2024

Research on LLM in medicine

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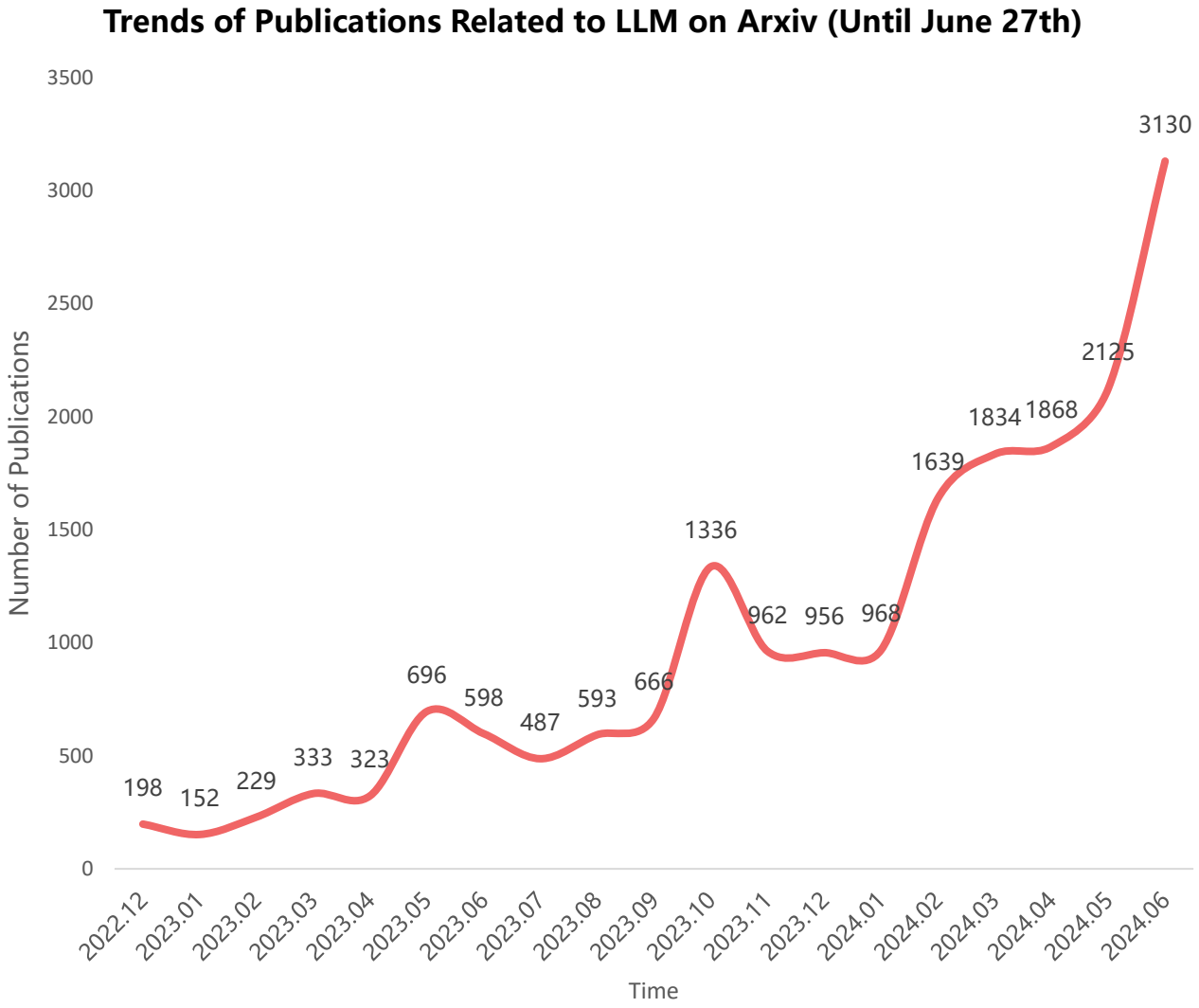
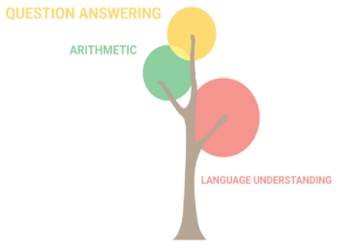
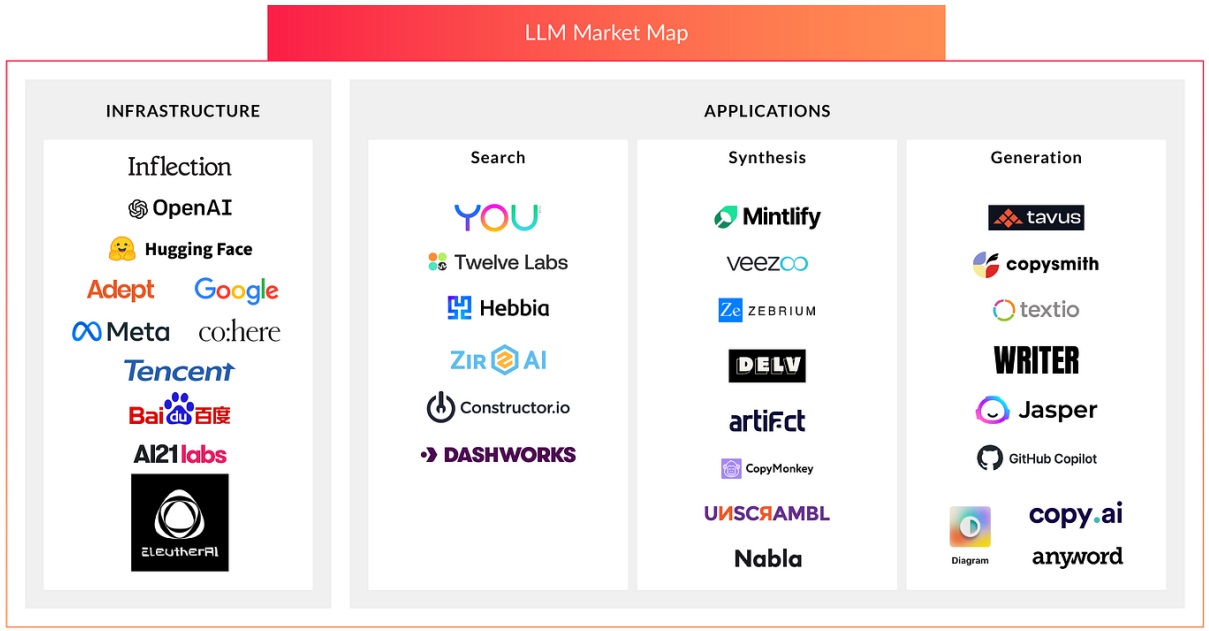
College of Biomedical Engineering & Instrumentation

Zhejiang University, China

LLM is changing the world

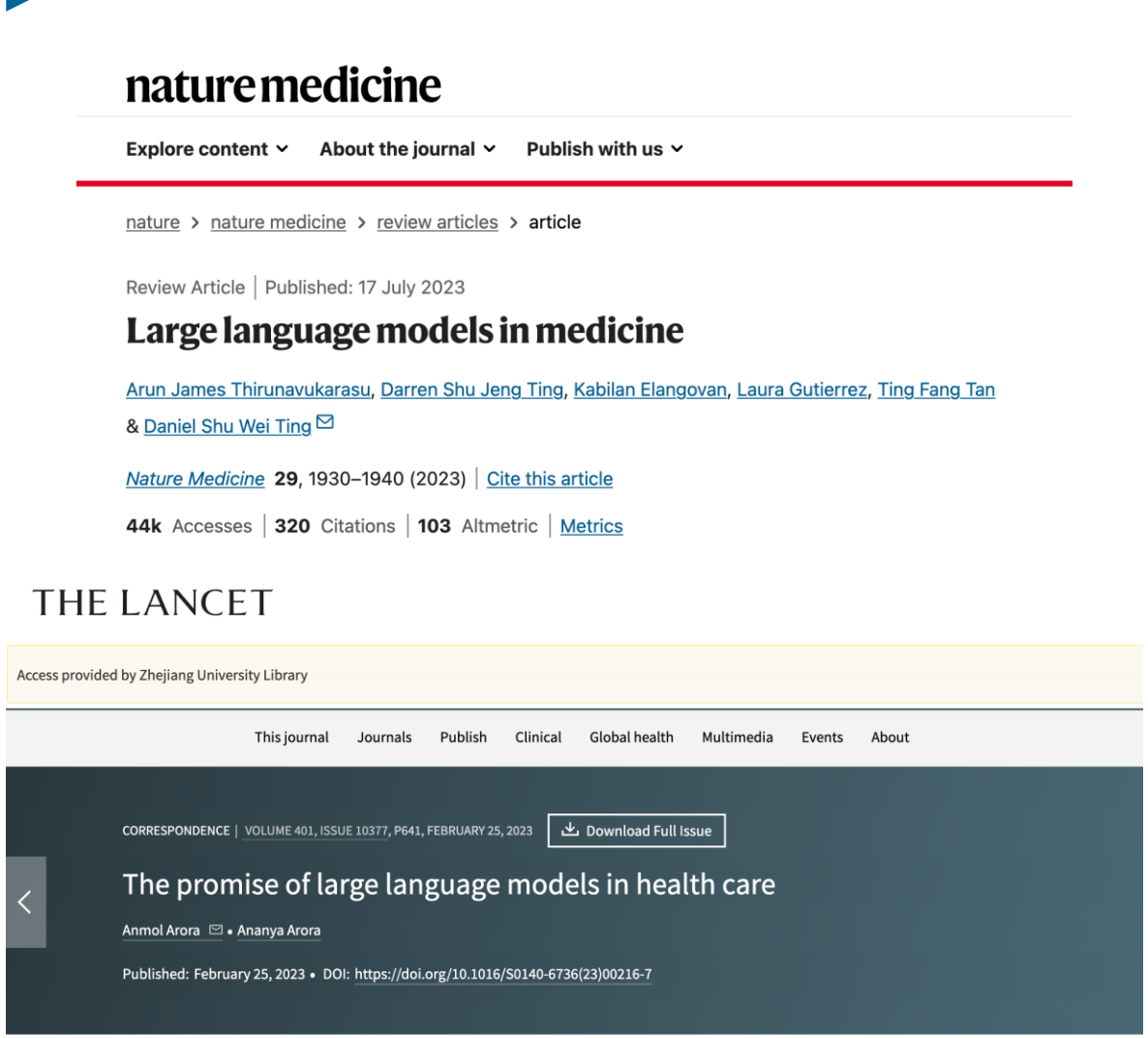






LLM has gained attention from both academia and industry

LLM is changing the world



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Review Article | Published: 17 July 2023

Large language models in medicine

Arun James Thirunavukarasu, Darren Shu Jeng Ting, Kabilan Elangovan, Laura Gutierrez, Ting Fang Tan & Daniel Shu Wei Ting

Nature Medicine **29**, 1930–1940 (2023) | Cite this article

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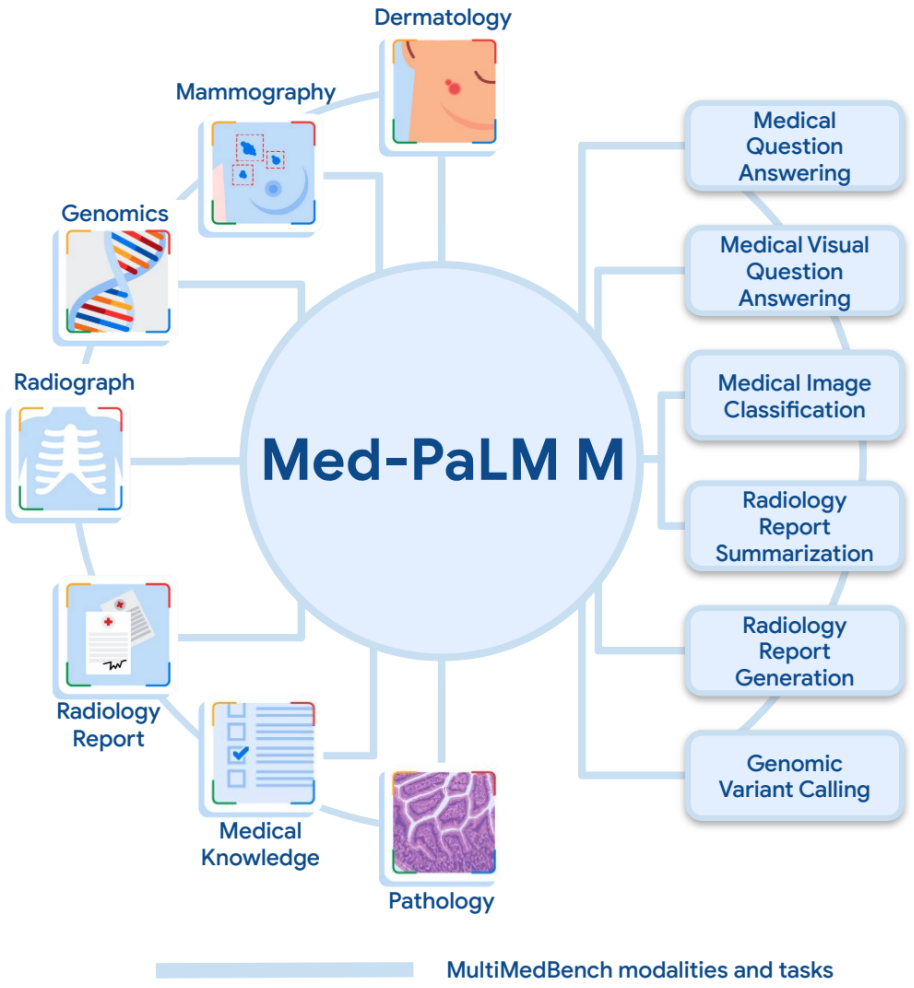
CORRESPONDENCE | VOLUME 401, ISSUE 10377, P641, FEBRUARY 25, 2023 Download Full Issue

