# Trustworthy Machine Learning for Healthcare

Stanford CS329T Fall 2023



Monica Agrawal Divya Gopinath

# Electronic Health Records (EHRs)

EHRs contain a wealth of patient data. And they have seen rapid adoption in the US:



	Hospitals with EHRs	<b>Office Physicians with EHRs</b>
2011	28%	34%
2021	96%	78%

Via https://www.healthit.gov/data/quickstats/national-trends-hospital-and-physician-adoption-electronic-health-records

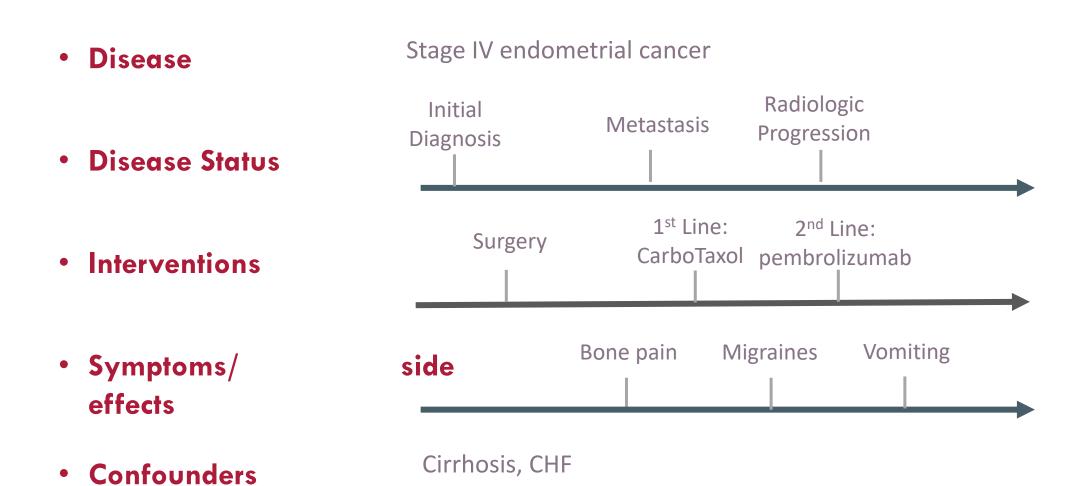
# Potential of EHRs

**Real-world evidence in EHRs** can facilitate personalized medicine. Clinical trials can't answer every question:

- What drug would lead to the **best outcome** for **this patient**?
- What is the patient's expected **disease trajectory**?
- What adverse events might come from this drug combination?



# Variables of Interest





Many of these variables are not in structured data, but trapped in **messy**, **free-text** clinical notes:



