	PubMedQA, MedMCQA, USMLE
HealAI [186]	SFT	Medical note data, instruction data	Medical Note Writing
BiMediX [183]	SFT	1.3 million English-Arabic dataset	An Arabic-English benchmark
Medical mT5 [188]	SFT	Multilingual medical corpus	Sequence Labelling, QA
EpiSemoGPT [191]	SFT	Related publications	Predicting epileptogenic zones
MedAGI [21]	SFT	Public medical datasets and images	SkinGPT-4, XrayChat, PathologyChat
Med-Flamingo [19]	SFT	Image-caption/tokens pairs	VQA-RAD, Path-VQA, Visual USMLE
LLaVA-Med [20]	SFT	Multimodal biomedical instruction	VQA-RAD, SLAKE, PathVQA
OphGLM [24]	SFT	Fundus image, knowledge graphs	Fundus diagnosis pipeline tasks [24]
LLM-CXR [177]	SFT	MIMIC-CXR	Report generation, VQA, CXR generation
JMLR [181]	SFT	MIMIC-IV dataset, medical textbooks, pubMed	USMLE, Amboss, MedMCQA, and MMLU-Medical
ClinicalGPT [178]	SFT+RLHF	Medical dialogues and QA, EHR	MedDialog, MEDQA-MCMLE, MD-EHR, cMedQA2
Polaris [185]	SFT+RLHF	Proprietary healthcare data	Healthcare conversational
Zhongjing [179]	PT+SFT+RLHF	Medical books, health records, clinical reports	CMtMedQA, Huatuo-26M
Qilin-Med [189]	PT+SFT+DPO	Medical QA, plain texts, knowledge graphs	CMExam, CEval, Huatuo-26M

* means the study focuses on evaluating the Healthcare LLM, rather than proposing a new LLM. PT means pre-training, ICL means In-context-learning (no parameters updated), SFT means supervised fine-tuning, RLHF means reinforcement learning from human feedback, and DPO means Direct Preference Optimization.

TABLE V

THE PERFORMANCE SUMMARIZATION FOR DIFFERENT HEALTHCARE LLMs ON THREE POPULAR DATASETS.

(%)	USMLE	MedMCQA	PubMedQA
FT BERT	44.62 [123]	43.03 [117]	72.20 [123]
Galactica	44.60	77.60	77.60
PMC-LLaMA	44.70	50.54	69.50
GatorTronGPT	42.90	45.10	77.60
DoctorGLM	67.60	-	-
MedAlpaca	60.20	-	-
Codex	60.20	62.70	78.20
Med-PaLM	67.60	57.60	79.00
Med-PaLM 2	86.50	72.30	81.80
GPT-4	86.70	73.66	80.40
Human	87.00	90.00	78.00

achieved 52.9% on MedMCQA dev [87].

BioMistral [182] is built upon the Mistral model and enhanced through additional pre-training on PubMed Central. BioMistral was evaluated across ten medical question-answering tasks, translated into seven languages, to assess its performance against both open-source and proprietary models. Notable achievements include an 86.5% accuracy on USMLE-style MedQA dataset questions, 72.3% on MedMCQA, and

75.0% on PubMedQA, showcasing its capability across varied medical specialties. The study also explored quantization and model merging techniques to optimize model efficiency and introduced the first large-scale multilingual evaluation of a medical LLM, highlighting its potential and robustness in diverse linguistic contexts.

JMLR introduces a method that enhances medical reasoning and question-answering by integrating the training of LLMs and information retrieval systems during the fine-tuning phase. This approach not only improves the model's ability to utilize medical knowledge effectively but also significantly cuts down on computational resources. JMLR achieves 72.8% accuracy on the MMLU-Medical dataset and 65.5% on the MedMCQA dataset, surpassing the Meditron-70B and Llama2-13B with RAG, which scored 68.9% and 54.9% respectively. For USMLE datasets, JMLR achieves 62.5% scores. Remarkably, JMLR required only 148 GPU hours for training, a substantial reduction compared to Meditron-70B's 42630 GPU hours.

MedAlpaca [172] addresses privacy concerns in healthcare by employing an open-source policy for on-site implementation. It utilizes the Medical Meadow collection for fine-tuning and employs LoRA [205] for task-specific weight updates and

8-bit technology for matrix multiplication and optimization, reducing memory requirements. In a zero-shot evaluation on USMLE Step 1, 2, and 3, MedAlpaca achieved accuracies of 47.3%, 47.7%, and 60.2% respectively. However, after applying LoRA and model quantization, accuracies dropped to 25.0%, 25.5%, and 25.5% for MedAlpaca-13b-LoRA, and further to 18.9%, 30.3%, and 28.9% for MedAlpaca-13b-LoRA-8bit, respectively.

Finally, The studies [178], [179], [185], [189] use multiple advanced training technologies. Among them, Zhongjing [179] is a groundbreaking Chinese medical LLM that integrates PT, SFT, and RLHF to enhance the handling of multi-turn medical dialogues, particularly in Chinese medicine. Developed on the LLaMA architecture, Zhongjing is trained using the CMtMedQA dataset, consisting of approximately 70,000 real doctor-patient dialogues across 14 medical departments. The model's effectiveness was evaluated using the CMtMedQA-test for multi-turn dialogues and the huatuo-26M for single-turn dialogues, focusing on three main dimensions—safety, professionalism, and fluency. Results show that Zhongjing excels in complex dialogue interactions, surpassing existing models like HuatuoGPT in these aspects by leveraging its diverse training approach.

Qilin-Med [189] proposed a Chinese medical LLM enhanced through a multi-stage training methodology, including domain-specific PT, SFT, DPO, and Retrieval Augmented Generation (RAG). Developed to address the limitations of over-reliance on SFT in medical LLMs, Qilin-Med utilizes a comprehensive dataset named ChiMed, containing diverse medical data tailored to each training stage. Performance evaluations show notable improvements: Qilin-Med achieved accuracies of 38.4% and 40.0% in the PT and SFT phases respectively on the CMExam test set, surpassing the baseline model Baichuan-7B by 7.5%. The integration of the RAG approach further enhanced its accuracy to 42.8% on CMExam. These advancements highlight Qilin-Med's capability in generating precise and contextually accurate responses, setting new benchmarks for medical LLMs, particularly in Chinese medical applications.

2) *Group by Features*: Further, we talk about LLMs from features of model sizes, language, and modality. For model size, it is a crucial measure to discuss, because it directly related to capabilities of model representation, generalisation, as well as computational resources and training time. We divide LLMs into three groups, extremely large ($>70B$), very large (13B-70B) and large (1B-12B). In our paper, there are 7/36 Healthcare LLMs are extremely large, 7/36 are very large, 19/36 are large.

Med-PaLM [86] and HealAI [186] are two the largest Healthcare LLM with 540B parameters. Med-PaLM [86], based PaLM [206], utilizes instruction prompt tuning for adapting LLMs to new domains with a few exemplars. This approach employs a shared soft prompt across multiple datasets, followed by a task-specific human-engineered prompt. The authors argue that existing medical question answering benchmarks [193] fail to provide a comprehensive analysis for clinical applications, leading to MultiMedQA benchmark. The study also introduced a 12-aspect framework

for human evaluation to assess the answers provided by Med-PaLM in various datasets. According to this framework, Med-PaLM and clinicians achieved a consensus of 92.6% and 92.9% respectively, highlighting the significance of rigorous evaluations and methodological advancements for developing reliable LLMs in clinical settings. Further, HealAI is based on Med-PaLM. However, there are no more details about its development.

Med-PaLM 2 [4] is the second large Healthcare LLM with 340B parameters, builds upon Google's Med-PaLM incorporating domain-specific medical Instruction Fine-Tuning. Despite its smaller size compared to the original PaLM's 540B parameters, Med-PaLM 2 outperforms its predecessor [4]. Med-PaLM 2 was evaluated across various datasets including USMLE [193], MedMCQA [87], PubMedQA [88], and MMLU clinical topics [89], achieving up to 86.5% accuracy on the USMLE dataset—a significant improvement over Med-PaLM's 67.2%. It also scored 72.3% and 75.0% on MedMCQA and PubMedQA, respectively. Long-form answers from Med-PaLM 2 are evaluated for various quality criteria and often preferred over those from physicians and the original Med-PaLM model. Med-PaLM 2 also introduces ensemble refinement in its prompting strategy, enhancing answer accuracy by generating multiple reasoning paths to refine the final response. Besides, Galactica and Me LLaMA [190] also have more than 100B parameters' models.

In the realm of language, English LLMs are predominantly mainstream. Following English, the second largest group of LLMs is designed for Chinese. BianQue [175], HuatuoGPT [22], BenTsao [23], SoulChat [25], DoctorGLM [171], MedChatZH [180], Zhongjing [179], and Qilin-Med [189] are Chinese LLMs.

DoctorGLM [171] is a pioneer Chinese LLM for Healthcare, focusing on cost-effective medical applications. DoctorGLM's training utilized the ChatDoctor [103] dataset, translating medical dialogues using the ChatGPT API. DoctorGLM reported a performance of 67.6% on the USMLE. Besides the above LLMs, there are also multilingual models, such as Apollo [187] and Medical mT5 [188].