The promise of large language models in health care

Anmol Arora • Ananya Arora

Published: February 25, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)00216-7

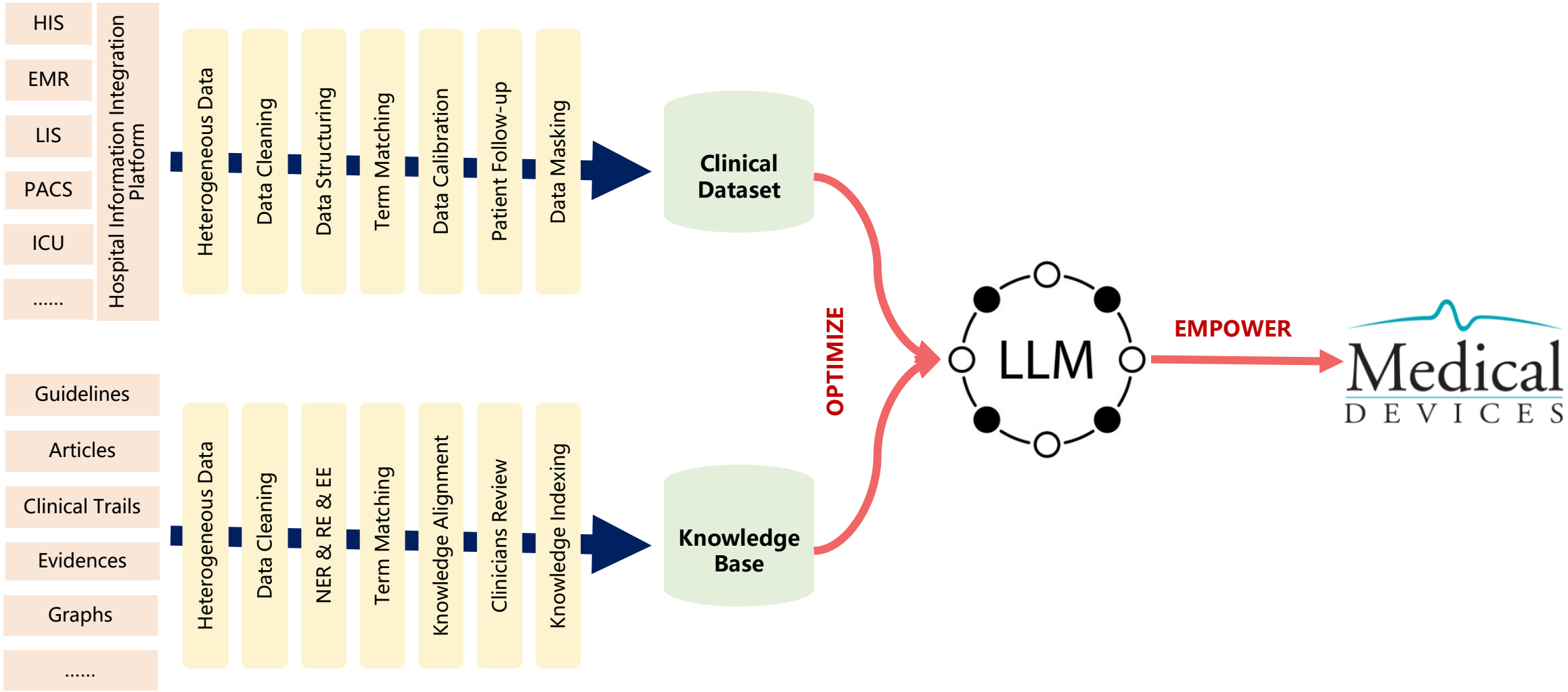


Med-PaLM M (Google)

The medical field is one of the key research focuses of LLM

Our research on LLM-medicine

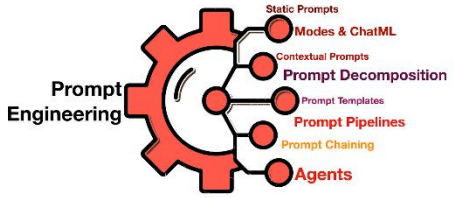
ZHEJIANG UNIVERSITY



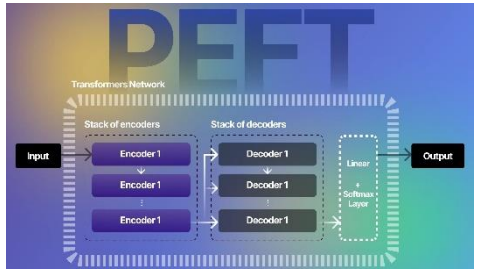
Methodology to optimize LLM and empower medical devices/systems with clinical data and knowledge

Our research on LLM-medicine

ZHEJIANG UNIVERSITY



Prompt Engineering



Parameter Efficient Fine-Tuning

Retrieval Augmented Generation

LLM Optimization Methods

Breast Cancer Out-of-hospital Management Agent

——Breast-COMA

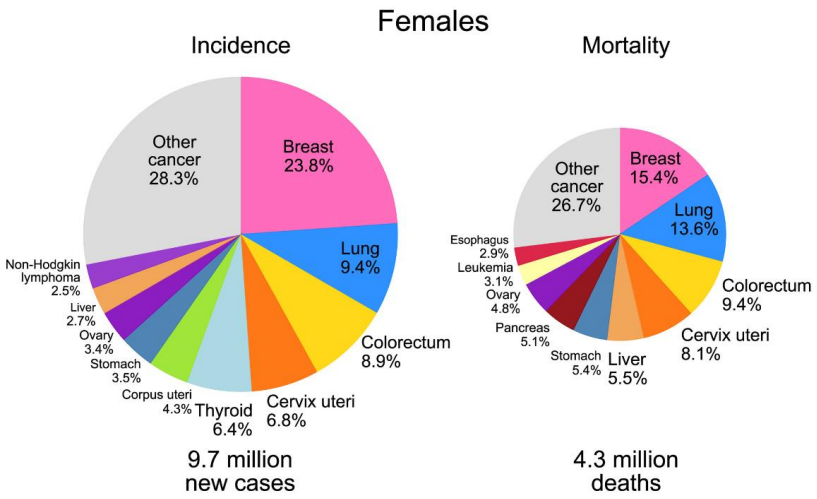
Tumor Board (Precision Oncology Decision Support)

——Patient Data Extraction & Applications

Breast Cancer Out-of-hospital Management Agent

Breast-COMA

Background of Breast-COMA



The incidence and mortality of breast cancer are the first among females globally.

Out of Hospital

Adverse Events

- Low White Blood Cell Count
- Lymphedema
- Liver Injury
- Heart Injury
- Nerve Injury
- ……

Accompanying Diseases

- Mental Illness
- Osteoporosis
- ……

Without Management

Decline of Health-Related Quality-of-Life (HRQoL)

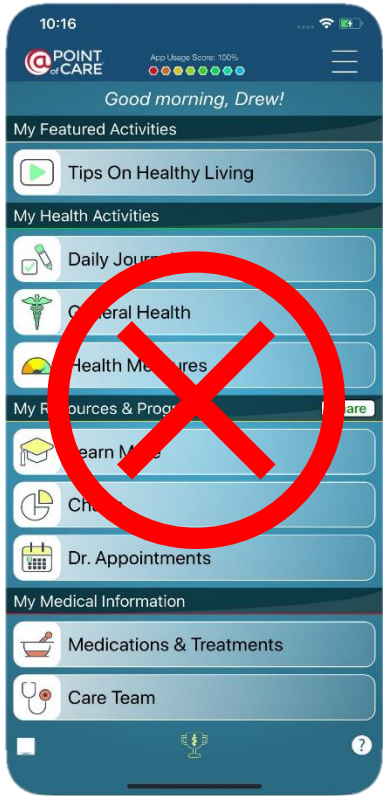
Decreasing of treatment adherence

Increasing of the risk of non-tumor-related mortality

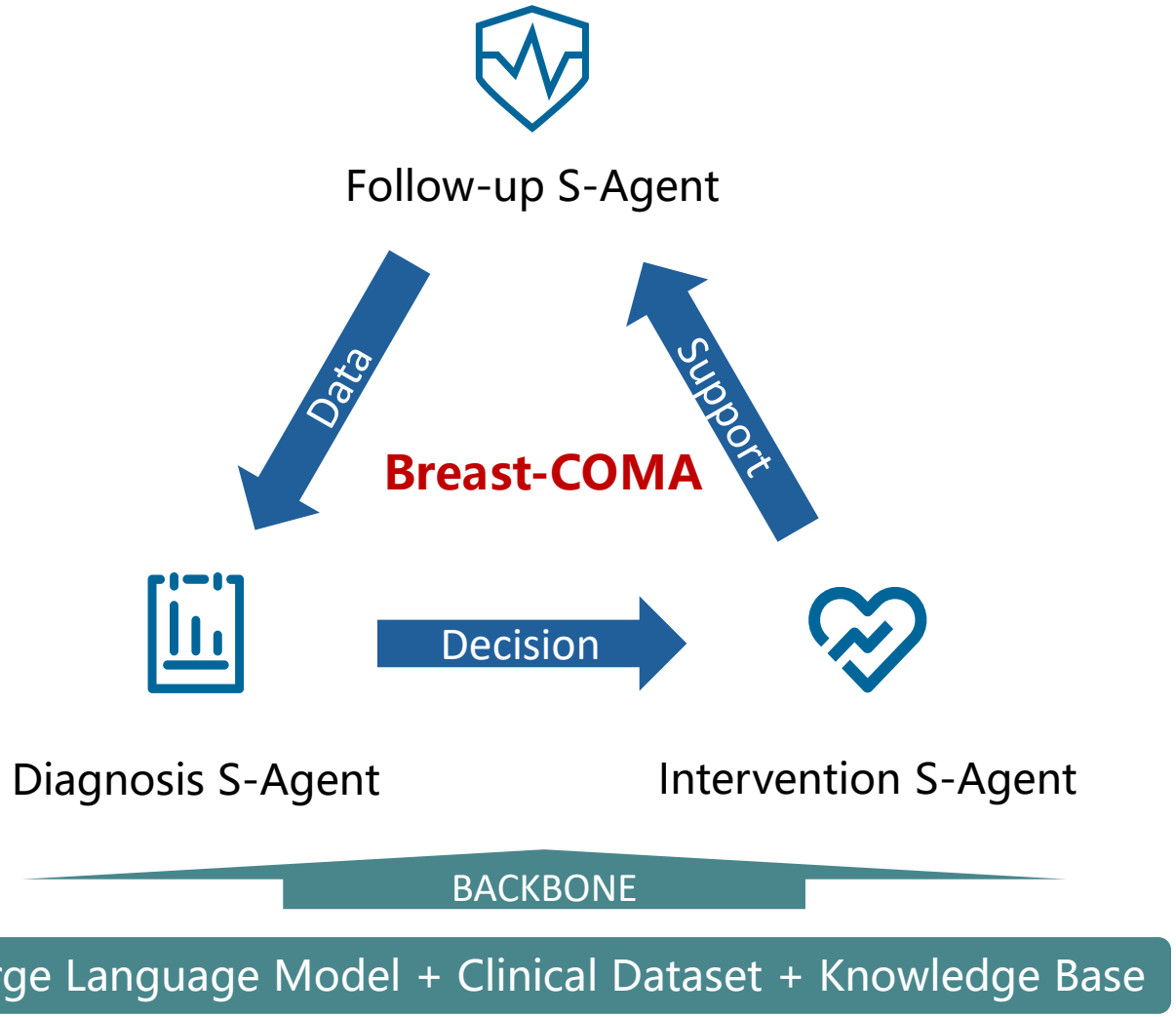
Adverse events and accompanying diseases threaten breast cancer patients' health out of hospital.