Efficiency of documentation

Splintered

care

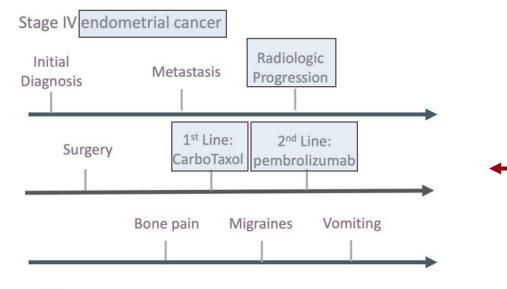
Deviation from original care plan

# How messy can notes be?

final for the second sec

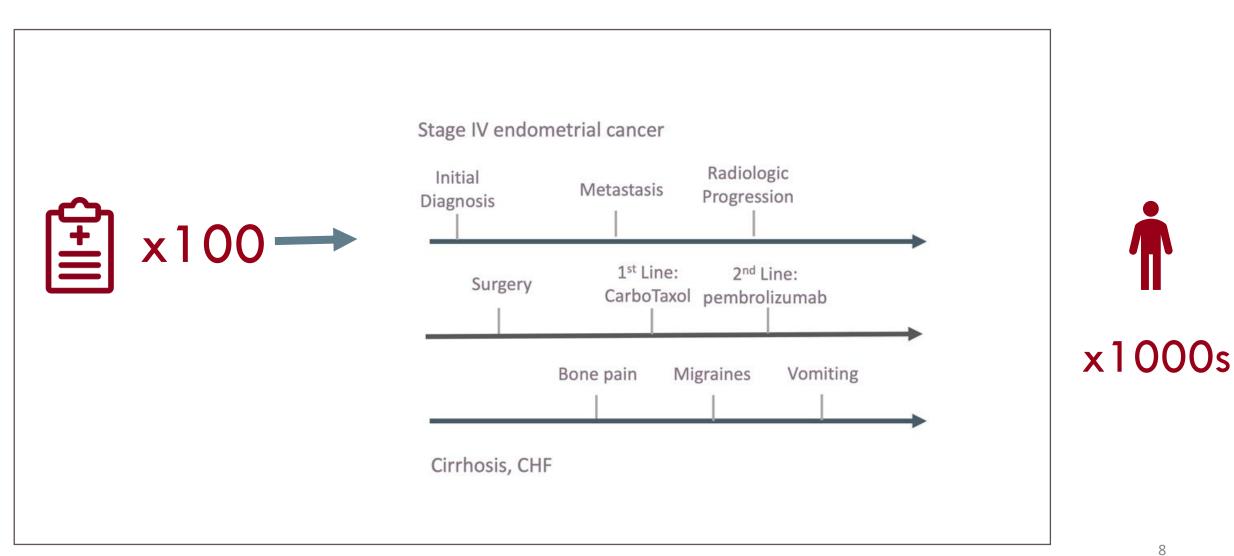
# Deciphering clinical text

"...pt progressed after 5 mos of CarboTaxo for EC. Will dc and discuss pembro..." "Patient progressed after 5 months of carboplatin/paclitaxel for endometrial cancer. Will discontinue for pembrolizumab"

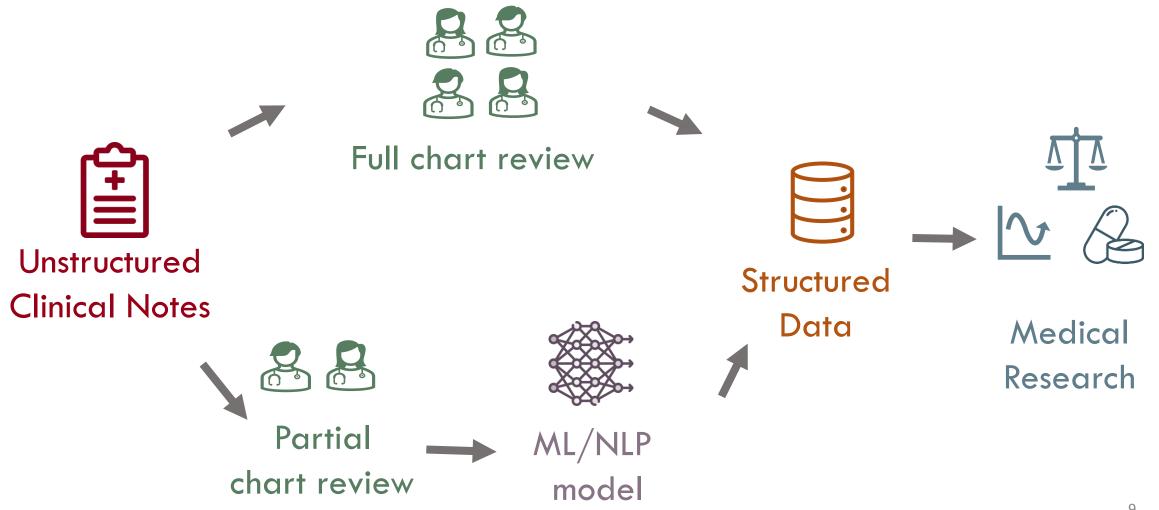


**Medication** Carboplatin + pembrolizumab paclitaxel **Endometrial Endometrial** Reason cancer cancer Status discontinued starting (implicit) **Reason for** progression Stop **Duration** Past 5 months