Besides the above features, multimodal ability is another important development branch, as medical data inherently consists of diverse modalities such as patient medical records, radiographic images, and physiological signals. By integrating varied data types, multimodal models can enhance the understanding of complex medical conditions from multiple dimensions, enabling more accurate interpretations and diagnoses.

Visual Med-Alpaca [174] is a LLaMa-7B based open-source biomedical model that handles multimodal tasks by integrating medical “visual experts”. It was trained using a collaboratively curated instruction set from GPT-3.5-Turbo and human experts, incorporating visual modules and instruction-tuning for tasks like radiological image interpretation and complex clinical inquiries. The instruction set was developed through a multi-step process utilizing diverse medical datasets from BigBIO [207] and a self-instruct approach within the biomedical domain, culminating in 54,000 high-quality question-answer pairs after several rounds of human filtering and editing.

OphGLM [24] is a multimodal model tailored for oph-

thalmic applications, integrating visual capabilities alongside language processing. It was developed starting from fundus images, creating a pipeline for disease assessment, diagnosis, and lesion segmentation. Additionally, OphGLM constructed a novel dataset for ophthalmic multimodal instruction-following and dialogue fine-tuning using disease-related knowledge and real-world medical dialogues, enhancing its ability to process and respond to ophthalmic-specific commands.

C. Summary

In this section, we present an overview of existing PLMs and LLMs in the Healthcare domain, highlighting their respective research focuses. Furthermore, we provide a comprehensive analysis of the performance of these LLMs on benchmark datasets such as USMLE, MedMCQA, and PubMedQA. The summarized results of these evaluations can be found in Table V. The intention behind this analysis is to showcase the progress in Healthcare QA development and offer a clear comparison between different Healthcare-focused LLMs. In conclusion, two of the most robust LLMs identified in this analysis are Med-PaLM 2 and GPT-4. It is important to note that while GPT-4 is a general-purpose LLM, Med-PaLM 2 is specifically designed for Healthcare applications. Additionally, it is worth highlighting that the gap between LLM performance and human performance has significantly narrowed, indicating remarkable progress in the development of LLMs for Healthcare-related tasks.

As mentioned earlier, one notable difference between PLMs and LLMs is that PLMs are typically discriminative AI models, while LLMs are generative AI models. Although there are auto-regressive PLMs like GPT-1 and GPT-2 also evaluated with classification tasks, auto-encoder PLMs have been more prominent during the PLMs period. As for LLMs, with their powerful capabilities, they have successfully unified various Healthcare tasks as QA or dialogue tasks in a generative way.

From a technological perspective, most PLM studies focus on improving neural architectures and designing more efficient pre-training tasks. On the other hand, LLM studies primarily emphasize data collection, recognizing the importance of data quality and diversity due to the over-parameterization strategy employed in LLM development. This aspect becomes even more crucial when LLMs undergo SFT to align with human desires. A study [4] reveals that the selection of mixed ratios of different training data significantly impacts the performance of LLMs. However, these mixed ratios of PT and SFT, often referred to as a “special recipe” from different strong LLM developers, are rarely publicized. Therefore, apart from SFT, we anticipate the emergence of more exciting and innovative methods for training LLMs, particularly those designed to handle unique features of Healthcare data.

In terms of the investigated Healthcare LLMs mentioned above, most of them are derived from general LLMs, except for GatorTron, Galactica, and GatorTronGPT. For these LLMs, SFT approach is the most commonly utilized training technique. Compared to SFT, RLHF/RЛАIF is less commonly employed, with only MedAlpaca and HuatuoGPT utilizing this technology. The main reason for this limited application of

RLHF/RЛАIF is believed to be the lack of sufficient stability, as mentioned in the study [208]. From this part of the survey content, we have identified two emerging trends. Firstly, there is a growing exploration of multi-model approaches, including LLaVA-Med, MedAGI, OphGLM, Visual Med-Alpaca, and Med-Flamingo. Secondly, Chinese Healthcare LLMs are rapidly developing, with examples such as DoctorGLM, ClinicalGPT, SoulChat, BenTsao, BianQue, and HuatuoGPT.

Finally, it is worth noting that many Healthcare LLM papers provide details about the prompts they used. This observation demonstrates the prompt brittleness, as different prompts can have a significant impact on the model’s performance. Modifications in the prompt syntax, sometimes in ways that are not intuitive to humans, can lead to significant changes in the model’s output [209]. This instability is more matters for Healthcare than other general applications.

IV. TRAIN AND USE LLM FOR HEALTHCARE

In this section, we review the training and usage of LLM for Healthcare. First, we introduce the training methods for LLMs. Then, the usage of LLMs, including fine-tuning, in-context learning, CoT, and AI-agent. To achieve the promising usage of LLMs, an efficient training frame and data are necessary. Thus we also summarize the commonly used training data for Healthcare LLM and efficient training framework. The whole content structural arrangement is shown in Figure 6. The goal of this section is making healthcare researchers aware of how pre-training or fine-tuning affects different healthcare-related tasks, and how can we use Healthcare LLMs in a more effective way.

A. Training Methods

1) From predicting tokens to follow instructions – SFT: Through the pretraining process, we can obtain a strong but uncontrolled model, which can perform precise token predictions but is insufficient to follow the user’s instructions in a useful way. In healthcare applications, such as patient interaction, diagnostics, or treatment plan generation, the model must not only understand the medical context but also align its responses to comply with medical protocols and patient needs. For instance, if doctors require LLMs to list as many potential diseases as possible to assist in diagnosing rare conditions, the LLMs should not merely suggest one or two likely candidates.

To address the issue mentioned, SFT can be employed to enhance the responsiveness of LLMs to given instructions, ensuring they react in a more desired manner. The instructions used in fine-tuning consist of three key components: the instruction, the inputs, and the outputs. The inputs are optional and, similar to open-ended generation with ChatGPT, depend entirely on the instructions provided. When both inputs and outputs are included, they form an instance, and it is possible to have multiple instances of inputs and outputs for a given instruction.

Figure 5 shows examples of instruction demonstrations, illustrating how specific directives can lead to tailored inputs and outputs. In a healthcare setting, this could mean generating patient care reports, interpreting medical images, or providing

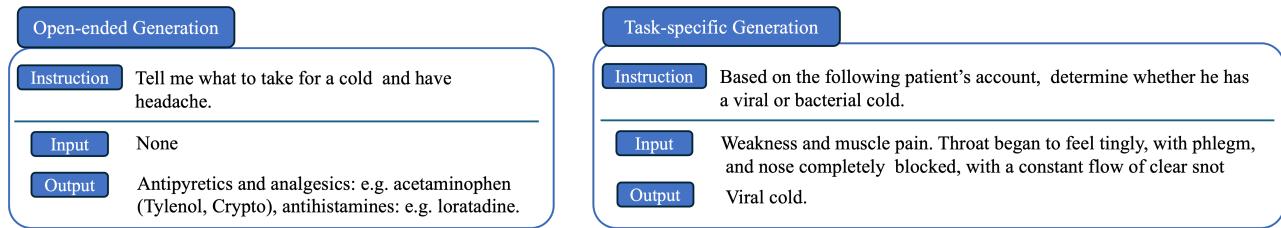


Fig. 5. The examples of instructions demonstrations. For open-ended generation task, there can just instructions without inputs. For task-specific instruction, a LLM needs respond to specific inputs.

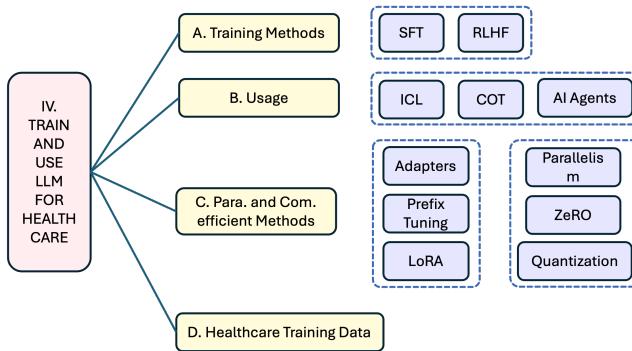


Fig. 6. The structural content arrangement for the section Train and Use LLM for Healthcare.

step-by-step guidance for medical procedures, all tailored to the specific needs and contexts outlined in the instructions. This fine-tuned capability of LLMs to follow detailed instructions can transform healthcare delivery by making it more precise, personalized, and efficient.

2) Reinforced Learning from Human Feedback (RLHF):

The goal of RLHF is to train AI systems to align with human goals, which remains the same as SFT. Actually, RLHF can be regarded as a cost-effective alternative to the SFT method with two differences: (1) SFT utilizes data from human responses for training, aiming to bring the model closer to human-like behavior without involving a direct comparison process. On the other hand, the RLHF process begins with training a reward model to rank, where different rewards (high or low) are assigned during the reinforcement learning stage (the rewards are scaled to have positive and negative values rather than both being positive). The introduction of a comparison process in RLHF helps guide the output of the model to align more closely with human behavior. (2) When considering the same amount of data, collecting data for SFT is generally more challenging compared to RLHF. Moreover, each piece of SFT data contains more information or training value than a piece of RLHF data in terms of ranking.