Target of Breast-COMA

Traditional APP's Disadvantage



- Steep learning curve
- Templated Interaction
- Manual support requirements



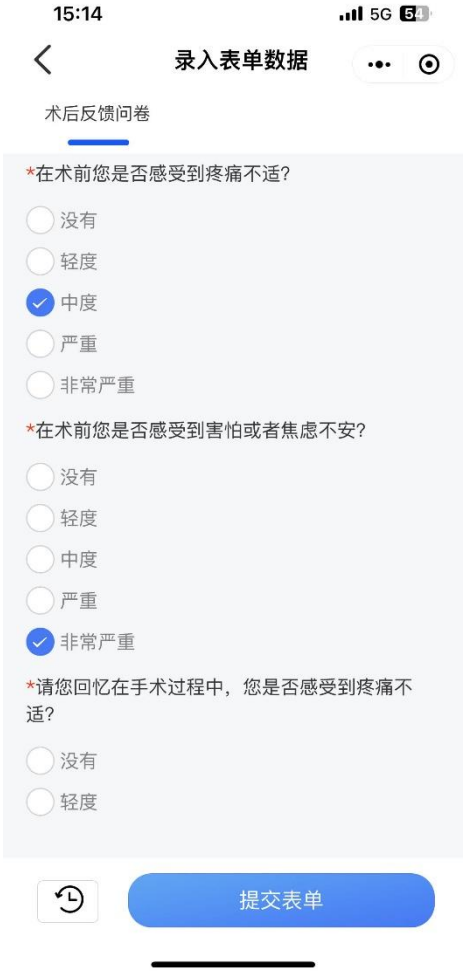
Breast-COMA：Follow-up S-Agent

How to monitor the patient's quality of life and occurrence of adverse events?

Self-reported by the patients

Patient Reported Outcome（PRO）：

Directly from the patient, any reports on the patient's health status, without interpretation by a clinician or other individuals.



- **Survey Fatigue**
- **Low interactivity**

Low Response Rate

CHAT BOT

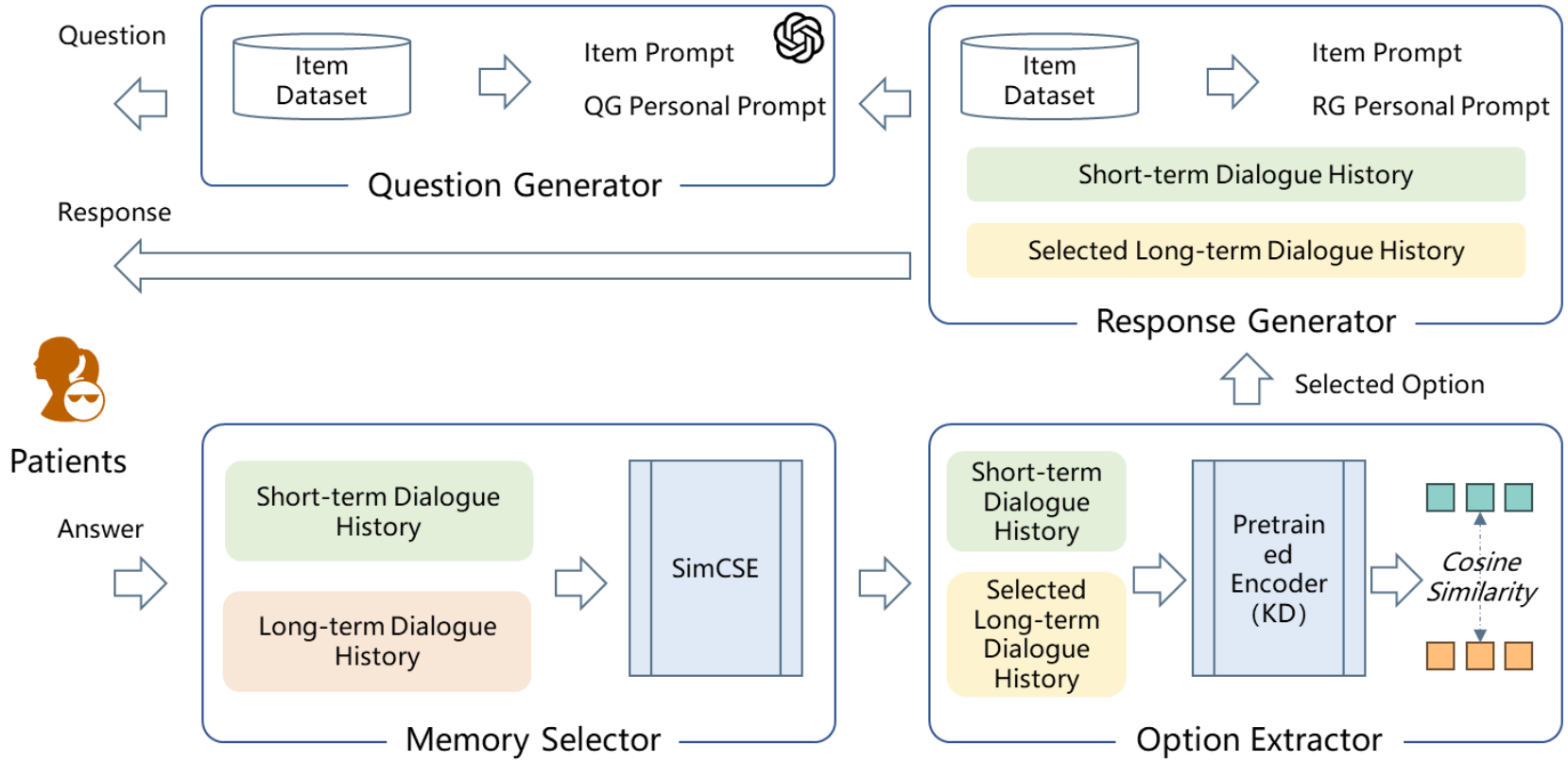
Chat-ePRO

"Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance," Health and quality of life outcomes, vol. 4, p. 79, 2006, doi: 10.1186/1477-7525-4-79.
M. J. Brady et al., "Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument.," JCO, vol. 15, no. 3, pp. 974–986, Mar. 1997, doi: 10/gr33s3.
N. N. Baxter, P. J. Goodwin, R. S. McLeod, R. Dion, G. Devins, and C. Bombardier, "Reliability and validity of the body image after breast cancer questionnaire," The breast journal, vol. 12, no. 3, pp. 221–232, 2006, doi: 10.1111/j.1075-122X.2006.00246.x.

Breast-COMA: Follow-up S-Agent

Chat-ePRO

Utilize **Prompt Engineering** and **Knowledge Distillation** to drive GPT-3.5 to collect PRO data automatically



Challenges

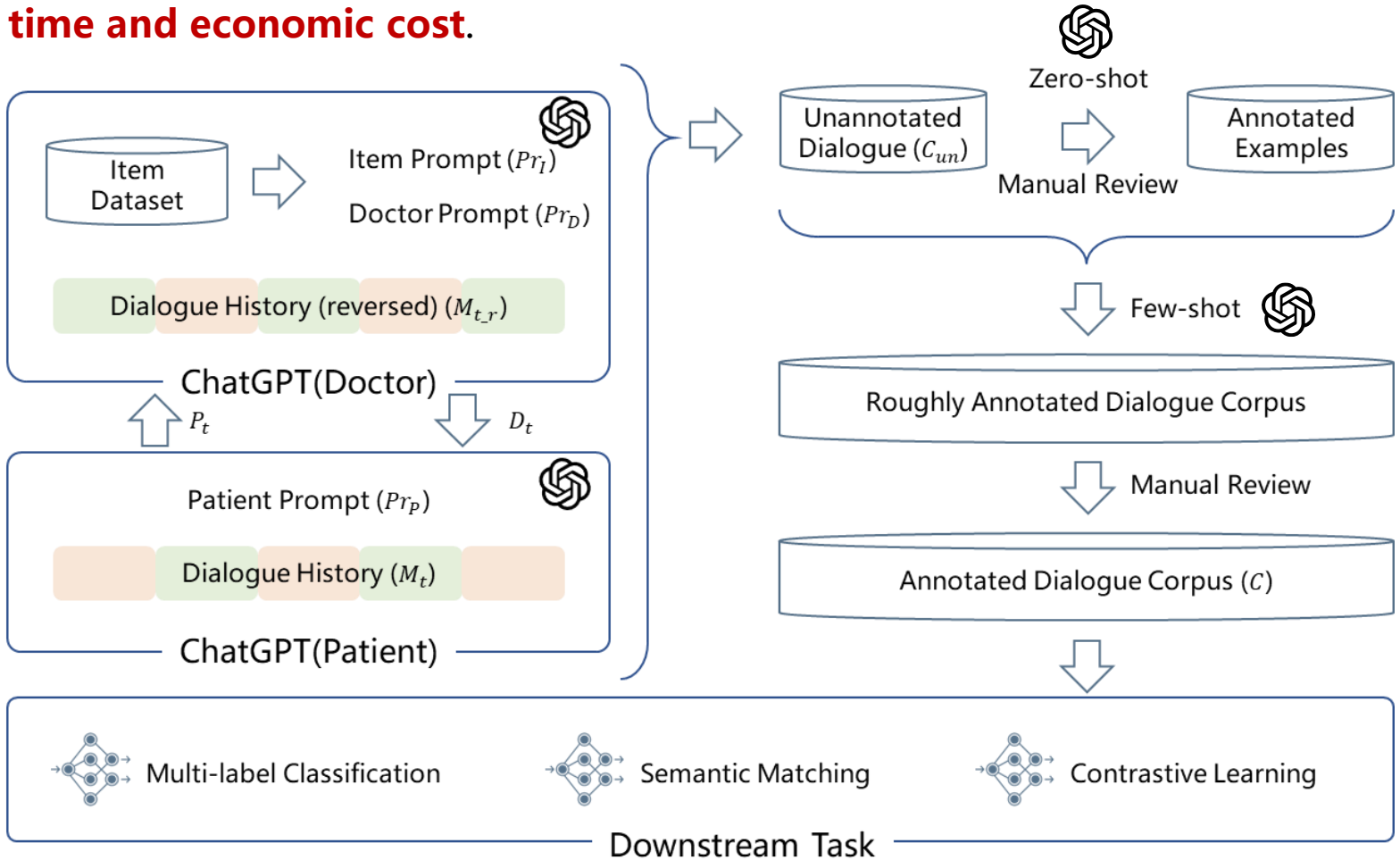
- How to instruct LLM to **actively collect target PRO forms**?
- How to **maintain context consistency** when dialogues are too long?
- How to **extract structured PRO data** from the dialogues economically in real time?

Chen Z, Wang Q, Sun Y, Cai H, Lu X. Chat-ePRO: Development and pilot study of an electronic patient-reported outcomes system based on ChatGPT. J Biomed Inform. 2024 Jun;154:104651. doi: 10.1016/j.jbi.2024.104651. Epub 2024 May 3. PMID: 38703936.

Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

☐ Follow-up S-Agent: Chat-ePRO —— Method

Challenge：How to extract structured PRO data from the dialogues economically in real time? Why not LLM? LLM’ s criteria are **difficult to align with the human** and are **unstable**. Furthermore, LLM will increase the system **time and economic cost**.



FACT-B　BIBCQ　TMI

92 Items　**18 Choices**

Generate

4K Annotated Dialogues

Breast-COMA：Follow-up S-Agent

☐ Chat-ePRO: Pilot Study Design

(c) Electronic Form-based ePRO

(d) Rule-based Chatbot ePRO

(e) Chat-ePRO

Breast-COMA：Follow-up S-Agent

☐ Chat-ePRO: Performance of Algorithm extracting structured data from dialogue

- **Dialogue Generation Ability**： **Low error rate** （Average： 4.3%）

Form Name	n_{Item}	n_{raw}	n_C	Error Rate
Fact-B	36	2160	2064	**4.4%**
BIBCQ	44	1144	1101	**3.8%**
TMI	12	840	800	**4.8%**

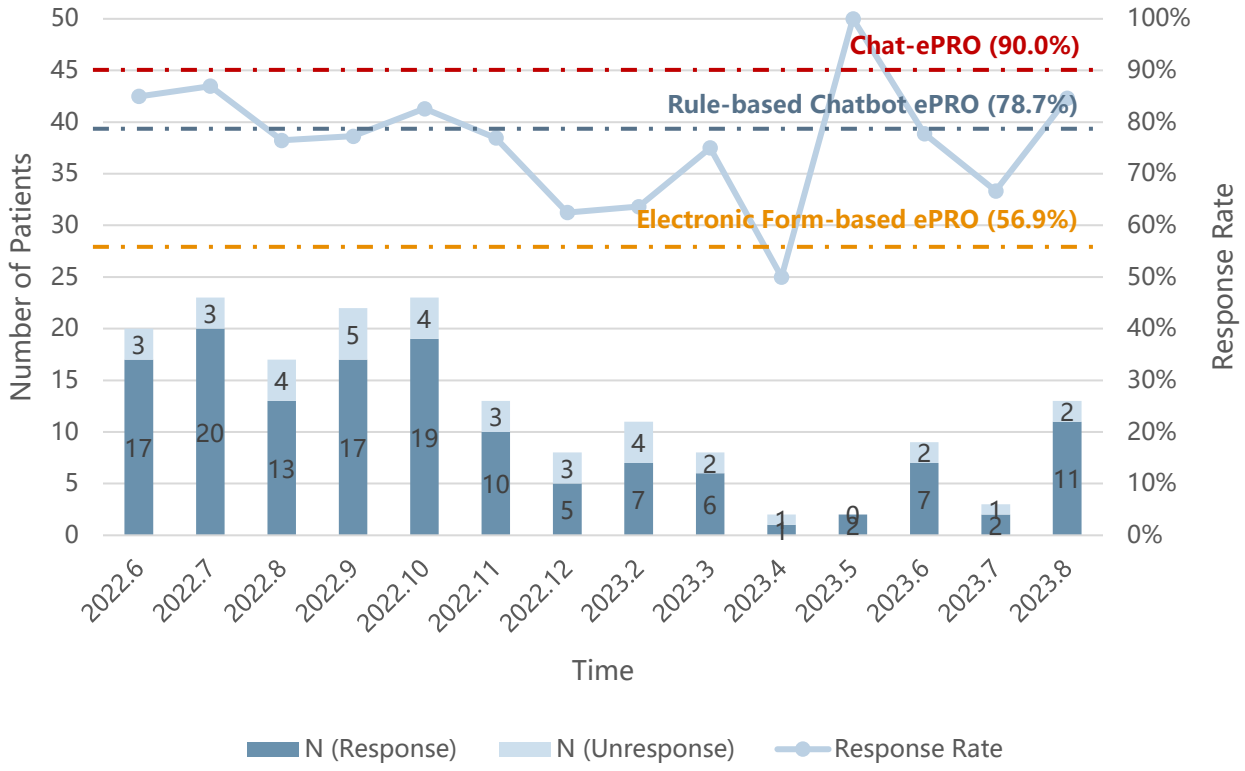
- **Data Extraction Ability**： **Improvement of F1** （F1： 0.78 → 0.96） ， **Decline of inference time** （8.2s → 1.2s） 。