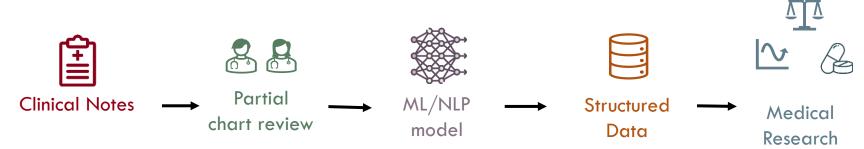
# A daunting task



### Status quo for information extraction



## Status quo for information extraction



	Variable	# of Training Data	_		
<u>Agrawal</u> , Adams, Nussbaum, Birnbaum. Machine Learning for Health ( <b>ML4H</b> ) NeurIPS Workshop, 2018.	Start/stop dates for oral medications	6,000+	] ]		Can recreate survival analyses
Birnbaum, Nussbaum, Seidl-Rathkopf, <u>Agrawal</u> , et al. arXiv, 2020.	Binary metastasis	17,000+		-	achieved by full chart review
Alkaitis, <u>Agrawal</u> , Riely, Razavi, Sontag. JCO Clinical Cancer Informatics, 2021.	Binary reason for stopping treatment	8,000+ and 1500+	J		

The partial chart review is still a huge bottleneck:

Varia	ble +
setting	specific

Large amount of annotation time

Difficult to share across institutions

# **Other Uses**

Central problem in EHRs (and in health data) is **information extraction**. How do we extract semi-structured insights from clinical data, that is:

- Customized to each use case
- Accurate
- Trustworthy, with provenance back to the original text
- Fast
- Cheaper
- •

### This is useful **across healthcare**:

- Real world evidence
- Clinical trial matching

## **Other Uses**

#### Information extraction is a core problem across all of healthcare.

**Clinical trial matching** Given clinical trial criteria, how can we find patients that are eligible? **Transfers and continuity** How can we concisely summarize a patient's history for a new doctor? Quality of care

How do we ensure that patients are receiving highquality care across institutions?

**Coding & billing** How can a hospital efficiently and accurately bill for the care delivered? Patient understanding How can we enable patients to understand their own medical record? **Decision support** 

How can we aid clinicians to administer the best possible care?

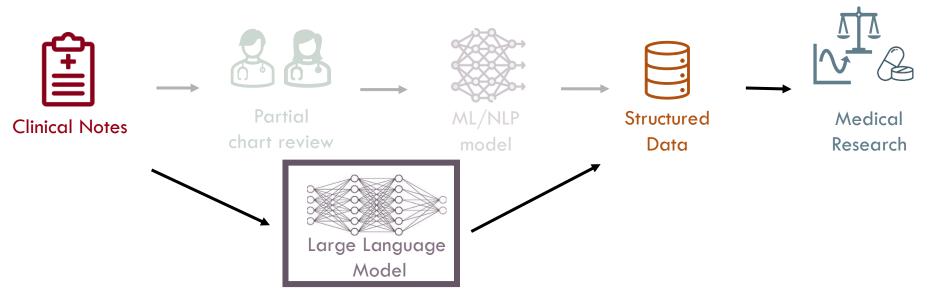
# Trustworthy ML for healthcare.

- Accuracy is paramount "good enough" doesn't cut it.
  - Long tail in clinical data (across subspecialties, patients, providers, presentations, ...)
  - Context is key, "d/c" could mean discharge in an ED note but discontinue in a medication list.
- Provenance/justification is key need to point back to the source to explain every decision.
- Humans need to be in the loop, but clinical expertise != ML expertise.

# Outline

- How can we leverage large language models to help in healthcare information extraction?
- How can we incentivize cleaner clinical documentation?
- How can human-Al teams contribute?

### Large Language Models for Clinical Text



### Large Language Models are Few-Shot Clinical Information Extractors

Empirical Methods in Natural Language Processing (EMNLP), 2022.