When RLHF is utilized in healthcare, it presents distinct advantages such as improved accuracy and reliability by learning from continuous feedback from medical professionals, and the ability to customize and personalize interactions based on specific clinical settings and patient needs. This enhances patient engagement by enabling more effective patient education and psychological support.

However, RLHF also faces challenges including potential

biases and errors in training data which can perpetuate inaccuracies or unfair medical advice, privacy and security concerns due to the handling of sensitive patient data, and the high costs and resource demands associated with deploying and maintaining RLHF systems. Additionally, while RLHF can enhance model performance on specific tasks, it may limit the model's generalizability across broader applications or unseen scenarios. Balancing these advantages and challenges is crucial in maximizing the positive impacts of RLHF while minimizing potential risks in healthcare applications.

3) *From Human Feedback to AI Feedback*: SFT and RLHF require substantial participation from human labor, which can be costly and unsustainable for continuous improvements to LLMs [210], specially for professional fields like Healthcare. Given these constraints, recent research has investigated the concept of self-instruction, where an LLM learns to instruct itself or is instructed by other LLMs, offering a potential solution to these challenges [160], [211]–[213].

Further, these methods developed as Reinforcement Learning with AI Feedback (RLAIF) to effectively leverage the strengths of both data types. For example, Baize [213] proposed a method called self-distillation with feedback (SDF) as an alternative to RLHF. They first utilized ChatGPT to automatically generate a high-quality multi-turn chat corpus for SFT. Following the SFT stage, Baize used itself to generate four responses, which were then utilized in the following self-distillation SDF process. Humpback [160] is another LLM study which employ RLAIF.

4) *Summary*: SFT, RLHF, and RLAIF offer tools to refine the precision and applicability of LLMs in medical contexts, a critical advancement given the complex ethical and operational demands of healthcare. SFT enhances LLMs' ability to follow medical protocols accurately, improving patient care by ensuring responses are clinically sound and contextually fitting. RLHF dynamically refines LLMs by integrating continual human feedback, adapting to intricate patient needs and medical developments, but must manage inherent biases and privacy concerns. RLAIF shifts LLM training towards sustainability by using AI-generated feedback to reduce costs and scale improvements, though this raises critical questions about output quality and reliability in healthcare contexts.

Overall, while these technologies promise significant enhancements to healthcare LLMs, they also necessitate a deeper reflection on their implementation. The integration of these advanced LLM training techniques must carefully consider not only the technological and practical impacts but also the broader ethical implications. Ensuring that these models serve

Demonstrations

Ex. 1 Male, 45 years old, complained of three weeks of persistent abdominal pain with intermittent fever and weight loss. Recent blood tests showed a high white blood cell count. What are the possible diseases?

1. Infectious diseases such as intestinal infections, peritonitis
2. Inflammatory bowel disease, such as Crohn's disease or ulcerative colitis
3. Tumours of the digestive system: e.g. colon cancer or other tumours of the gastrointestinal tract

Ex. 2 Female, 58 years old, complains of severe headaches, blurred vision, and a tingling sensation in her arms. Blood tests indicate elevated erythrocyte sedimentation rate. What are the possible diseases?

1. Temporal arteritis, which often presents with headache, visual disturbances, and elevated ESR.
2. Multiple sclerosis, which can cause neurological symptoms including tingling and blurred vision.
3. Brain tumors, which may manifest neurologic deficits such as blurred vision and tingling in limbs.

Test Instance

Question Male, 34 years old, reports persistent shortness of breath, chest pain, and occasional coughing. Recent chest X-ray revealed a small mass in the lung. What are the possible diseases?

Answer

1. Lung cancer, particularly if the mass is malignant.
2. Tuberculosis, which can cause persistent cough, chest pain, and localized masses.
3. Benign lung tumors, such as a hamartoma, which may present as a mass on imaging but with less severe symptoms.

Fig. 7. An In-context Learning example for Healthcare QA task.

the best interests of patients and align with medical ethics will be crucial as these technologies become more deeply integrated into healthcare systems. This balance between innovation and responsibility defines the path forward for LLMs in healthcare.

B. Usage

1) *From Fine-tuning to In-context Learning*: In-context learning (ICL) holds significant potential in healthcare by enabling LLMs to generate responses that closely align with demonstrated examples, such as predicting the three most likely diseases based on symptoms presented in input data as shown in Figure 7. This technique involves merging demonstration examples with test inputs, thereby enriching the model's ability to apply specific knowledge from the demonstrations, without necessitating updates to its parameters based on specific domain data. For LLMs tailored for healthcare, ICL can further refine these models to align more closely with the specific expectations and needs of healthcare professionals. Because sometimes the inputted instructions may not correctly reflect people's true intentions due to complex Healthcare terms, providing examples will be more directly and easier.

However, the effectiveness of ICL in healthcare relies on several nuanced factors including input distribution, label space, demonstration format, and input-label mapping. These factors determine how well the model's outputs match the requirements of medical diagnostics. For instance, ensuring that both the demonstration inputs and the actual application inputs come from similar medical contexts (input distribution) is crucial. Likewise, the labels used in training must semantically align with those in practical healthcare scenarios (label space). The structure of the demonstrations (demonstration format) also needs careful consideration to ensure that the model can accurately parse and learn from them.

Research such as the study cited in [214] investigates these aspects, revealing that the alignment of input distribution, label space, and demonstration format significantly influences

ICL's performance. While the precision of input-label mapping is less critical when label spaces are correctly aligned, inconsistencies in any of these areas can diminish the utility of ICL in real-world healthcare applications, as shown in Figure 8. Therefore, meticulous attention to these parameters is essential to harness the full potential of ICL in enhancing diagnostic accuracy and efficiency in healthcare settings. However, Healthcare professionals are often not aware of these issues related to computer expertise, resulting in LLMs not performing at their full potential.

2) *From System 1 Deep Learning To System 2 Deep Learning – Chain-of-Thought*: According to the report by Bengio et al. [215], two distinct categories of Deep Learning systems exist, namely System 1 and System 2. System 1 encompasses the current applications of deep learning, including image recognition, face recognition, machine translation, sentiment classification, speech recognition, and autonomous driving. On the other hand, System 2 represents the future potential of deep learning, involving tasks such as reasoning, planning, and other logic-based and reasoning-oriented activities.

System-1 tasks in the field of NLP have been largely resolved, demonstrating significant progress. However, progress in System-2 tasks has been limited until recently when the emergence of advanced LLMs triggered a significant shift. The study [16] proposed the CoT prompting, which found it can significantly improve the reasoning and planning performance of LLM by adding a series of intermediate steps. As shown in Figure 9, the example uses CoT to guide the model through a detailed reasoning process, from identifying symptoms to linking them with possible diseases and suggesting appropriate diagnostic tests. This method helps in structuring the model's output in a way that simulates clinical reasoning, making it easier for healthcare professionals to follow the thought process and potentially enhancing decision-making in clinical settings.

Furthermore, the study [216] found that by just adding a sentence "Let's think step by step", the reasoning ability of

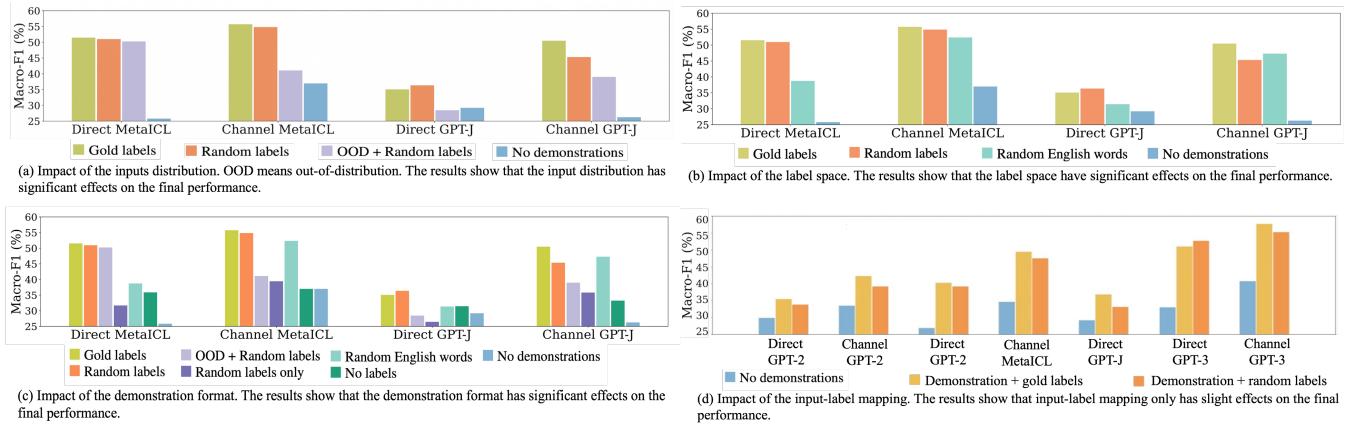


Fig. 8. What Makes In-Context Learning Work? ★ The data of figures comes from the study [214]. We perform the proper arrangement and layout for discussions ★. We only list the classification task (x-axis) here and sub-figure (d) shows parts of the original results for clarity.