	Fact-B			BIBCQ			TMI		
Task	P	R	F1	P	R	F1	P	R	F1
Classification	0.90	0.88	0.88	0.81	0.83	0.81	0.83	0.80	0.78
Semantic Matching	0.90	0.87	0.88	0.79	0.76	0.74	0.85	0.84	0.84
Contrastive Learning	**0.93**	**0.90**	**0.91**	**0.92**	**0.91**	**0.90**	**0.96**	**0.95**	**0.96**
Zero-shot (ChatGPT)	0.57	0.54	0.54	0.66	0.62	0.57	0.73	0.74	0.73
Few-shot (ChatGPT)	0.77	0.70	0.67	0.75	0.81	0.75	0.80	0.83	0.78

Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

Follow-up S-Agent: Chat-ePRO —— Result

Pilot Study Result:



Chat-ePRO significantly improved the response rate

Ok, I've recorded your answer. The next question is, "Because I am not in good health, I cannot meet the needs of my family." Do you think that description matches your feelings?
The options are: 0: Not at all; 1: a little bit; 2: some; 3: equivalent; 4: Very much

Can you define what is the needs of my family?

"Family needs" refer to household activities in daily life, such as cooking, washing, etc., or caring for family members, such as spending time with children, caring for the elderly, etc. This question wants to know if your physical condition is affecting your ability to complete these family activities. Please choose the best answer according to your situation in the past 7 days.

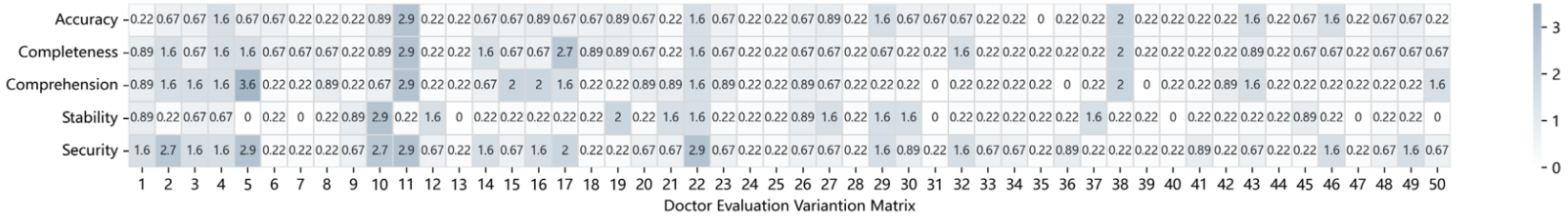
Not at all

Chat-ePRO could respond to queries and guide patients to finish PRO forms.

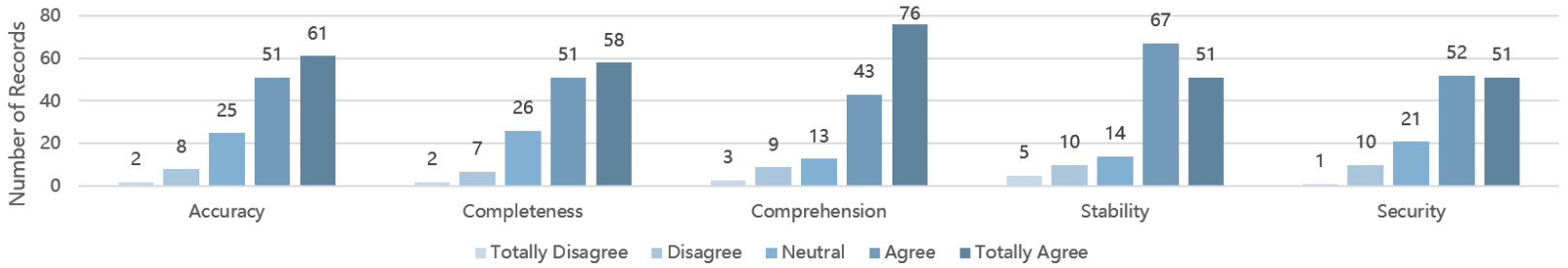
Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

☐ Follow-up S-Agent: Chat-ePRO —— Result

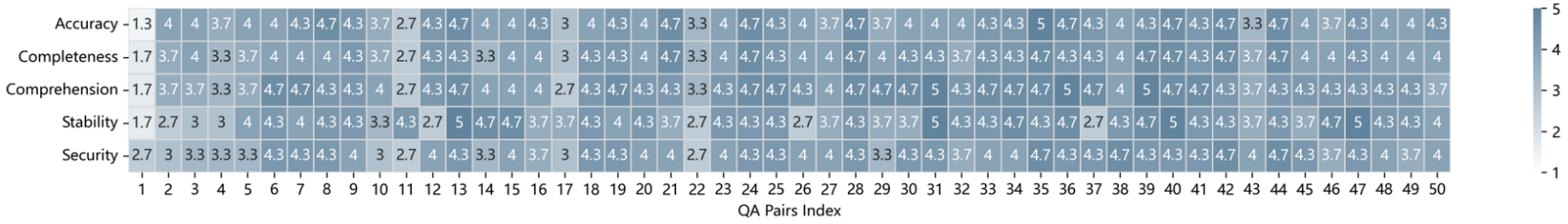
Pilot Study Result：



(a) Variance of Evaluation Scores



(b) Subjective Evaluation Result



(c) Evaluation Scores of QA Pairs

After removing the divergence (var>2) :

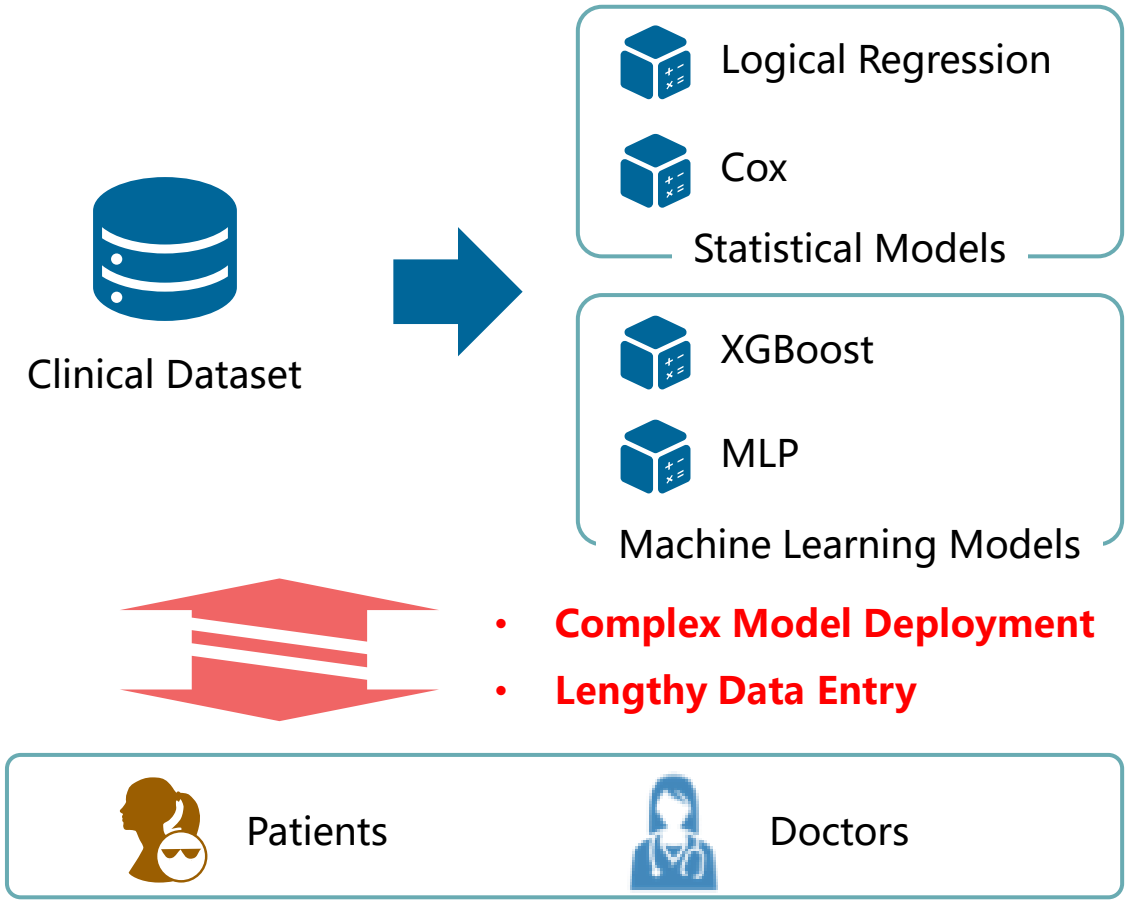
- 8% of doctors held negative attitude to Chat-ePRO
- 78% of doctors held positive attitude to Chat-ePRO

Breast-COMA：Diagnosis S-Agent (In progress)

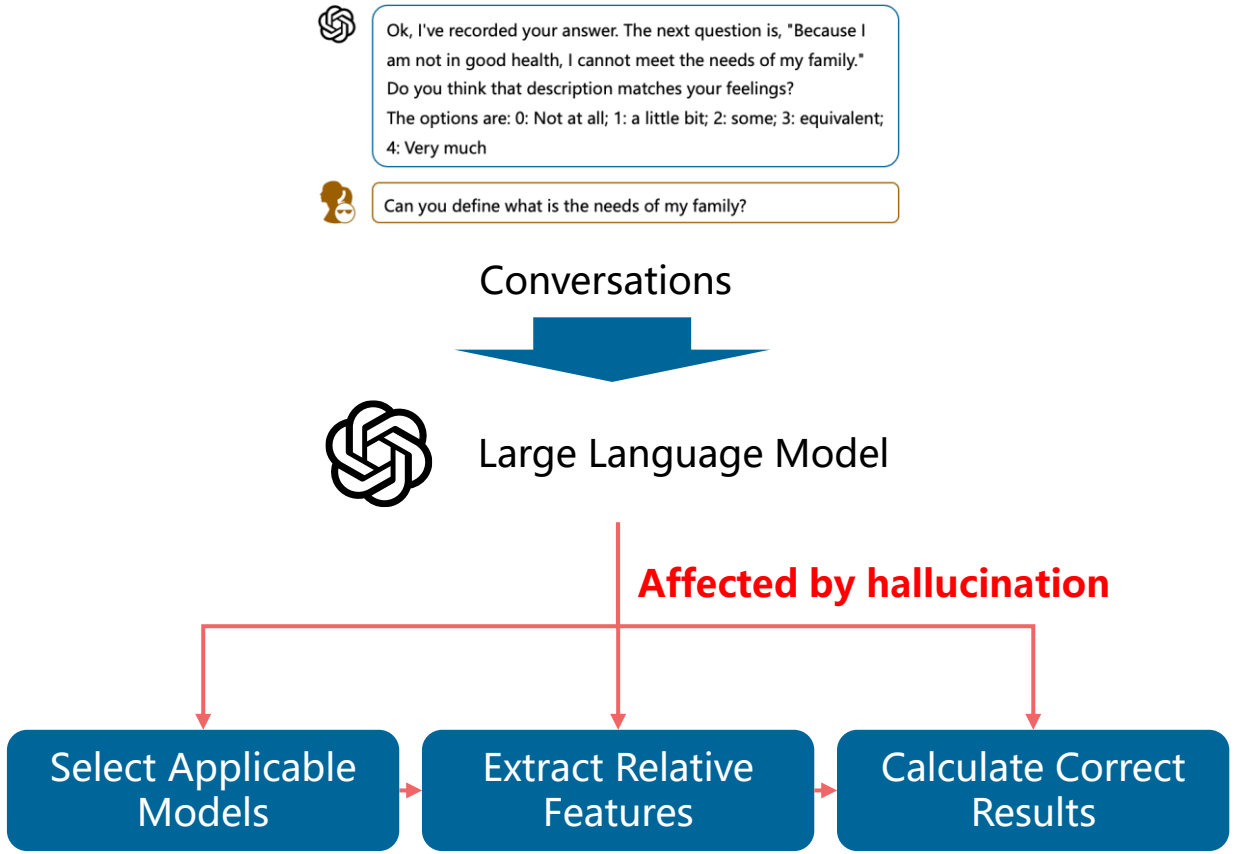
☐ Diagnosis S-Agent: RP-LLM—— Introduction (In Progress)