Monica Agrawal, Stefan Hegselmann, Hunter Lang, Yoon Kim, David Sontag

# Can large language models help us structure clinical data?

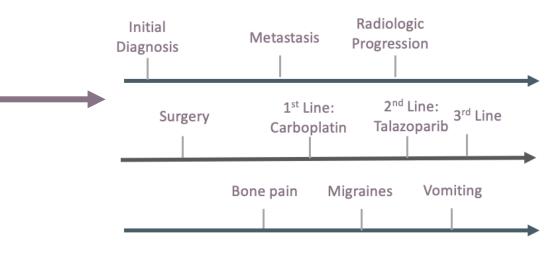


The Drum

<u>Ryan Reynolds enlists</u>
<u>AI-powered ChatGPT in</u>
<u>'mildly terrifying' new</u>
<u>Mint Mobile ad</u>

1 day ago

Triple-negative breast cancer, invasive ductal carcinoma



# Challenge #1: Clinical Text Availability

Most existing labeled data sets are under **data use agreements** and can't be sent over APIs directly, without special agreements

Benchmarking with existing publicly labels could suffer from *label leakage* 

# **Creation of Benchmark Datasets**

We re-annotate the existing publicly available CASI dataset to release **three new** few-shot extraction **datasets**:

- Clinical coreference resolution
- Medication + status classification
- Medication + attribute relation extraction

Each contains 5 examples for development (e.g. prompt design) and 100 examples for test

# Challenge #2: Obtaining structured, evidence-backed output

**Goal:** List medications, and their reason, dosage, and frequency, as available.

Input: "[...] 500mg of metformin b.i.d. [...]"

Expected completion:

"Medication: metformin Dosage: 500mg Frequency: b.i.d."

Issue #1: Narrative format

Issue #2:

Hallucinations

**Reality:** 

"The medication taken is metformin for the reason of diabetes at a dosage of 500mg..."

19

# Encouraging quoted structured output

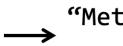
### Naive

#### Zero-shot prompt:

approach:

Input: 500 mg of metformin b.i.d. Prompt: Label medications. Include dosage, reason, ... The medication taken is metformin for...

Complex post-processing (resolver) of LM output



# Encouraging quoted structured output

Our

#### **One-shot quoted example + guidance:**

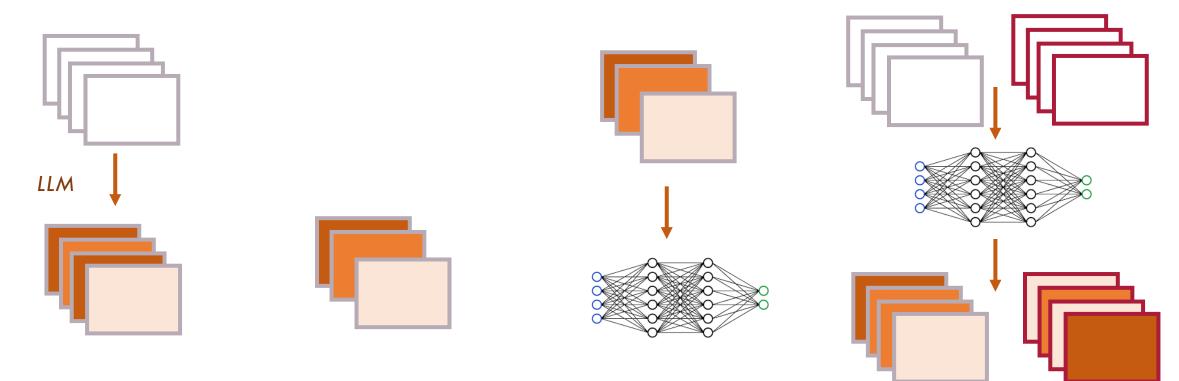
approach:

Input: He takes ibuprofen daily [...].
Prompt: Label medications. Include dosage, reason, ...
-medication: "statin", frequency: "daily"
Input: 500 mg of metformin b.i.d.[...].
Prompt: Label medications. Include dosage, reason, ...
-medication: "metformin", dosage: "500mg", "frequency"

# Challenge #3: Deployability

- HIPAA compliance\*
- Unwieldy size of models
- Model sensitivity to prompt wording
- Model miscalibration and overconfidence
  - When available