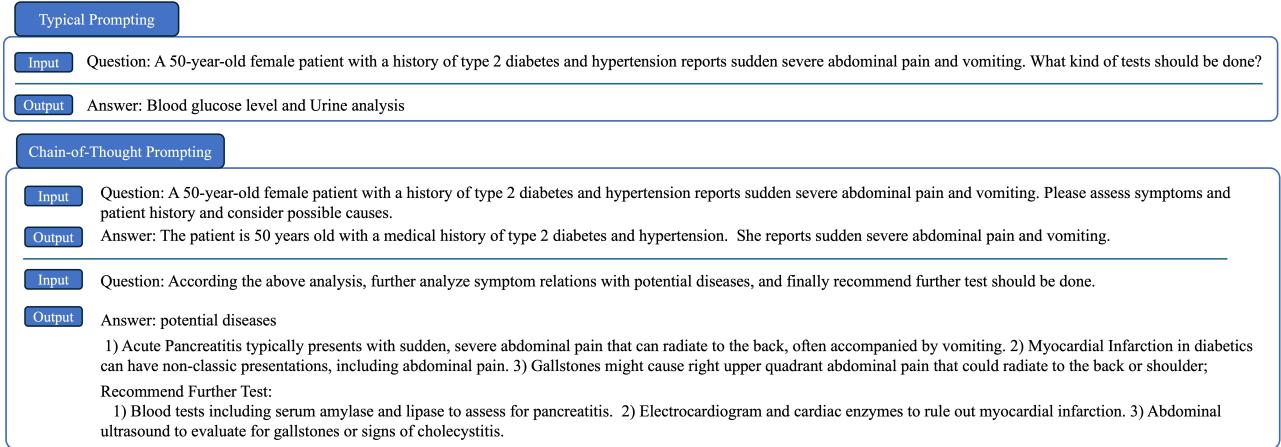


Fig. 9. An example of Chain-of-Thought (CoT). CoT is the sequential and logical prompts, which can help LLM split a complex problem into multiple simple steps.

LLMs can be significantly boosted. For example, adding this simple sentence can raise accuracy from 17.7% to 78.7% on MultiArith [217] dataset, and from 10.4% to 40.7% on GSM8K [218] dataset. Later, there are many CoT studies [22], [25], [175] aiming to enhance the logical reasoning ability of LLM in various Healthcare applications by exploring different prompting.

3) AI Agents: The core idea behind recent AI agents is to build autonomous agent systems that utilize LLMs as their central controllers. These systems consist of several components, including Planning, Memory, Tool Use, and Action, as described in the study [219]. The planning component plays a crucial role in breaking down complex tasks into smaller and manageable sub-goals. This enables the agent to handle large tasks more efficiently by tackling them step by step. The Memory component provides the agent with the ability to store and retrieve information over extended periods. It typically utilizes an external vector store and fast retrieval mechanisms, allowing the agent to retain relevant knowledge and recall it as needed. With the Planning and Memory components in place, AI agents can take actions and interact with external

tools. AutoGPT⁴ is an example of such an autonomous agent system. It leverages GPT-4 to autonomously develop and manage operations. When provided with a topic, AutoGPT can think independently and generate steps to implement the given topic, along with implementation details. This shows the agent's ability to plan, utilize its memory, and take appropriate actions to accomplish tasks autonomously.

As far as we know, AI agents have not been widely adopted in the Healthcare field. However, we anticipate the development of more capable AI agent systems in this domain. For instance, it is possible to train specialized models for different medical processes, such as hospital guidance, auxiliary diagnosis, drug recommendation, and prognostic follow-up. These relatively small models can be integrated into a comprehensive AI medical system, where an LLM serves as the central controller. Additionally, specialized disease systems can be established for each department within the Healthcare system. The LLM can play a crucial role in determining which specialized disease systems should be involved in a particular case, resulting in effectively allocating resources and

⁴<https://github.com/Significant-Gravitas/Auto-GPT>

providing specialized care. Overall, the vision is to leverage AI agents and LLMs to create comprehensive and specialized AI systems in Healthcare, covering various medical processes and enabling efficient decision-making and patient care.

C. Parameters-efficient and Compute-efficient Methods

1) *Parameters-efficient Methods*: as the model parameter size gets bigger and bigger, the cost of doing full fine-tuning on downstream task dataset is getting higher and higher. To alleviate this problem, a series of parameters-efficient tuning methods are proposed to help pretrained LLMs efficiently adapt to a variety of downstream tasks. These are very practical methods when adopting general LLMs to the Healthcare field.

In general, there are three main typical methods used in parameters-efficient optimizations: Adapters, Prefix Tuning, and LoRA. **Adapter** methods [220]–[222] involve inserting smaller neural network modules into the intermediate layers of PLMs or LLMs. During fine-tuning, only the parameters of the adapter modules are trained while keeping the rest of the model parameters fixed. **Prefix Tuning** [11], [223] is another approach where a trainable prefix is added to the input sequence or hidden layers. Prefix Tuning fixes the pre-training parameters of PLMs or LLMs, optimizes only the task-specific prefixes, and requires only one copy of a small number of prefixes for each task to be stored during deployment. **LoRA** [205] involves approximating the parameter update of a full-rank weight matrix with a low-rank matrix, thereby necessitating training only a small ascending-dimensions matrix and a small descending-dimensions matrix.

2) *Compute-efficient and Memory-efficient Methods*: Generally, when we train LLMs, the parameters of models, gradients, and optimized states take up the Video Random Access Memory (VRAM) of GPUs. When one single GPU cannot satisfy training requirements, **Data Parallelism (DP)**, **Model Parallelism (MP)**, and **Pipeline Parallelism (PP)** are three compute-efficient and memory-efficient strategies.

DP replicates model parameters across each device to efficiently manage computations by dividing a mini-batch evenly among all processes, where each performs forward and backward propagation on different data subsets. MP, suited for LLMs that exceed GPU VRAM capacity, distributes different layers across devices using operator-level parallelism, though not all operators can be split. MP is considered a vertical split of LLMs, while PP horizontally partitions the model across devices, using micro-batching to manage pipeline bubbles. Both MP and PP, while memory-efficient, require significant inter-device communication, making them less compute-efficient.

Based on the parallelism scenarios mentioned above, a series of **ZeRO**-related studies are introduced [224]–[226], presenting a set of memory optimization techniques. This series includes ZeRO, ZeRO-Offload, and ZeRO-Infinity, which aim to eliminate redundant parameters, utilize CPU and Random Access Memory (RAM), and introduce NVMe for improved performance. All the above functions are integrated into the library DeepSpeed in Huggingface⁵.

⁵https://huggingface.co/docs/transformers/main/main_classes/deepspeed

Quantization approximates the weights or activation values from high bit widths (Float32) to lower ones (INT16, INT8, INT4), effectively discretizing continuous values and requiring compatible hardware for acceleration. It reduces the size of LLMs (e.g., a reduction to a quarter size when using INT4) and enhances computational efficiency. This is particularly significant in deploying Healthcare LLMs and supporting diverse mobile devices with AI cores. For instance, a study [227] utilized 8-bit operations for matrix multiplication and optimization in specific layers, allowing models like OPT-175B/BLOOM to run on a single server with consumer GPUs.

D. Healthcare Training Data

As mentioned earlier, the transition from PLMs to LLMs brings a significant shift from a model-centered approach to a data-centered approach. Increasing the volume of pre-training data has become a key factor in enhancing the general capabilities of LLMs. In line with this, we have gathered and organized various datasets for training Healthcare LLMs, as presented in Table VI. Besides the medical training data, we also list three Github projects which integrate many general instruction and RLHF training data, including Awesome Instruction Datasets⁶, Awesome-text/visual-instruction-tuning-dataset⁷, and Awesome-instruction-tuning⁸. We aim to assist those interested in training or fine-tuning Healthcare LLMs in easily identifying the appropriate datasets.

In general, the most common sources of data for Healthcare LLMs include EHR, scientific literature, web data, and public knowledge bases. When considering the data structure, QA and dialogue data are the most frequently encountered. Additionally, apart from the conventional text data used in LLMs, it is crucial to acknowledge the significance of multimodal data. Given that the Healthcare domain inherently involves text, images, and time series data, multimodal LLMs offer a promising direction for further research. We anticipate that multimodal LLMs will receive expedited attention in future studies. Following, we briefly introduce some representative data sets to provide a general view.

EHR. The Medical Information Mart for Intensive Care III dataset (MIMIC III) is widely recognized as one of the most widely used EHR datasets. It encompasses a comprehensive collection of data from 58,976 unique hospital admissions involving 38,597 patients who were treated in the intensive care unit at the Beth Israel Deaconess Medical Center between 2001 and 2012. Furthermore, the dataset includes 2,083,180 de-identified notes that are associated with these admissions. MIMIC III provides valuable and extensive information for research and analysis in the field of Healthcare, which facilitates many PLMs and LLMs developments, such as MIMIC-BERT [136], GatorTron [166], and MedAGI [21].