RP-LLM: Breast Cancer **R**isk **P**rediction **L**arge **L**anguage **M**odel Enhanced by Machine Learning Models

- **Poor clinical accessibility of prediction models**

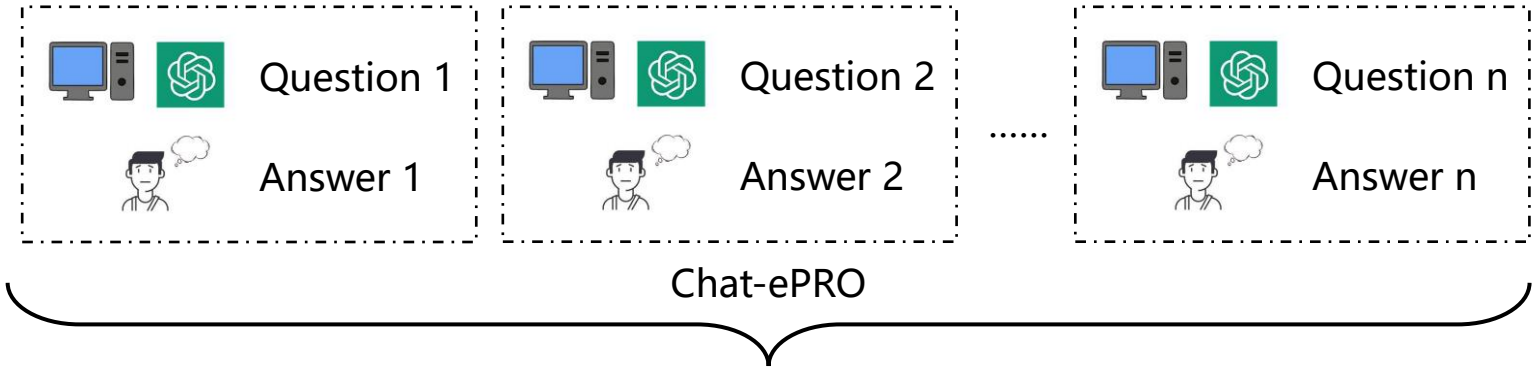


- **Difficult for large language model to predict stably**



Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

☐ Diagnosis S-Agent: RP-LLM—— Method (In Progress)



Collect and structure the information of each features needed to calculate in risk predication model.

The risk prediction model is calculated based on the collected feature information.

LLM provides basic diagnostic opinions by comprehensively considering the results of the risk prediction model’ s result and conversation contents.

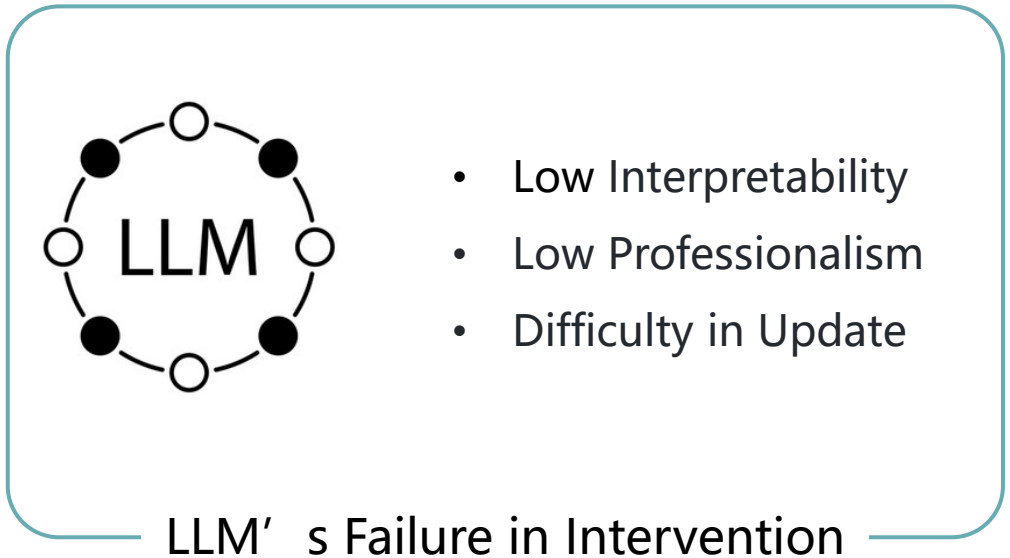
Evaluation Matrix:

- Risk Prediction Accuracy
- Data Collection Accuracy
- User Preference
- Expert Evaluation

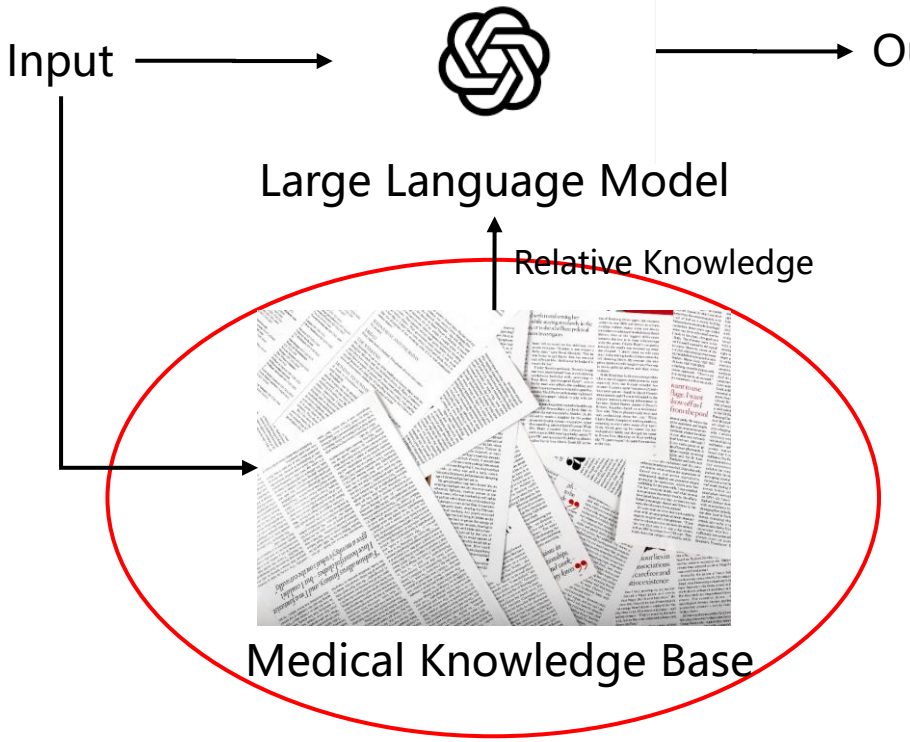
Breast-COMA：Intervention S-Agent (In progress)

☐ Intervention S-Agent: MM-BRAG —— Introduction (In Progress)

MM-BRAG: Optimizing **M**ulti-**m**odal Large Language Models for **B**reast Cancer via **R**etrieval **A**ugmented **G**eneration



RAG

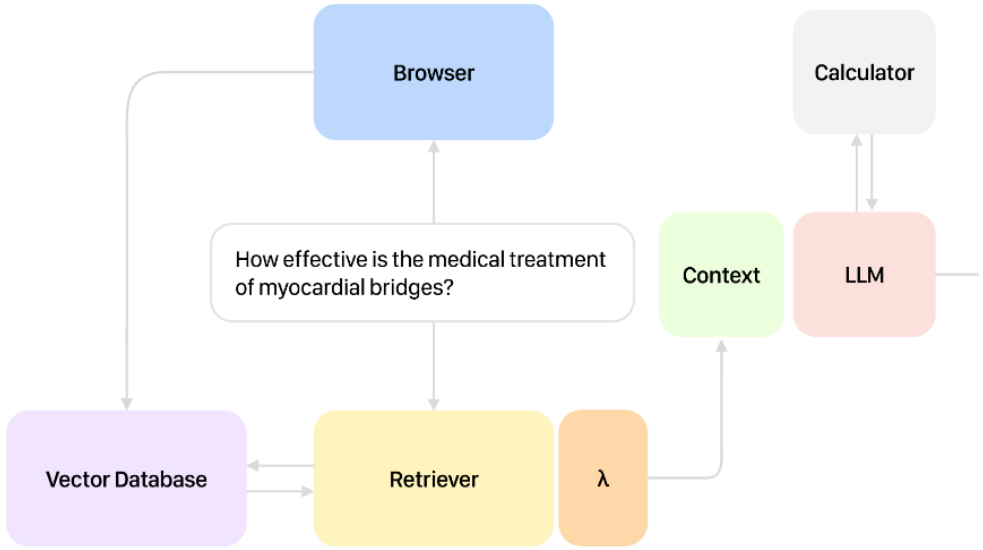


Complexity of Medical Knowledge: Multi-modal, Multi-resources

Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

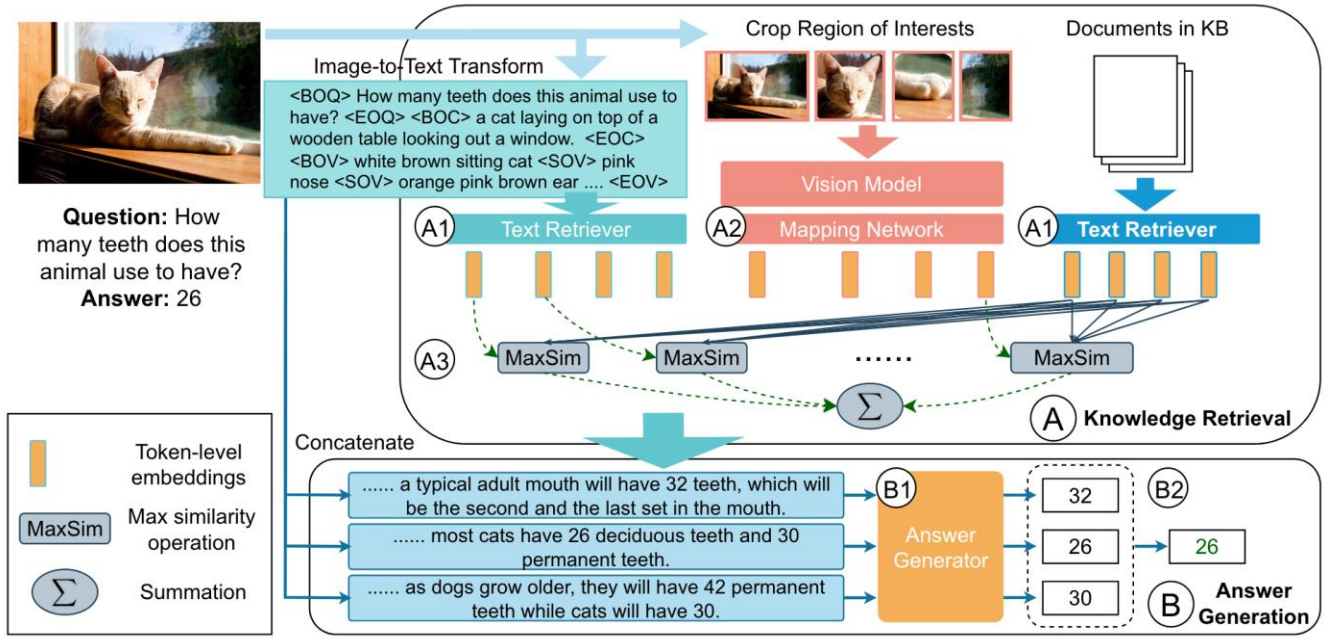
☐ Intervention S-Agent: MM-BRAG —— Related Work (In Progress)

Medical LLM with RAG



Almanac (Stanford, 2024)

Retrieval-Augmented Visual QA



FLMR (University of Cambridge, 2024)

Knowledge base is limited to text format

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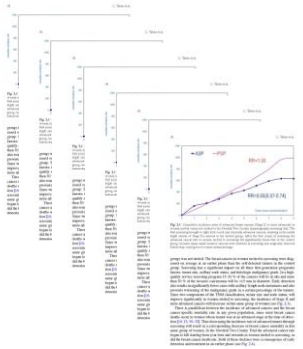
Zakka, C., Shad, R., Chaurasia, A., Dalal, A.R., Kim, J.L., Moor, M., Fong, R., Phillips, C., Alexander, K., Ashley, E., Boyd, J., Boyd, K., Hirsch, K., Langlotz, C., Lee, R., Melia, J., Nelson, J., Sallam, K., Tullis, S., Vogelsong, M.A., Cunningham, J.P., Hiesinger, W., 2024. Almanac — Retrieval-Augmented Language Models for Clinical Medicine. NEJM AI 1, AIoa2300068. https://doi.org/10.1056/AIoa2300068

Lin, W., Chen, J., Mei, J., Coca, A., Byrne, B., n.d. Fine-grained Late-interaction Multi-modal Retrieval for Retrieval Augmented Visual Question Answering.