# Treating LLM Outputs as Weak Labels



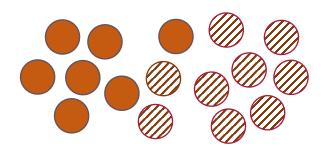
Step 1: Get LLM outputs on publicly available data

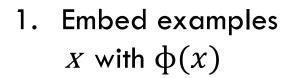
Step 2: Identify confident outputs\*

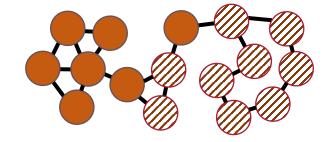
Step 3: Train smaller model on confident outputs Step 4: Run smaller model on same or new data sets

## Selection of confident outputs

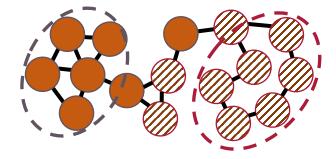
Deep models are often wildly overconfident and miscalibrated – how can we determine when to trust their outputs?







2. Make K-Nearest Neighbors graph in  $\varphi$ 



3. Select examples from the most homogeneous regions

## Selection of confident outputs

We use the cut statistic to define ``most homogeneous regions"

$$\int \frac{J_u - \mu_u}{\sigma}$$

n

$$\sum_{v \in N(u)} w_{uv} I_{uv} \quad (1 - \hat{P}_{\hat{y}_u}) \sum_{v \in N(u)} w_{uv}$$
  
(Weighted) sum of alike Expected (weighted) sum of  
neighbors alike neighbors, if normal

### **Results: Clinical Acronym Disambiguation**

*Input:* Clinical Text Snippet + Overloaded Acronym *Output:* Multiple-choice Expansion of Acronym

Algorithm	CASI Acc.	CASI Macro F1	_
Random	0.31	0.23	_
Most Common	0.79	0.28	
BERT (from Adams et al. (2020))	0.42	0.23	
ELMo (from Adams et al. (2020))	0.55	0.38	Zero-shot LM
LMC (from Adams et al. (2020))	0.71	0.51	baseline trained on MIMIC data
GPT-3 edit + R: 0-shot	0.86	0.69	
GPT-3 edit + $R$ + weak sup	0.90	0.76	_

### **Results: Clinical Acronym Disambiguation**

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GPT-3 edit + R: 0-shot	0.86	0.69	*	*
GPT-3 edit + R + weak sup	0.90	0.76	0.78	0.69

## **Example: Medication Information Parsing**

*Input:* Clinical text snippet *Output:* Medications, dosage, route, frequency, reason, duration

> Baseline supervised on different clinical dataset

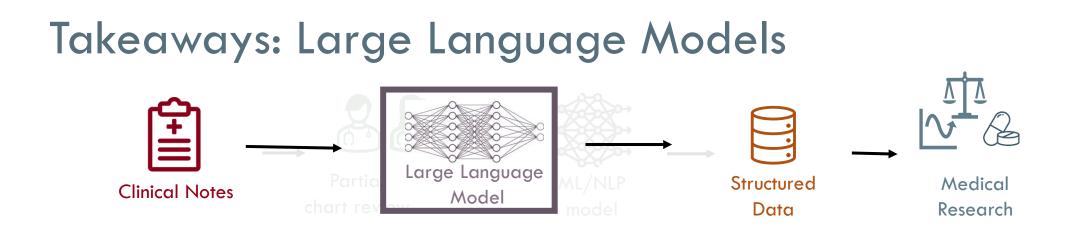
Subtask	Algorithm	Medication	Dosage	Route	Frequency	Reason	Duration
Token-level	PubMedBERT + CRF (Sup.)	0.82	0.92	0.77	0.76	0.35	0.57
	GPT-3 + R: 1-shot	0.85	0.92	0.87	0.91	0.38	0.52

OpenAl Engines: text-davinci-edit&001

### Bonus: what might these models be learning from?

We classified sources of colloquial clinical jargon ("fx", "fracture") in a subset of Common Crawl data