Scientific Literature. PubMed is a freely accessible search engine that provides access to the MEDLINE database, which contains references and abstracts related to life sciences and biomedical topics. It serves as a comprehensive resource with

⁶<https://github.com/jianzhnie/awesome-instruction-datasets>

⁷<https://github.com/yaodongC/awesome-instruction-dataset>

⁸<https://github.com/zhilizju/Awesome-instruction-tuning>

TABLE VI
HEALTHCARE DATA CAN BE USED TO TRAIN LLMs.

Data	Type	size	Link
MIMIC-III	EHR	58,976 hospital admissions for 38,597 patients	Homepage
MIMIC-IV	EHR	covering a decade of admissions between 2008 and 2019	Homepage
CPRD [228]	EHR	over 2,000 primary care practices and include 60 million patients	Homepage
PubMed	Scientific Literature	35M citations and abstracts of biomedical literature	Data Link
PMC	Scientific Literature	8 million full-text article records	Data Link
RCT [229]	Scientific Literature	4,528 abstract	Data Link
MS'2 [230]	Scientific Literature	470,402 abstract	Data Link
CDSR [231]	Scientific Literature	7,805 abstract	Data Link
SumPubMed [232]	Scientific Literature	33,772 abstract	Data Link
The Pile	Scientific Literature	825 GB English text	Data Link
S2ORC [233]	Scientific Literature	63,709 abstract	Data Link
CORD-19 [234]	Scientific Literature	1M papers	Data Link
MeQSum [235]	Medical Question Summarization	1000 instances	Data Link
CHQ-Sum [236]	Medical Question Summarization	1507 instances	Data Link
UMLS	Knowledge Base	2M entities for 900K concepts	Homepage
COMETA [237]	Web Data (social media)	800K Reddit posts	Homepage
MedDialog [238]	Dialogue	3.66 million conversations	Homepage
CovidDialog [239]	Dialogue	603 consultations	Homepage
Medical Flashcards [172]	Dialogue	33955 instances	Data Link
Wikidoc [172]	Dialogue	67704 instances	Data Link
Wikidoc Patient Information [172]	Dialogue	5942 instances	Data Link
MEDIQA [240]	Dialogue	2208 instances	Data Link
CORD-19 [234]	Dialogue	1056660 instances	Data Link
MMMLU [234]	Dialogue	3787 instances	Data Link
Pubmed Causal [241]	Dialogue	2446 instances	Data Link
ChatDoctor [242]	Dialogue	215000 instances	Data Link
Alpaca-EN-AN [243]	English Instructions	52K instructions	Data Link
Alpaca-CH-AN [243]	Chinese Instructions	52K instructions	Data Link
ShareGPT	Conversations	61653 long conversations	Data Link
WebText	Web Data	40 GB of text	Data Link
OpenWebText	Web Data	38 GB of text	Data Link
Colossal Clean Crawled Corpus	Web Data	806 GB of text	Data Link
OpenI	EHR, multimodal	3.7 million images from about 1.2 million papers	Homepage
U-Xray [244]	multimodal	3,955 reports and 7,470 images	Homepage
ROCO [245]	multimodal	81,000 radiology images and corresponding captions	Homepage
MedICaT [246]	multimodal	17,000 images includes captions	Homepage
PMC-OA [247]	multimodal	1.6M image-caption pairs	Homepage
CheXpert [248]	multimodal	224,316 chest radiographs with associated reports	Homepage
PadChest [249]	multimodal	160,000 images with related text	Homepage
MIMIC-CXR	multimodal	227,835 imaging studies for 64,588 patients	Homepage
PMC-15M [250]	multimodal	15 million Figure-caption pairs	Homepage
OpenPath [251]	multimodal	208,414 pathology images related descriptions	Homepage

☆ Although there are datasets available for Instruction Fine-Tuning, such as MultiMedQA and the USMLE test, we have opted not to include them in this list. These datasets are typically employed for evaluation purposes rather than serving as primary resources for Instruction Fine-Tuning.

over 32 million citations for biomedical literature, including content from MEDLINE, life science journals, and online books. These citations may also include links to full-text content available on PubMed Central and publisher websites. The PubMed abstracts alone contain approximately 4.5 billion words, while the full-text articles available on PubMed Central (PMC) contribute around 13.5 billion words. These datasets consist of high-quality academic and professional text, making them particularly suitable for training Healthcare LLMs. Various PLM and LLM models, such as BioBERT [78], BioELECTRA [252], GatorTron [166], and MedAlpaca [172], have been trained using PubMed data. PubMed's vast collection of biomedical literature serves as a valuable foundation for advancing research and development in the Healthcare domain.

Web Data. Web data includes any text we can obtain from the Internet. Social media is one of the most commonly used data types. Reddit is a popular online platform that combines social news aggregation, content rating, and discussion features. Users can contribute various types of content, including links, text posts, images, and videos. The platform is organized into user-created boards called “communities” or “sub-reddits”, covering a broad range of topics. Popular

posts with more up-votes rise to the top of their respective sub-reddits and can even make it to the site's front page. The study [253] crawled health-themed forums on Reddit to form COMETA corpus as LLMs training data. Tweets are also usually employed to collect data, and COVID-twitter-BERT [156], Twitter BERT [254], and TwHIN-BERT [255] are trained with these data.

Public Knowledge Bases. There exist many Healthcare-related knowledge bases, such as UMLS [256], CMeKG [257], BioModels [258], and DrugBank [259]. Among them, UMLS is one of the most popular, which is a repository of biomedical vocabularies developed by the US National Library of Medicine. The UMLS has over 2 million names for 900,000 concepts from more than 60 families of biomedical vocabularies, as well as 12 million relations among these concepts. Based on this structured data, the US Medical Licensing Examination (USMLE) is organized and usually employed to test Healthcare LLMs. CMeKG [257] is a Chinese medical knowledge graph that has been constructed by referring to authoritative international medical standards and a wide range of sources, including clinical guidelines, industry standards, medical textbooks, and other medical texts. This knowledge

Instruction: In the following paragraph, several chemicals and diseases are mentioned. Your task is to identify the chemical-disease relations and present them in the format of (Subject, Object).

Input: To test the validity of hypothesis that hypomethylation of DNA plays an important role in the initiation of carcinogenic process, 5.azacytidine (5-AzC) (10 mg/kg), an inhibitor of DNA methylation, was given to rats during the phase of repair synthesis induced by the three carcinogens, benzo[a]pyrene (200 mg/kg), N-methyl-N-nitrosourea (60mg/kg) and 1,2-dimethylhydrazine (1,2-DMH) (100 mg/kg)."

Output: (benzo[a]pyrene, initiation of carcinogenic process), (5-AzC, initiation of carcinogenic process), (1,2-DMH, initiation of carcinogenic process), (N-methyl-N-nitrosourea, initiation of carcinogenic process)

Fig. 10. An example of instruction instance. The instance comes from the study [260].

TABLE VII
THE STATISTICS OF COMPUTATION COST FOR EXISTING HEALTHCARE LLM.

Model Name	Total data size	epoch	Batch size	GPU type	GPU number	GPU time
Visual Med-Alpaca	54k data points	3	128	A100-80G	4	2.51 hours
GatorTron	>90 billion words	10	-	A100	992	6 days
Galactica	-	-	-	A100-80G	128	-
ChatDoctor	100k conversations	3	192	A100	6	3 hours
DoctorGLM	3.5G	1	4	A100-80G	1	8 hours
PMC-LLaMA	75B tokens	5	128	A100	8	7 days
Visual Med-Alpaca	44.8MB* (without images)	-	128	A100-80G	4	2.51 hours
BianQue 1.0	9 million samples	1	-	RTX 4090	8	16 days
GatorTronGPT	277B tokens		1,120/560	A100-80G	560	26 days
HuatuoGPT	226,042 instances	3	128	A100	8	-
LLaVA-Med	15 million figure-caption pairs	-	-	A100	8	15 hours
Med-Flamingo	1.3M image-caption pairs	-	400	A100-80G	8	6.75 days

TABLE VIII
ESTIMATED FLOPS AND TRAINING TOKENS FOR DIFFERENT MODEL SIZES.

Parameters	FLOPs	FLOPs (in Gopher unit)	Tokens
400 Million	1.92e+19	1/29, 968	8.0 Billion
1 Billion	1.21e+20	1/4, 761	20.2 Billion
10 Billion	1.23e+22	1/46	205.1 Billion
67 Billion	5.76e+23	1	1.5 Trillion
175 Billion	3.85e+24	6.7	3.7 Trillion
280 Billion	9.90e+24	17.2	5.9 Trillion
520 Billion	3.43e+25	59.5	11.0 Trillion
1 Trillion	1.27e+26	221.3	21.2 Trillion
10 Trillion	1.30e+28	22515.9	216.2 Trillion

★This estimation comes from the study [261]★. Gopher is another LLM study [262] used to compare.

graph serves as a comprehensive resource for medical information. Building upon the CMeKG, HuaTuo [23] utilizes diverse instructional data for its instruction tuning process.