Breast Cancer Out-of-hospital Management Agent —— Breast-COMA

☐ Intervention S-Agent: MM-BRAG —— Method (In Progress)



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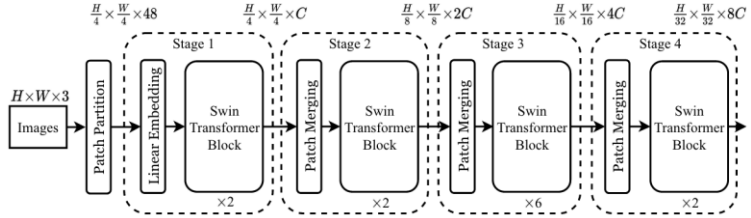

Image Encoder **(Cold)**

Image Embedding

Chunks

Transformer Encoder **(Hot)**

Chunk Embedding

Retrieval

Query Embedding

Query

Dialogue History

Qwen-VL

Multi-modal LLM **(Hot)**

Intervention S-Agent: MM-BRAG —— Result (In Progress)

- Step1: Collecting breast cancer multi-modal knowledge base

Guidelines
Articles
Books
Brochures

→ Text knowledge base (55K, 200 tokens per chunk)

→ Image knowledge base (19K)

- Step2: Collecting breast cancer model evaluation dataset

Public Dataset
Exams
Book

→ Dialogue Dataset (61K) → Human Aligment Evaluation

→ Exam Dataset (0.9K) → Professionality Evaluation

→ BookQA Dataset (4K) → Multi-modal Retriever Evaluation

- Step3: Training and evaluating MM-BRAG (In Progress)

Discussions of Breast-COMA

- **Privacy issue:**

  Using the ChatGPT API resulted in **patients' data being public,** violating patients' privacy rights.

- **Security issue:**

  LLM **lacks professionalism and interpretability**, posing potential security risks to patients.

- **Prompt engineering limitations:**

  Prompt design **lacks clear optimization directions** and relies on human experience.

  Few-shot is extremely sensitive to example selection, distribution, and design.

  It is difficult for LLM to **balance accuracy and cost**.

Tumor Board

Patient Data Extraction & Applications

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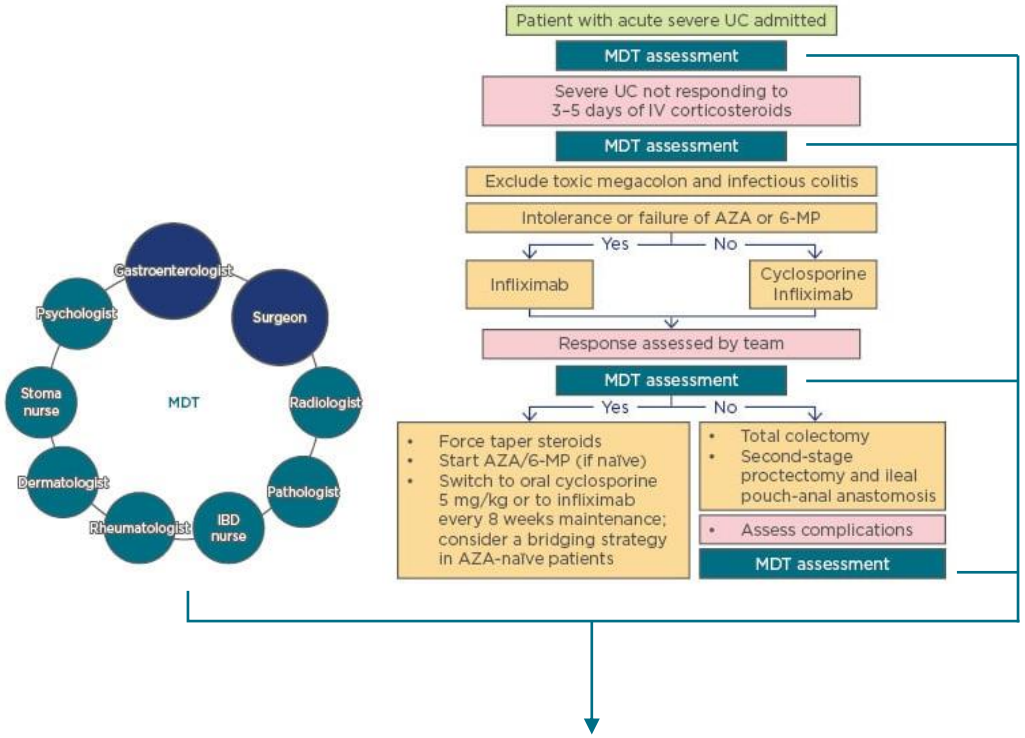
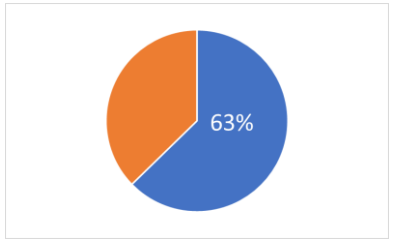
MDT is a core component of precision medicine



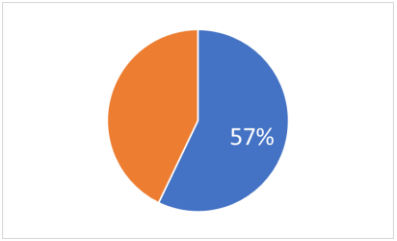
- MDT decision making and evaluation throughout the patient's treatment
- Many-to-one，patient-centered treatment

Key to MDT: integration of patient information

- Patients with **long duration**: requiring a concise and comprehensive summary



Proportion of patients with a disease duration of more than 6 months (40/63)
23.06-23.11, BZ, Breast MDT

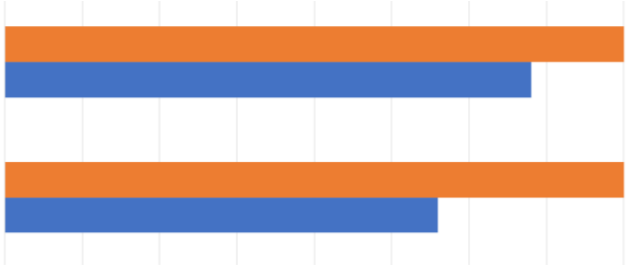


Proportion of patients with a disease duration of more than 6 months (40/63)
23.05-23.11, BZ, Gastroenterology MDT

- Participants with **various background**: requiring a quick common consensus

Patient Timeline could support MDT

"its use replaces the **time-consuming and frustrating** process of searching for various key information within distributed reports"



Feedback before and after application of Patient Timeline (Centre Léon Bérard & ROCHE)

the level of satisfaction （6.8->8）
the confidence in decision-making （5.6->8）

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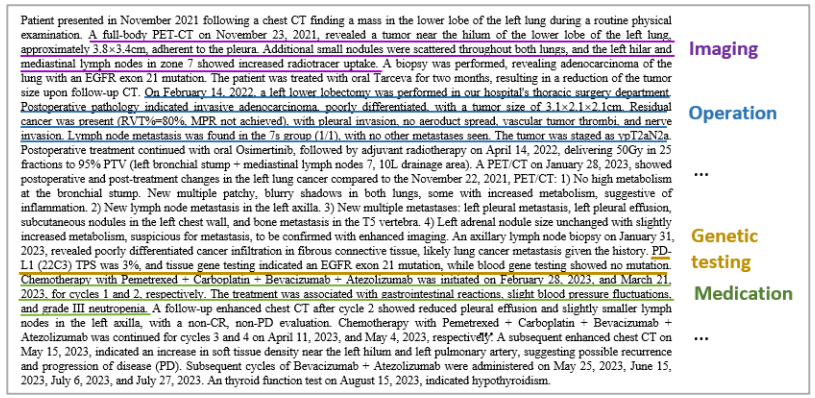
☐ OptimalMEE: Optimizing LLMs for MEE

Task Description

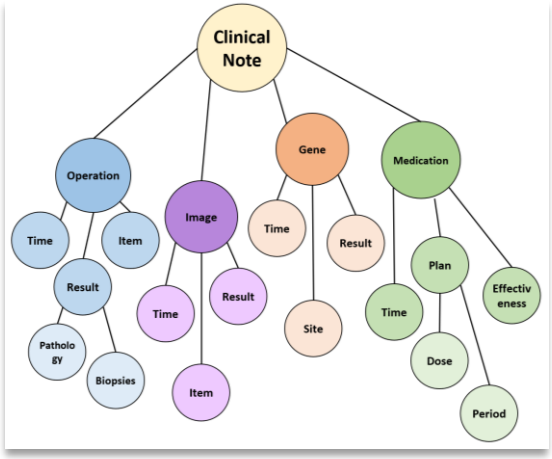
Extract multiple events of different event types from clinical notes

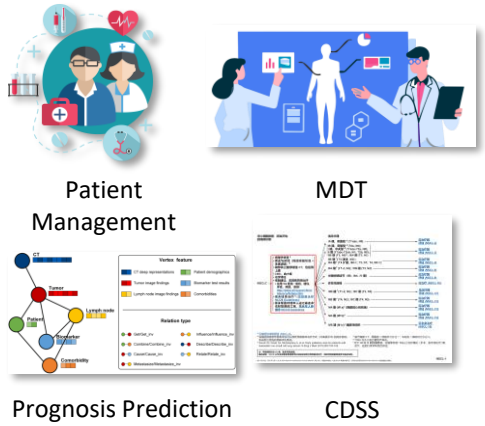


MEE

Event Detection

Element Extraction





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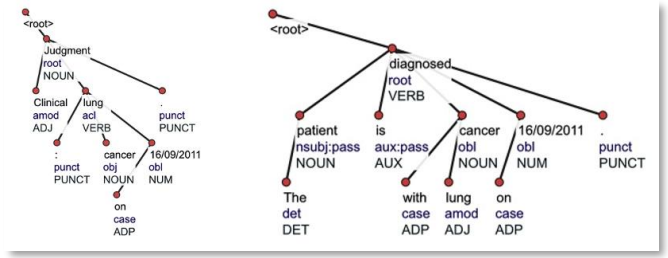
OptimalMEE: Optimizing LLMs for MEE

Traditional Methods

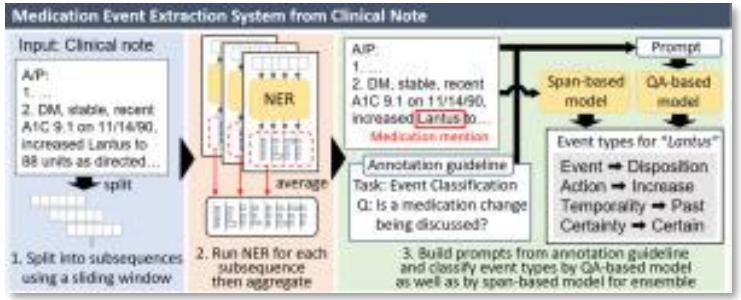
a. Rule-based Methods

- Dictionary, Template, Dependency Tree, …



b. Deep Learning-based Methods

- Subtasks: NER, RE, Classification, …



Challenges

Event Elements Scattering

21 mutation, while blood gene testing showed no mutation. Chemotherapy with Pemetrexed + Carboplatin + Bevacizumab + Atezolizumab was initiated on February 28, 2023, and March 21, 2023, for cycles 1 and 2, respectively. The treatment was associated with gastrointestinal reactions, slight blood pressure fluctuations, and grade III neutropenia. A follow-up enhanced chest CT after cycle 2 showed reduced pleural effusion and slightly smaller lymph nodes in the left axilla, with a non-CR, non-PD evaluation. Chemotherapy with Pemetrexed + Carboplatin +

Event Overlapping

lymph nodes were observed in the mediastinum or at the hilum of both lungs. Bronchoscopy revealed extrinsic compression stenosis in the dorsal segment of the lower lobe of the right lung. Biopsy pathology indicated adenocarcinoma with an EGFR exon 19 mutation. The patient was treated with oral targeted therapy using Icotinib for

Entity Confusion

area). A PET/CT on January 28, 2023, showed postoperative and post-treatment changes in the left lung cancer compared to the PET/CT on November 22, 2021: 1) No high metabolism at the bronchial stump. New multiple patchy,