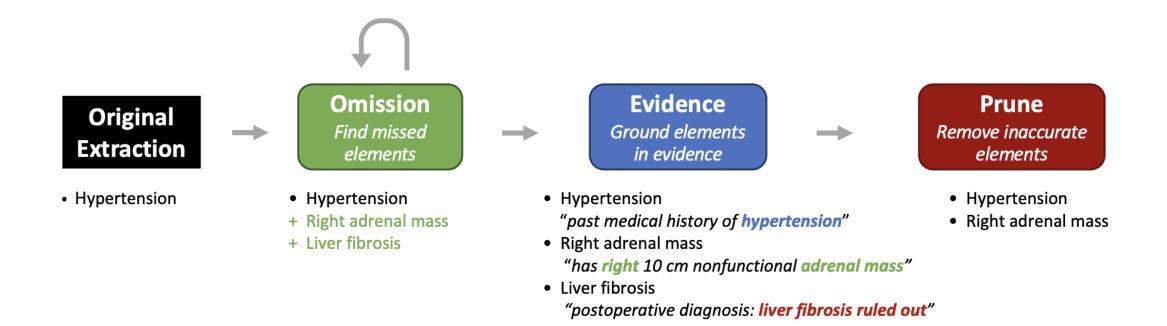
Source	Median %	43% of mentions
Research Articles	16%	for qhs +
Patient Health Resources	15%	bedtime
Commercial Health	14%	
Clinician Forums	13%	41% of
Patient Blogs + Forums	6%	mentions for carbo +
		carboplatin



The reasoning capabilities of and medical knowledge within LLMs could transform clinical information extraction

We developed further techniques to boost model performance, as naïve application of these models is insufficient

# Follow-up: Increasing Reliability



#### Self-verification Improves Few-Shot Clinical Information Extraction

Zelalem Gero et al, IMLH 2023.

### Case Study: LLMs for clinical trial matching

Core problem: how do we match patients to trials?

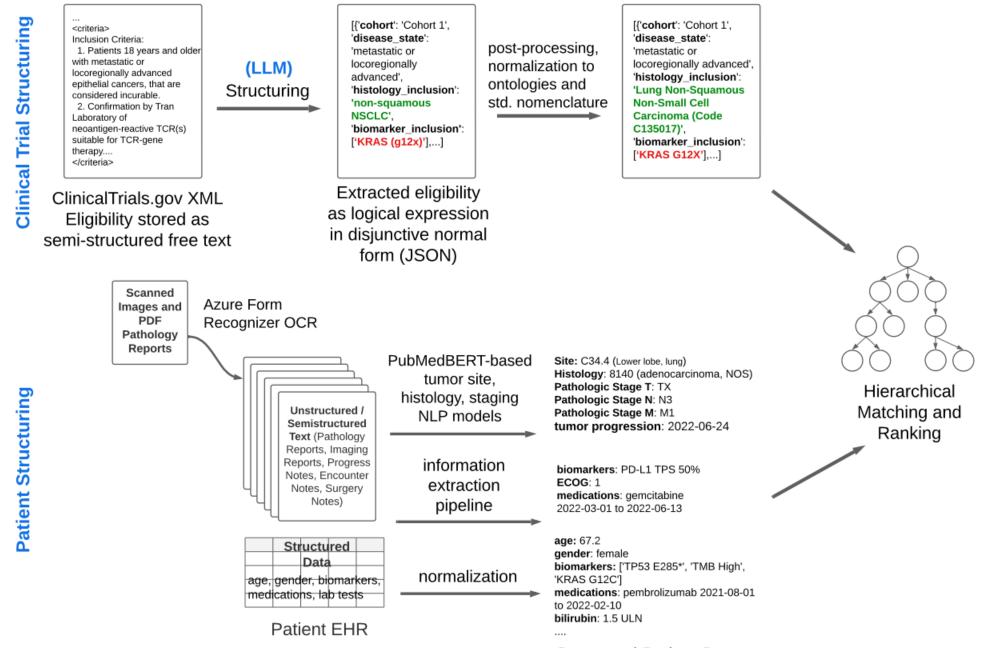


#### Inclusion Criteria:

-Histologically or cytologically confirmed high-grade neuroendocrine tumor that has progressed on first line therapy, excluding small cell lung cancer (SCLC). High grade includes any neuroendocrine neoplasm with a Ki-67 of >=20% or with mitotic count of more than 20 mitoses per high power field or any poorly differentiated neoplasm or any neoplasm lacking these that is deemed high grade by pathology consensus, based on other markers (necrosis or IHC demonstrating p53 or RB mutation).