Data for Instruction Fine-Tuning. The aforementioned data typically consists of general text that is commonly used for pretraining PLMs or LLMs. However, when transitioning from PLMs to LLMs, instruction data becomes crucial to equip LLMs with the capability of following instructions effectively. Unlike PLMs, which primarily focus on next-word prediction, LLMs place greater emphasis on responding to specific instructions.

To illustrate, an instruction instance is presented in Figure 10. In this example, the LLM is tasked with identifying chemical-disease relations and understanding that its response should align with the given instruction, rather than predicting the next word. By leveraging a sufficient amount of instruction data for fine-tuning, an LLM can appropriately generate the desired output, as demonstrated in Figure 10. This emphasizes the importance of instruction-based training for LLMs to achieve accurate and contextually relevant responses.

E. Summary

In Section IV-C, we present a comprehensive overview of two fundamental resources crucial for LLMs – the training tools and data. Specifically, Section IV-C2 highlights compute-efficient and memory-efficient methods. These cutting-edge technologies hold significant value as they effectively lower the entry barrier for researchers and practitioners interested in exploring the realm of LLMs. When it comes to the data used for training LLMs, the volume often surpasses the capacity of human teams to manually perform quality checks. Consequently, data collection processes heavily rely on heuristic rules for selecting data sources and applying filters. In the context of LLM training, there are various data challenges to address, including the high cost of Healthcare data, near-duplicates, contamination in benchmark data, personally identifiable information, and the mixture of domains during pre-training and fine-tuning tasks.

Based on the above information, one of the primary concerns in developing an LLM – the computational cost, is involved. By considering the training framework, data requirements, and the size of the LLM itself, an estimation of the overall computational cost can be obtained. We have summarized the relevant computation costs from existing studies in Table VII. Table VIII comes from the study [261], which estimates the relation among the model size, the dataset size, and the training FLOPs when we need to train an LLM from scratch. These data can serve as a helpful reference for those seeking to estimate the expenses associated with LLM development.

V. EVALUATION METHOD

Presently, there is a wide range of LLMs available for general NLP tasks and Healthcare applications. Selecting appropriate evaluation methods for intelligent applications is

TABLE IX
THE HEALTHCARE EVALUATION OF LLMs.

Categories	Studies	Models	Scenarios	#Num	Conclusions
Medical Ex.	[263]	ChatGPT	Primary Care	674	Average performance of ChatGPT is below the mean passing mark in the last 2 years.
	[264]	ChatGPT	Medical licensure	220	ChatGPT performs at the level of a third-year medical student.
	[265]	ChatGPT	Medical licensure	376	ChatGPT performs at or near the passing threshold.
Medical Q&A.	[266]	ChatGPT	Physician queries	284	ChatGPT generates largely accurate information to diverse medical queries.
	[267]	ChatGPT, GPT-4, Bard, BLOOMZ	Radiation oncology	100	Each LLM generally outperforms the non-expert humans, while only GPT-4 outperforms the medical physicists.
	[90]	ChatGPT, Claude	Patient-specific EHR	–	Both models are able to provide accurate, relevant, and comprehensive answers.
	[268]	ChatGPT	Bariatric surgery	151	ChatGPT usually provides accurate and reproducible responses to common questions related to bariatric surgery.
	[269]	ChatGPT	Genetics questions	85	ChatGPT does not perform significantly differently than human respondents.
Medical Gen.	[270]	ChatGPT	Fertility counseling	17	ChatGPT could produce relevant, meaningful responses to fertility-related clinical queries.
	[271]	GPT-3.5, GPT-4	General surgery	280	GPT-3.5 and, in particular, GPT-4 exhibit a remarkable ability to understand complex surgical clinical information.
	[272]	GPT-3.5, GPT-4	Dementia diagnosis	981	GPT-3.5 and GPT-4 cannot outperform traditional AI tools in dementia diagnosis and prediction tasks.
Medical Ce.	[273]	ChatGPT	Gastroenterology	20	ChatGPT would generate relevant and clear research questions, but not original.
	[274]	ChatGPT, GPT-4	Radiology report	138	ChatGPT performs well and GPT-4 can significantly improve the quality.
Medical Ce.	[275]	ChatGPT	Benchmark tasks	34.4K	Zero-shot ChatGPT outperforms the state-of-the-art fine-tuned models in datasets that have smaller training sets.
	[276]	ChatGPT	Clinical and research	–	ChatGPT could potentially exhibit biases or be susceptible to misuse.

★ The Healthcare evaluation of LLMs includes Medical examination (Ex.), medical question answering (Q&A), medical generation (Gen.), and medical comprehensive evaluation (Ce.).

of utmost importance, especially in Healthcare field which involved Safety of people's lives and health. An effective evaluation not only ensures the accuracy and reliability of LLMs in processing healthcare data and generating diagnostics, but also enhances user trust in the technology through a systematic validation process. Additionally, the assessment methodology helps to ensure that Healthcare LLM is secure and compliant in its design and operation, which is especially critical for adhering to stringent healthcare industry standards and regulations.

In this section, we review studies focusing on Healthcare evaluation, discussing aspects such as robustness and bias. Finally, we will conclude by highlighting future directions for health evaluation and providing a summary.

A. Healthcare Evaluation

Different from general NLP tasks, the field of Healthcare is characterized by its high level of specialization. Evaluating LLMs in this domain necessitates assessing their capacity to comprehend and utilize medical knowledge and terminology. The evaluation process may involve designing test cases tailored to specific tasks and challenges within the medical field.

According to the different forms of evaluation, we categorize the current relevant work into four folds: medical examination, medical question answering, medical generation, and medical comprehensive evaluation. The medical examination form involves verifying model performance through standard medical tests or examinations. Differently, medical question answering involves utilizing questions posed or collected by human experts to make assessments. Medical generation focuses on generating new medical descriptions or knowledge based on a given input. The studies on medical comprehensive evaluation aim to provide assessments across various application scenarios rather than focusing on a single aspect. Besides the special Healthcare we have discussed in

Section III-B, Table IX also summarize some studies which evaluate general LLMs on Healthcare data.

In the form of medical examination, the study [263] evaluated the strengths and weaknesses of ChatGPT in primary care using the Membership of the Royal College of General Practitioners Applied Knowledge Test (AKT). It is observed that ChatGPT's average performance (60.17%) is below the mean passing mark in the last 2 years (70.42%), demonstrating further development is required to match the performance of qualified primary care physicians.

The role of QA in Healthcare LLMs is critical, leading to many studies on medical QA evaluation. The study [267] used 100 multiple-choice questions in radiation oncology physics from a medical physicist to test LLMs' abilities. Four LLMs (ChatGPT, GPT-4, Bard⁹, and BLOOMZ¹⁰) were compared with medical physicists and non-experts, with GPT-4 outperforming the physicists. However, when majority vote scoring was used, only the team of physicists significantly outperformed GPT-4. The same study [267] also assessed LLMs for patient-specific questions from EHRs, confirming that ChatGPT and Claude provide accurate responses across various settings. The study [270] on fertility counseling found only 6.12% of ChatGPT's factual statements incorrect, highlighting LLMs' ability to generate relevant clinical responses. Yet, limitations include unreliable source citation and potential for misinformation.

The evaluation of medical generation can provide further insights into the level of control that LLMs have over medical knowledge. It is significant to pinpoint the most pressing and important research questions. To this end, the study [273] evaluated the potential of chatGPT for identifying research priorities in gastroenterology from four key topics. Several experienced experts reviewed and rated the generated research

⁹<https://bard.google.com/>

¹⁰<https://github.com/bigscience-workshop/xmtf>

questions. It seems ChatGPT would generate relevant and clear research questions. However, the generated questions were not considered original. The study [274] investigated the feasibility of using ChatGPT and GPT-4 to translate radiology reports into plain language. According to the evaluation by radiologists, ChatGPT performs well and can successfully translate radiology reports into plain language with an average score of 4.27 in the five-point system.

Numerous studies have been conducted to assess the extensive capabilities of Healthcare LLMs. For instance, the research [275] conducted a thorough evaluation of ChatGPT's zero-shot capabilities across several benchmark biomedical tasks like relation extraction, document classification, question answering, and summarization, finding that zero-shot ChatGPT performs comparably to specialized models like BioGPT and BioBART that have been fine-tuned. Additionally, the study [276] performed a targeted investigation into ChatGPT's applicability in four specific clinical and research contexts: clinical practice support, scientific research production, potential misuse in medicine and research, and reasoning on public health matters. The findings indicate that ChatGPT delivers robust performance across a range of healthcare-related tasks.