HOW TO

ACCURATELY identify and correlate event elements

EXHAUSTIVELY extract multiple medical events

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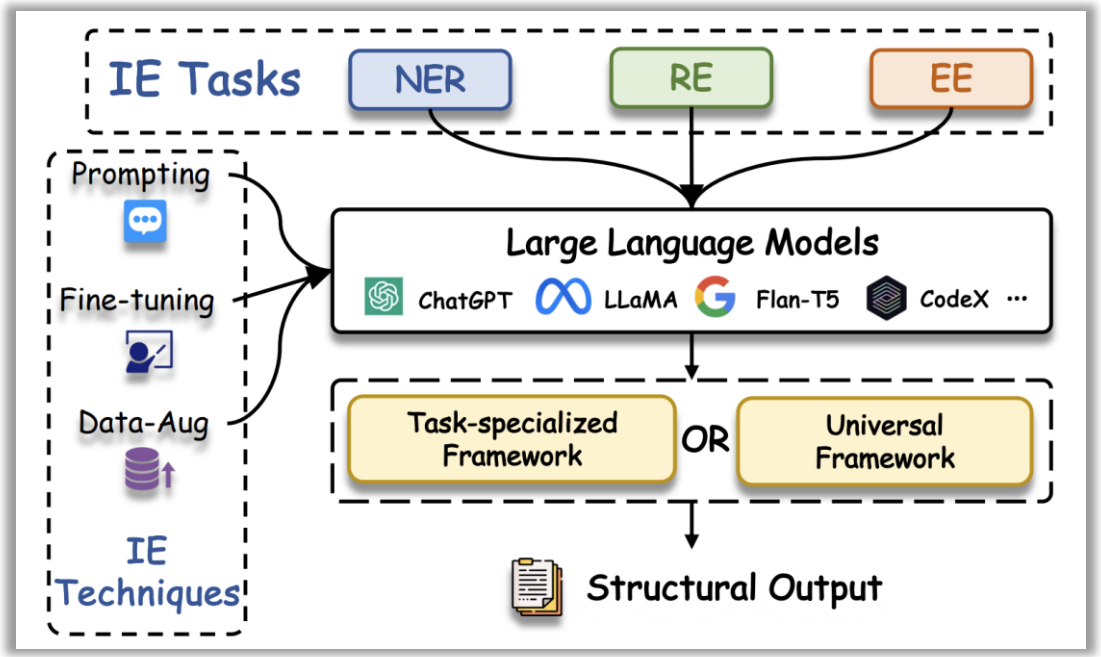
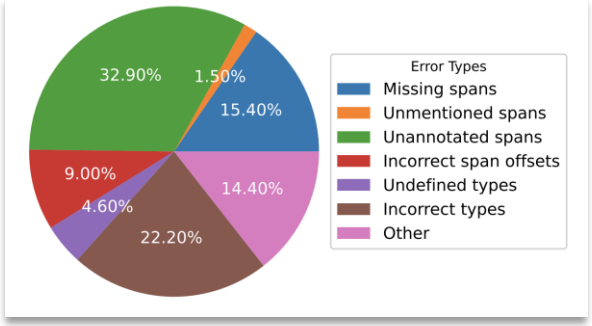
Large Language Models provide a new solution for Information Extraction

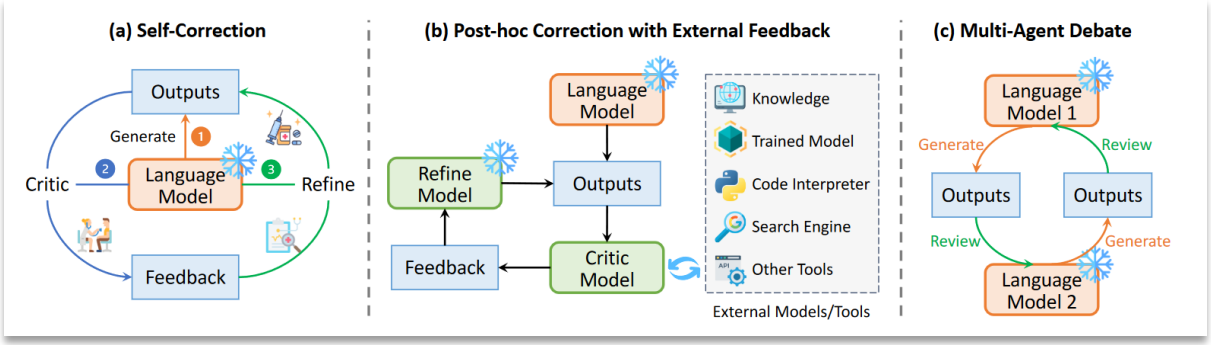
- Powerful ability of semantic understanding: new paradigm for IE



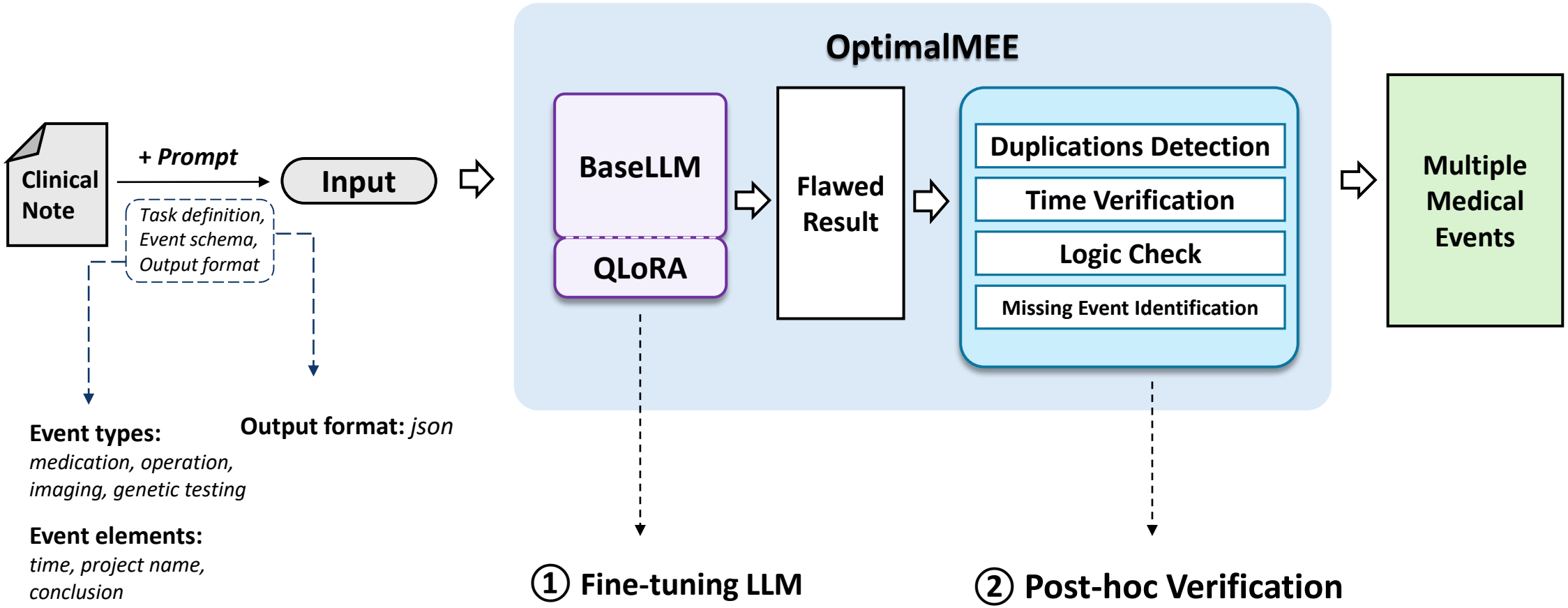
- Generative model: hallucination; need for optimization



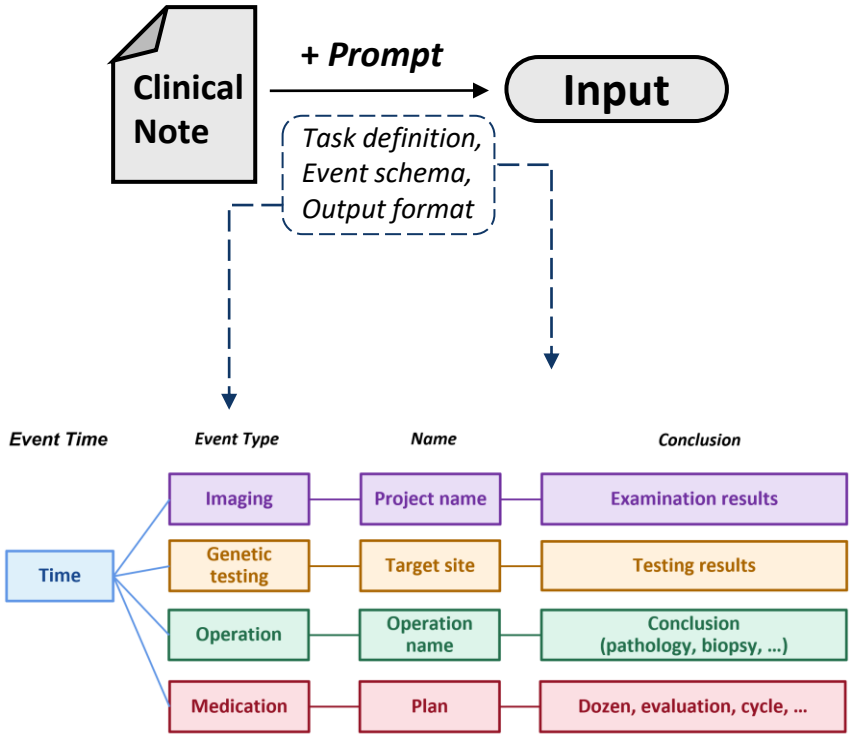
- Post-hoc correction: effective improvement



Optimizing LLMs for MEE through Fine-tuning and Post-hoc Verification



Optimizing LLMs for MEE through Fine-tuning and Post-hoc Verification



Please complete the task of extracting medical event information from the provided clinical note:

The given clinical note includes clinical events belonging to the following four types:

#Imaging, Genetic Testing, Operation, Medication#.

Please return the extracted event time, event type, event project name, and conclusion for the medical event belonging to **#Imaging, Genetic Testing, Operation, Medication#** in **JSON** format:

{"time": "","event_type": "","project": "","conclusion": ""};

if any information item is empty, please fill it with NONE.

Do not create events or times on your own.

The clinical note to extract is as follows:

"""*{text}*"""

...
{
"time": "2014-04",
"event_type": "Imaging",
"project": " chest CT scan",
"conclusion": " a nodule in the anterior segment of the left upper lobe of the lung
"
},
{
"time": "2014-05-19",
"event_type": "Operation",
"project": "left upper lobe wedge resection ",
"conclusion": " squamous cell carcinoma, Grade II-III, in the left upper lobe of the lung"
},
...

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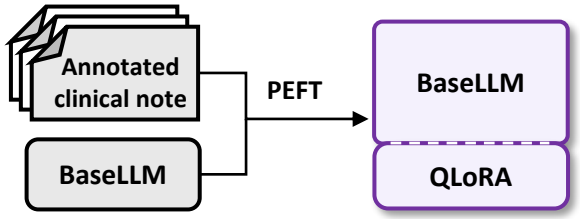
Parameter-efficient fine-tuning (PEFT)



- QLoRA
- Finetuning with limited samples
- Align the model with annotation

MAIN-Dataset: 505 clinical notes on **medical history** of 158 patients with lung cancer from **Hospital A**

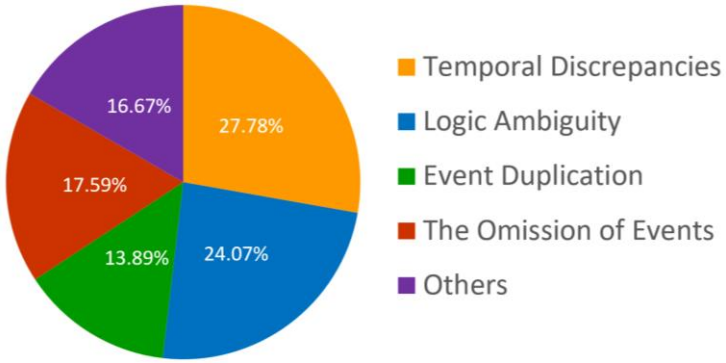
→ PEFT: train, validation, test (100 : 15 : 390)

To simulate the real situation in the clinical domain: labeled data is limited

Statistics	MAIN-Dataset
Total number of clinical notes	505
The average number of events per note	4.21
Maximum number of events in one note	9
Total number of @Imaging	759
Total number of @Operation	340
Total number of @Gene Test	77
Total number of @Medication	952

Post-hoc Verification

- Error analysis on 108 extracted medical events from 50 clinical notes.



- **Temporal Discrepancies**
  Cross-check： **Locating by other elements**
- **Logic Ambiguity**
  Cross-check： **Sequence of *Project & Conclusion***
- **Event Duplication**
  Self-check： **Repetition of three elements**
- **The Omission of Events**
  Chain-LLM： **Detection & re-extraction**

Extracted Event :

{
""time"": ""2015-2"",
""event_type"": ""Imaging"",
""project"": ""Chest CT"",
""conclusion"": ""Left lung lesion enlarged compared to the previous state""
}

X

In January 2015, the patient presented with hemoptysis without obvious triggers. The chest CT showed the left lung lesion enlarged compared to the previous state, which was not diagnosed and treated. In February 2015, the patient was re-admitted due to increased hemoptysis.

Corrected Event:

{
""time"": ""2015-1"",
""event_type"": ""Imaging"",
""project"": ""Chest CT"",
""conclusion"": ""Left lung lesion enlarged compared to the previous state""
}

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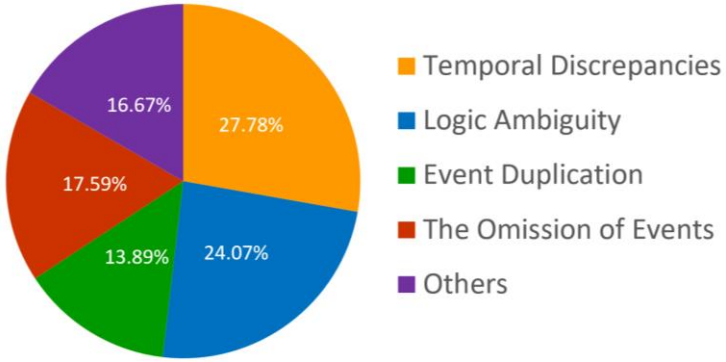
Post-hoc Verification

- Error analysis on 108 extracted medical events from 50 clinical notes.