Scaling Clinical Trial Matching Using Large Language Models: A Case Study in Oncology

Cliff Wong et al, MLHC 2023.

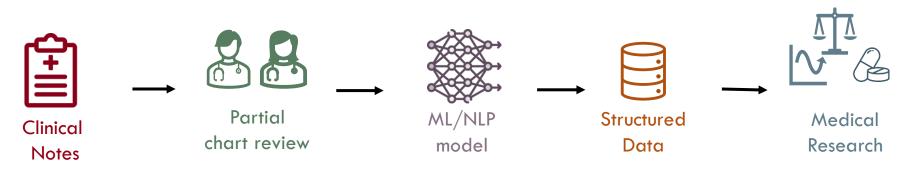


Structured Patient Data

# Outline

- How can we leverage large language models?
- How can we incentivize cleaner clinical documentation?
- How can human-Al teams contribute?

### Re-imagining clinical documentation



#### Fast, Structured Clinical Documentation via Contextual Autocomplete

Machine Learning for Healthcare (MLHC), 2020

Divya Gopinath, Monica Agrawal, Luke Murray, Steven Horng, David Karger, David Sontag

#### MedKnowts: Unified Documentation and Information Retrieval for EHRs

User Interface and Software Technology (**UIST**), 2021 Luke Murray, Divya Gopinath, Monica Agrawal, Steven Horng, David Sontag, David Karger

#### Conceptualizing ML for Dynamic Information Retrieval of EHR notes

Machine Learning for Healthcare (MLHC), 2023

Sharon Jiang, Shannon Shen, Monica Agrawal, Barbara Lam, Nicholas Kurtzman, Steven Horng, David Karger, David Sontag,

### Re-imagining clinical documentation



#### What if we could collect high-quality clinical data at the point of care, without increasing physician burnout?

#### Fast, Structured Clinical Documentation via Contextual Autocomplete

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Sharon Jiang, Shannon Shen, Monica Agrawal, Barbara Lam, Nicholas Kurtzman, Steven Horng, David Karger, David Sontag,

# EHRs have usability issues

## WHY DOCTORS HATE THEIR COMPUTERS

Digitization promises to make medical care easier and more efficient. But are screens coming between doctors and patients?

By Atul Gawande

November 5, 2018

Issue #1: Time for Data Entry

Issue #2: Time for Information Retrieval

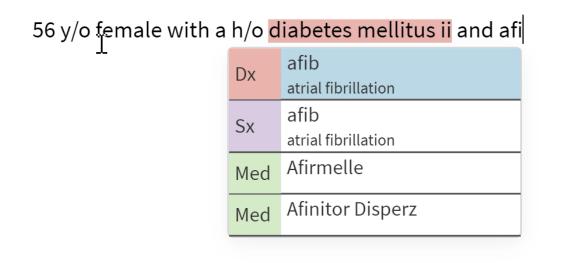
# Challenge of Data Entry

#### Linguistic Characteristics of Medical Notes

Many of the entries on the medical records are in the form of notes which are neither complete sentences nor single word entries, but linguistic strings of an intermediate type, which we will hereafter call fragments. Fragments are a compressed type of linguistic material resulting from various transformations which have the effect of making linguistic strings shorter by reducing or deleting material. The writer of these stretches of material must make his entries brief, in order to save time and effort, but also make them informative and unambiguous. For this reason the deleted material has to be easily recover-

Anderson et al , Grammatical Compression in Notes and Records, ACL 1975<sup>38</sup>