B. Evaluation of Robustness and Bias

To assess how well a model performs when faced with uncertainties, perturbations, or unexpected inputs, researchers have been studying robustness evaluation techniques. For instance, in the field of general NLP tasks, studies have explored the robustness of LLMs in areas such as semantic parsing [277] and vision-language tasks [278]. In the Healthcare domain, the evaluation of LLMs' robustness is relatively limited. One notable example is the evaluation of ChatGPT's robustness in translating radiology reports [274]. In this work, the original radiology reports were divided into 25 key information points, and the correctness and completeness of each point were evaluated in a point-by-point manner in the translated reports. The overall translation quality was found to be satisfactory for only 55.2% of the translated points, indicating ample room for improvement in the robustness of LLMs in Healthcare settings.

LLMs are generated through training on extensive text datasets, which can inherently contain various biases and imbalances. When the model is consistently exposed to specific biases or particular points of view during training, it tends to learn and reflect those biases, leading to biased outputs during text generation. In the manual evaluation process, the presence of biases can also arise due to the diverse academic backgrounds and perspectives of the experts involved. Each expert may have their own subjective interpretation or evaluation criteria, which can introduce deviations in the evaluation results [265].

C. Future Directions for Health Evaluation

The study [5] found that present evaluation methodologies heavily rely on prompt engineering and established benchmark datasets. Different prompt formulations can lead to contrasting evaluation outcomes. Furthermore, the assessment of expert

systems frequently hinges on utilizing (in-domain) datasets that were originally employed for training those systems. An ambiguity persists regarding potential inadvertent exposure of the scrutinized data, such as publicly available datasets and established scientific knowledge, during the training of Large Language Models (LLMs). These aspects could introduce bias into the comparison between LLMs and their corresponding baselines, impeding a fair assessment.

According to the current studies of Healthcare evaluation, we conclude the following four future directions.

Increase the evaluation of faithfulness. Healthcare professionals and patients place significant trust in the accuracy and reliability of information provided by LLMs. However, due to the unique nature of the medical domain, there is a risk that LLMs may generate false knowledge or hallucinations, which could potentially lead to serious accidents or harm. Therefore, evaluating the faithfulness of LLMs becomes crucial to identify instances where these models may generate hallucinations and mitigate their impact.

Towards comprehensive and multitask evaluation. The current evaluation practices predominantly concentrate on assessing the performance of LLMs on one specific medical task, which might not provide a comprehensive understanding of their capabilities across the entire medical applications. Consequently, there is a clear need for a multitask evaluation system that can comprehensively evaluate the performance of LLMs across various medical tasks.

Towards multi-dimensional evaluation. While current evaluation efforts have primarily centered around accuracy, there is a growing recognition of the need for a multidimensional evaluation framework. It should consider various aspects beyond accuracy, such as the correctness of interpretation, robustness, hallucination ratio, content redundancy, biased description, and ICL capability.

Increase privacy protection in the evaluation process. Medical applications inherently involve sensitive data privacy concerns that surpass those of other NLP tasks. Consequently, safeguarding privacy during the evaluation process becomes of utmost importance. One potential solution to address this challenge is the adoption of federated learning approaches [279], which enable the implementation of large-scale evaluation systems while preserving privacy.

VI. IMPROVING FAIRNESS, ACCOUNTABILITY, TRANSPARENCY, AND ETHICS

Fairness, accountability, transparency, and ethics are four important concerns in the AI domain. According to the study [280], *Fairness* holds paramount significance in guaranteeing that AI does not perpetuate or exacerbate established societal disparities; *Accountability* plays an important role in ensuring that individuals responsible for the conception and execution of AI can be held answerable for their decisions; *Transparency* assumes a critical role in ensuring that AI remains open to scrutiny and amenable to audits for possible biases or inaccuracies; *Ethics*, similarly, assumes a pivotal role in guaranteeing that AI is constructed and utilized in manners that align with prevailing social values and norms.

In the Healthcare domain, we believe that these four aspects are even more critical because the primary focus is on patient well-being and safety. In this context, the utmost importance lies in ensuring patients receive optimal care marked by equitable access to medical services. Additionally, the transparent and trustworthy nature of Healthcare decisions, the accountability in delivering accurate medical diagnoses and treatments, the safeguarding of patient confidentiality, and the adherence to elevated ethical standards emerge as distinct and noteworthy considerations, setting Healthcare apart from AI applications in other domains and more.

A. Fairness

Fairness within the context of LLMs and NLP refers to the principle of equitably treating all users and preventing any form of unjust discrimination. This essential concept revolves around the mitigation of biases, aiming to guarantee that the outcomes produced by an AI system do not provide undue advantages or disadvantages to specific individuals or groups. These determinations should not be influenced by factors such as race, gender, socioeconomic status [15], or any other related attributes, e.g., different input languages [281] and processing tasks [282], striving for an impartial and balanced treatment of all users. This fundamental tenet aligns with the broader objective of promoting equality and inclusivity within the applications of LLMs and NLP.

The biases from LLMs can be attributed to the uneven distribution of demographic attributes in pre-training corpora [104]. Such an argument also holds for the Healthcare sector [283]. As an example, neural models trained on publicly accessible chest X-ray datasets tend to exhibit underdiagnosis tendencies in marginalized communities, including female patients, Black patients, Hispanic patients, and those covered by Medicaid insurance [284]. These specific patient groups often experience systemic underrepresentation within the datasets, resulting in biased algorithms that may be susceptible to shifts in population demographics and disease prevalence. Furthermore, several global disease classification systems display limited intra-observer consensus, implying that an algorithm trained and assessed in one country may undergo evaluation under a dissimilar labeling framework in another country [285], [286].

Current common practices to improve AI fairness in the Healthcare domain focus on pre-processing, in-processing, and post-processing [283]. Importance weighting is a pre-processing technique, which involves adjusting the significance of less frequent samples from protected subgroups. Similarly, resampling endeavors to rectify sample-selection bias by acquiring more equitable subsets of the initial training dataset and can be naturally employed to address the underrepresentation of specific subgroups.

For LLMs, bias mitigation methods are frequently studied in the context of instruction fine-tuning and prompt engineering [287]. The representative technique for instruction fine-tuning is RLHF. In the case of InstructGPT, GPT-3 is refined through a process involving RLHF, specifically aimed at adhering to human instructions. The procedure involves three sequential steps: firstly, gathering human-authored demonstration data to guide GPT-3's learning; secondly, assembling

comparative data consisting of model-generated outputs assessed by annotators to construct a reward model that predicts outputs preferred by humans; and lastly, fine-tuning policies based on this reward model [288]. The aforementioned process offers a valuable chance to rebalance the data and incorporate additional security measures to prevent biased behavior in the model. However, it is important to note that obtaining demographic information can sometimes be challenging due to privacy and ethical concerns in medical practices. This creates an obstacle when we aim to ensure fairness while also protecting privacy.

B. Accountability

LLMs are prone to amplifying the inherent social biases present in their training data, and they may produce hallucinatory or counterfactual outputs. This issue is compounded by their lack of robustness, making them vulnerable to perturbations and deviations from expected performance, especially when faced with diverse inputs or scenarios. In the healthcare sector, these problems can have grave implications because the outputs of LLMs can directly impact people's health and even their lives. Consequently, ensuring accountability becomes a crucial concern when deploying LLMs in healthcare settings.

Effective accountability acts as a vital safeguard, ensuring that LLMs can be reliably integrated into the Healthcare field. Specifically, accountability entails that when healthcare LLMs err or yield undesirable outcomes, clear attribution of responsibility enables swift identification of the responsible parties. This facilitates prompt remedial actions and appropriate compensation for affected patients. Addressing these issues not only resolves specific problems but also helps prevent similar issues in the future, thereby enhancing both patient and public trust in healthcare LLM applications.

The hallucinations problem presents a main obstacle to accountable AI. In the evaluation conducted by the study [289], ChatGPT was evaluated using fact-based question-answering datasets, revealing that its performance did not exhibit enhancements in comparison to earlier versions. Consequently, the reliability of ChatGPT in tasks necessitating faithfulness is called into question. For instance, its potential fabrication of references in the context of scientific article composition [290] and the invention of fictitious legal cases within the legal domain [291] accentuate the potential risks associated with its use in critical domains.

Further, McKenna et al. [292] and Li et al. [293] investigate the root reason of hallucinations. These studies pinpoint the root cause of the hallucination problem: LLMs tend to memorize training data, especially in relation to word frequencies. This fundamental cause indicates that completely resolving the hallucination issue is challenging. Consequently, even the most advanced LLMs may still produce incorrect information. For such reason, we have to make an effective accountability before applying Healthcare LLMs in real medical scenarios.

Actually, accountability in AI is not just about correcting errors but also about implementing preventative measures that maintain trust and safety, particularly when AI decisions impact human lives. A direct preventive measure is to facilitate

user participation in modeling decisions. The study [5] contended that enabling users to access human-generated source references is crucial for enhancing the reliability of the model's responses. The study [294] advocated for the involvement of both AI developers and system safety engineers in evaluating the moral accountability concerning patient harm. Additionally, they recommend a transition from a static assurance model to a dynamic one, recognizing that ensuring safety is an ongoing process and cannot be entirely resolved during the initial design phase of the AI system before its deployment.