- Temporal Discrepancies
  Cross-check: **Locating by other elements**
- Logic Ambiguity
  Cross-check: **Sequence of *Project & Conclusion***
- Event Duplication
  Self-check: **Repetition of three elements**
- The Omission of Events
  Chain-LLM: **Detection & re-extraction**

Extracted Event :

{
""time"": ""2013-12"",
""event_type"": ""Imaging"",
""project"": ""Chest CT"",
""conclusion"": "" The condition was stable. ""
}

In November 2012, the chest CT showed the condition was stable. In December 2013, the chest CT suggested the lesion enlarged.

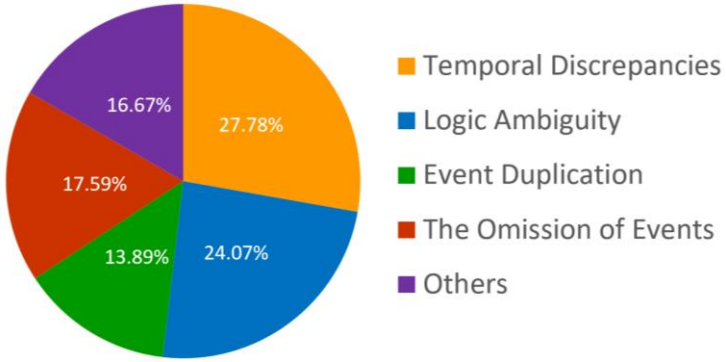
The conclusion is located before the project name.

Corrected Event:

{
"" time "" : "" 2013-12 "",
"" event_type "" : ""Imaging "",
"" project"" : ""Chest CT "",
"" conclusion "" : "" The lesion enlarged.""
}

Post-hoc Verification

- Error analysis on 108 extracted medical events from 50 clinical notes.



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  Cross-check： **Locating by other elements**
- **Logic Ambiguity**
  Cross-check： **Sequence of *Project & Conclusion***
- **Event Duplication**
  Self-check： **Repetition of three elements**
- **The Omission of Events**
  Chain-LLM： **Detection & re-extraction**

Extracted Event 1:

{
""time"": ""2021-08-10"",
""event_type"": "" Imaging"",
""project"": "" Chest CT"",
""conclusion"": "" Bilateral intrapulmonary exudative changes""
}

Extracted Event 2:

{
""time"": ""2021-08-10"",
""event_type"": "" Imaging "",
""project"": "" Chest CT"",
""conclusion"": "" Ground glass shadow shows no reduction""
}

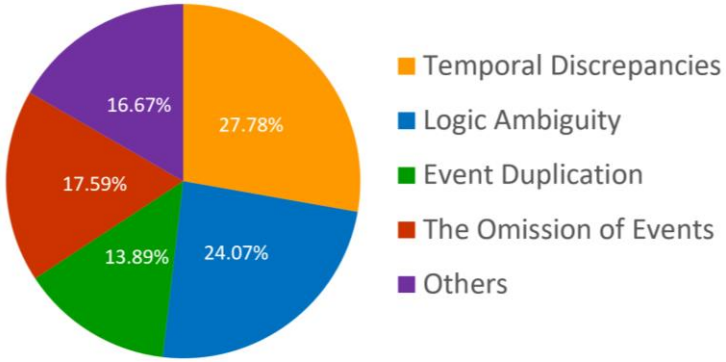
***Self-check*: SAME**

Merged Event:

{
""time"": ""2021-08-10"",
""event_type"": "" Imaging "",
""project"": "" Chest CT"",
""conclusion"": "" Bilateral intrapulmonary exudative changes. Ground glass shadow shows no reduction""
}

Post-hoc Verification

- Error analysis on 108 extracted medical events from 50 clinical notes.



- Temporal Discrepancies
  Cross-check： **Locating by other elements**
- Logic Ambiguity
  Cross-check： **Sequence of *Project & Conclusion***
- Event Duplication
  Self-check： **Repetition of three elements**
- The Omission of Events
  Chain-LLM： **Detection & re-extraction**

Extracted Event:

{
""time"": ""2022-11-10"",
""event_type"": "" Operation "",
""project"": "" puncture biopsy "",
""conclusion"": "" Lung adenocarcinoma, predominantly alveolar, with genetic testing suggesting the EGFR exon 21 L858R mutation""
}

Detection —Yes→ *LLM re-extraction*

Extracted Event 1:

{
""time"": ""2022-11-10"",
""event_type"": "" Operation "",
""project"": "" puncture biopsy "",
""conclusion"": "" Lung adenocarcinoma, predominantly alveolar""
}

Extracted Event 2:

{
""time"": ""2022-11-10"",
""event_type"": "" Genetic Testing "",
""project"": "" Genetic Testing "",
""conclusion"": "" genetic testing suggesting the EGFR exon 21 L858R mutation""
}

Results

Models	MicroF1	Operation			Imaging			Gene Test			Medication		
		Precision	Recall	F1 score	Precision	Recall	F1 score	Precision	Recall	F1 score	Precision	Recall	F1 score
Rule	0.513	0.625	0.714	0.667	0.447	0.514	0.478	0.727	1.000	0.842	0.717	0.223	0.340
ReDEE	0.415	0.250	0.312	0.278	0.727	0.121	0.208	0.188	0.328	0.239	0.400	0.563	0.468
Only-LLM	0.764	0.833	0.917	0.873	0.898	0.567	0.695	0.333	0.474	0.391	0.838	0.754	0.794
5-shot-LLM	0.592	0.944	0.756	0.840	0.739	0.472	0.576	1.000	0.438	0.609	0.902	0.354	0.508
QLoRA-LLM	0.804	0.803	0.770	0.786	0.740	0.767	0.753	0.360	0.450	0.400	0.892	0.851	0.871
OptimalMEE	**0.902**	**1.000**	**0.960**	**0.979**	**0.835**	**0.880**	**0.857**	**0.769**	**1.000**	**0.870**	**0.912**	**0.908**	**0.910**
w/o Duplication	0.890	1.000	0.960	0.979	0.817	0.880	0.847	0.704	0.950	0.809	0.916	0.874	0.895
w/o Omission	0.859	1.000	0.960	0.979	0.759	0.773	0.766	0.682	0.750	0.714	0.916	0.874	0.895
w/o Time	0.844	0.916	0.878	0.897	0.757	0.767	0.762	0.615	0.800	0.696	0.909	0.874	0.891
w/o Logic	0.888	0.930	0.892	0.910	0.818	0.862	0.840	0.769	1.000	0.870	0.919	0.905	0.912
Generalization	0.809	1.000	0.778	0.875	0.902	0.873	0.887	1.000	0.700	0.824	0.846	0.647	0.733

Generalization-Dataset: 16 clinical notes on **discharge summary** of 16 patients with lung cancer from **Hospital B**

- **The large language model**
  shows greater efficiency.
- **The PEFT method**
  aligns the model with limited annotation.
- **The post-hoc verifications**
  trace back and refine the output.

Patient Data Mining & Applications —— Tumor Board

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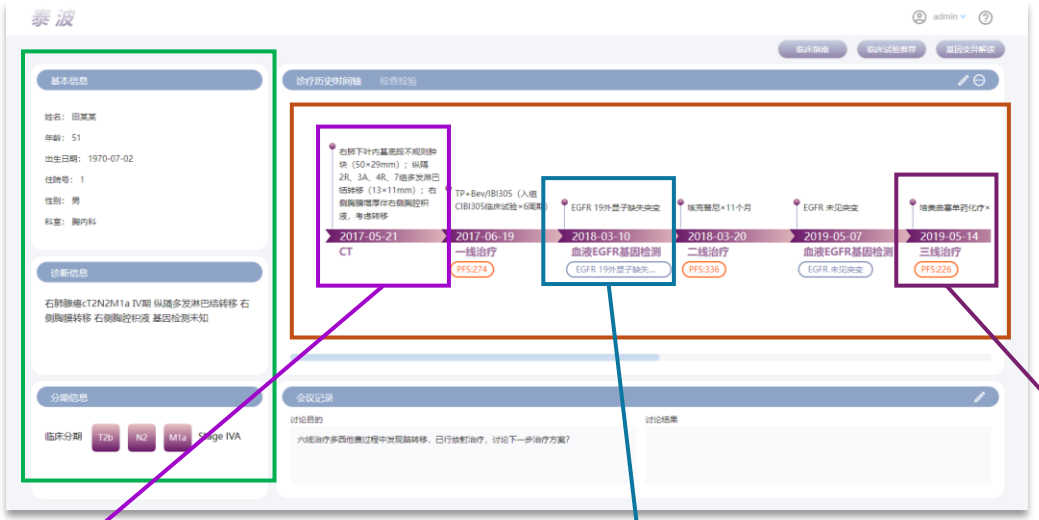
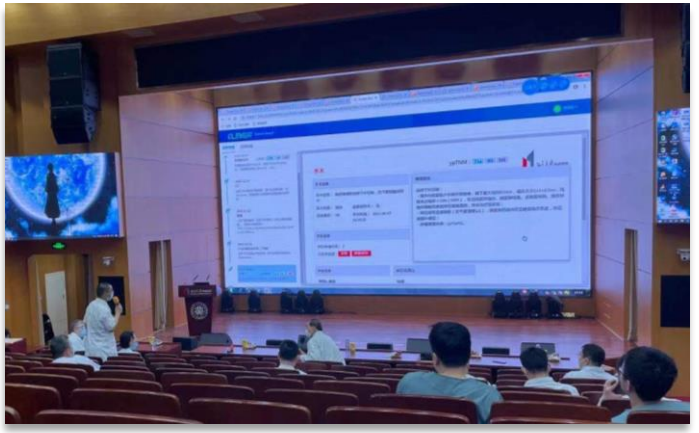
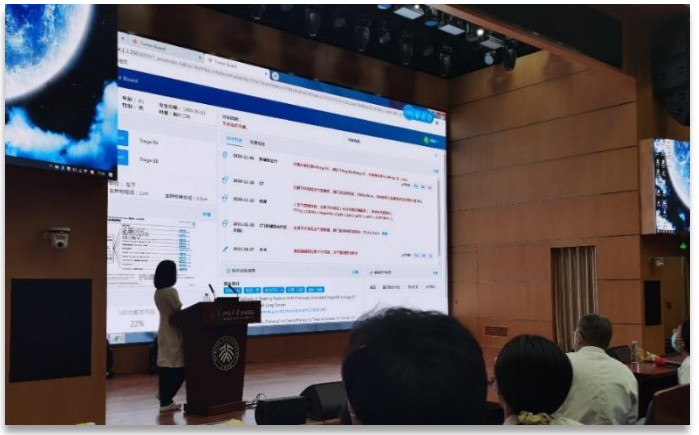
Application: TumorBoard

- Basic
  - Basic Info.
  - Diagnosis
  - Staging



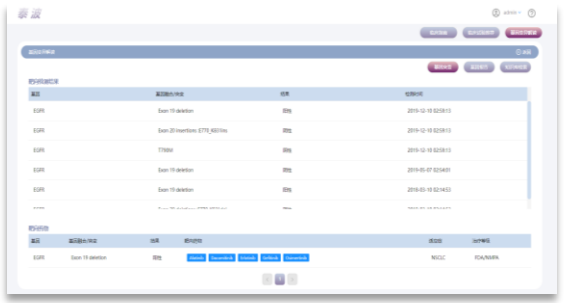
- Timeline Navigator
  - 1/ Visible OptimalMEE
  - 2/ Multi-duration view
  - 3/ Quick expert consensus



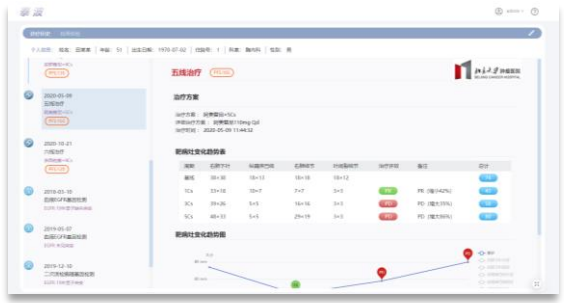


- CT Examination

- Genetic results parsing



- Medication



Discussion & Conclusion

- Compared with traditional methods, the LLM-based Optimal MEE shows **low reliance on labor annotation**.
- The proposed four-step post-hoc verification could effectively improve the **accuracy** of the extracted events.
- The Optimal MEE provides **a solution** to information extraction in the clinical domain and lays the groundwork for further applications.

LIMITATIONS:

- **More generalizability evaluations** on wider datasets are needed
- High cost on **computational recourse**: GPU-based

IN THE FUTURE:

- Expansion of **data sources & broader needs**:
  interaction with multi-dimension data and multiple clinical notes

Thank you!