The study [295] proposed a solution to tackle the issue of accountability, advocating for the education and training of prospective AI users to discern the appropriateness of relying on AI recommendations. However, imparting this knowledge to practitioners demands a considerable investment of effort. Healthcare professionals frequently grapple with overwhelming workloads and burnout, making comprehensive training on AI a significant challenge. Moreover, not all Healthcare practitioners possess adequate statistical training to comprehend the underlying mechanics of AI algorithms. In addition to education, the study [295] recommended the establishment of policies and mechanisms to ensure the protection of both clinicians and AI within the Healthcare domain.

C. Transparency

The limited transparency of neural networks has been widely criticized, presenting significant obstacles to their application in the Healthcare domain. LLMs and PLMs are complex neural network models, which further exacerbate the challenges associated with interpretability. In recent years, there have been efforts to understand the inner workings of PLMs in Healthcare contexts. Probing PLMs have been extensively employed to uncover the underlying factors contributing to their performance [296]. For example, the study [297] examined PLMs' disease knowledge, while the study [298] conducted in-depth analyses of attention in protein Transformer models, yielding valuable insights into their mechanisms.

In the general machine learning domain, a transparent model is typically characterized by decision-making processes akin to those of white-box models, e.g., decision tree-based models or linear regression models. It often encompasses post hoc explanations [299], model-specific explanations [300] or model-agnostic explanations [301]. Sometimes, the explanation insights are derived from feature maps [302], generated natural language [303], factual and counterfactual examples [304], or decision-making evidence [305].

For PLMs, the study [299] introduced an innovative method accompanied by quantitative metrics aimed at mitigating the limitations observed in existing post hoc explanation approaches, as outlined in the literature. These drawbacks include reliance on human judgment, the necessity for retraining, and issues related to data distribution shifts during the occlusion of samples. The method proposed in this study allows for a quantitative assessment of interpretability methods without the need for retraining and effectively addresses distribution shifts between training and evaluation sets.

In the era of LLMs, CoT prompting [16] has emerged as a potential method for providing a certain level of interpretability

by generating reasoning steps. The technique empowers LLMs to break down complex, multi-step problems into more manageable intermediate steps. This enables the allocation of additional computational resources to problems demanding deeper reasoning steps. Moreover, it offers a transparent view of the LLM's behavior, shedding light on its potential process of arriving at a specific answer and offering insights for identifying and rectifying errors in the reasoning path. Essentially, a chain of thought can be perceived as a systematic, step-by-step thought process leading to the derivation of an answer. However, this approach faces two primary challenges: the high cost of annotations required for CoT and the evaluation of interpretability. Acquiring demonstrations with annotated reasoning steps is an expensive task, particularly in professional fields such as Healthcare. Additionally, evaluating the generated reasoning results as explainable justifications and ensuring their usability pose significant challenges.

D. Ethics

The ethical concerns about using LLMs for Healthcare have been widely discussed. Healthcare LLMs typically possess a wide range of patient characteristics, including clinical measurements, molecular signatures, demographic information, and even behavioral and sensory tracking data. It is crucial to acknowledge that these models are susceptible to memorize training data and simply reproducing it for users, resulting in compromising the privacy of users. As mentioned in Section IV-D, EHRs serve as important training data, alongside public scientific literature and web data. However, it is worth noting that EHRs may contain sensitive information such as patient visits and medical history, and exposing such data could lead to physical and mental harm to patients. It is important to recognize that de-identification techniques employed in EHR records may not always guarantee complete safety. Recent studies have shown that there can be instances of data leakage from PLMs in the general domain, allowing for the recovery of personal health information from models trained on such data sources [306], [307]. Additionally, approaches such as KART [308] have been proposed to assess the vulnerability of sensitive information in biomedical PLMs using various attack strategies.

The Federated Learning (FL) [309] is a promising technology to alleviate the above problem. By allowing the model to be trained directly on the devices where the data originates, FL keeps sensitive patient information localized, reducing the risk of data breaches. Moreover, it can help in creating more generalized and unbiased models by learning from a diverse array of decentralized data sources, thus covering a broader spectrum of patient demographics and conditions.

Generally, it is imperative for stakeholders in the healthcare sector to engage in continuous ethical reviews and updates of the guidelines governing the use of LLMs. This includes regular assessments of the models for biases, implementing rigorous privacy safeguards, and ensuring transparent and explainable AI systems. Moreover, active collaboration between ethicists, technologists, clinicians, and patients is necessary to harness the benefits of healthcare LLMs while minimizing their risks.

VII. FUTURE WORK AND CONCLUSION

A. Future Work

1) *Medical knowledge enhancement*: In the knowledge-intensive Healthcare domain, models infused with medical knowledge hold tremendous potential for applications, which has been explored many years [125], [310]. The studies [311]–[313] illustrates the integration of domain-specific knowledge into the pre-training and fine-tuning process. However, a major drawback of this method is that the knowledge remains fixed once training is complete, making it difficult to incorporate specific knowledge or update the overall knowledge without retraining. Also, updating model parameters lead to catastrophic forgetting, compromising other aspects of the model's capabilities. Recently, retrieval-based LLMs [314], [315] may offer a more promising solution to these challenges, allowing for more flexible and adaptable knowledge integration.

2) *Integration with Healthcare process*: Current AI healthcare solutions are fragmented and largely experimental due to several challenges identified in existing studies [316]. Firstly, integrating AI with hospital IT systems is complex, as it requires accessing and standardizing vast amounts of data stored in diverse formats across various systems, impacting daily operations. Additionally, the consolidation of hospitals introduces further complexity by necessitating the unification of disparate IT systems, a process that is costly and technically demanding. Finally, regulatory uncertainties and incomplete laws concerning AI in healthcare, which vary by region and involve complex ethical considerations, further complicate the development and application of AI technologies.

3) *Effective Interaction with Patients and Doctors*: Despite the existing fluency of LLMs in human communication, the unique nature of the medical domain necessitates specific requirements for the interaction between LLMs and their users, namely doctors and patients. These requirements include the ability of LLMs to proactively inquire about symptoms, pose targeted questions, and effectively manage the pace and flow of conversations. Additionally, it is desirable for LLMs to perceive and appropriately address patient emotions such as anxiety and fear, thereby providing suitable emotional support. Moreover, an augmentation to the dialogue system could involve incorporating a virtual human design. This design would enable the model to portray a doctor's image, encompassing elements such as tone, speech speed, and facial expressions, with the intention of enhancing rapport in communication.

4) *Hallucinations, Misunderstandings and Prompt Brittleness*: Hallucinations, misunderstandings, and prompt brittleness are three fundamental challenges encountered by both general LLMs and Healthcare LLMs. As we mentioned, these “hallucinations” can pose significant issues, particularly when users are unfamiliar with the discussed concepts, as they may struggle to identify the inaccuracies in the model's output. Misunderstandings represent a misalignment problem where the behavior of LLMs fails to align with human values, objectives, and expectations. In other words, LLMs may provide incorrect actions or responses despite receiving proper instructions. Prompt brittleness signifies that even minor modifications to the input prompt can yield

dramatically different outputs, as first observed in the study by [317]. In the Healthcare context, these issues could lead to unacceptable consequences. While additional instructions or reinforcement learning from human feedback can partially mitigate these challenges, they do not fully satisfy the stability requirements within the Healthcare domain. Regarding prompt brittleness, the current state of prompt engineering heavily relies on extensive experimentation, with a limited theoretical understanding of why a specific phrasing or formulation of a task is more sensible beyond achieving improved empirical results. Consequently, the development of LLMs that exhibit robustness to different prompt styles and formats remains an unsolved problem.

B. Conclusion

Recently, there has been a growing interest in LLMs and their potential applications across various fields. In this study, we provided a comprehensive survey specifically focusing on Healthcare LLMs. Our survey encompassed an extensive examination of data, technologies, applications, fairness, accountability, transparency, ethics, and limitations associated with Healthcare LLMs. A noteworthy transformation has been observed from Discriminative AI to Generative AI, as well as from model-centered to data-centered approaches, marking a significant shift from PLMs to LLMs. This transition has enabled Healthcare LLMs to support more advanced applications beyond conventional NLP-based fundamental tasks. Consequently, the emergence of these advanced applications has inspired numerous related studies.

To facilitate the development of Healthcare LLMs, various instruction datasets and training and inference technologies have been proposed. These resources have played a crucial role in accelerating the progress of LLMs, particularly within the Healthcare domain. Our objective is to summarize these existing resources, providing valuable support to researchers intending to embark on the development of their own Healthcare LLMs.

However, despite the opportunities presented by Healthcare LLMs, several significant challenges persist, impeding their implementation in Healthcare settings. Issues pertaining to interpretability, privacy protection, medical knowledge enhancement, integration with Healthcare processes, and effective interaction with patients and doctors pose substantial obstacles. These challenges hinder the translation of innovative LLMs into practical adoption within the Healthcare field. Consequently, physicians and other Healthcare professionals must carefully consider the potential benefits and limitations associated with LLMs as they navigate the selection and integration of these models into their medical practice.

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