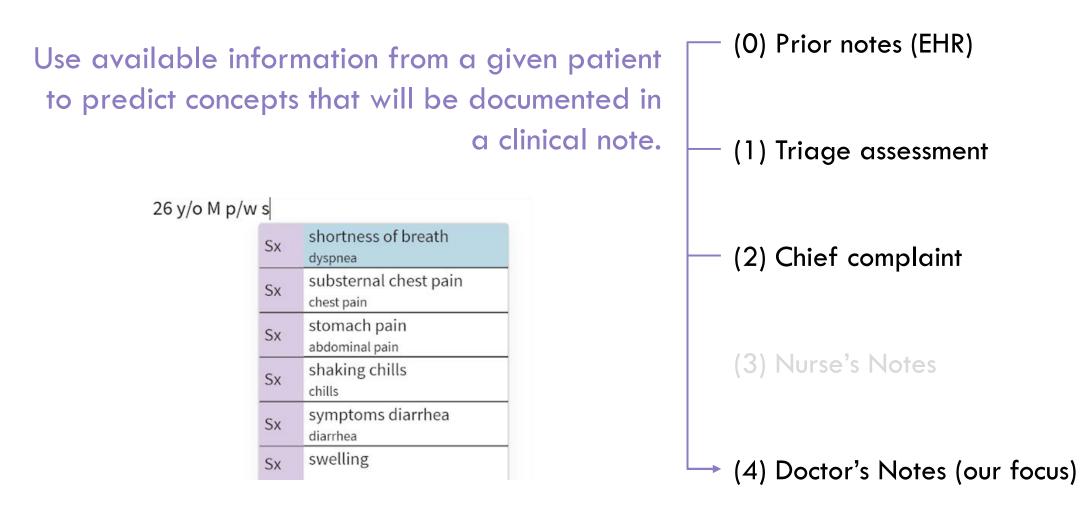
# Solution: Streamlining Data Entry



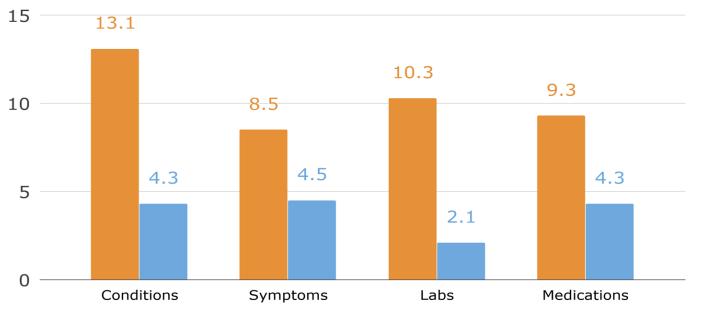
#### **Contextual autocomplete**

- Personalized to each patient
- Automatically normalizes concepts to ontologies as the note is being written
- Decreases documentation burden with fewer keystrokes

# Sources of supervision



# We dramatically reduced the **keystroke burden** of data entry in a **live setting**.



Keystroke Burden by Concept Type

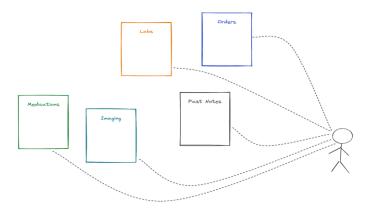


Current EHRs Live Contextual Autocomplete (in BIDMC's ED)

#### **Challenge of Information Retrieval**

Doctors have to manually synthesize past data into data driven narratives

- Past Labs
- Past Medications
- Relevant Notes
- Relevant Imaging





Solution: Streamlining Information Retrieval

HPI	Edit Lock: yours	Overview	Мар	All
33 y/o F who pres	ents with chills (no	0 / 01 / 10 //		
fever, no nausea,	+fatigue ). She has a			
history of vaginal	bleeding, s/p			
hysterectomy a	nd oophorectomy).			
She also has a h/o				
РМН				
Medications				
FH				
SH				
	]			
ROS				

Solution: Streamlining Information Retrieval

HPI 33 y/o F who present fever, no nausea, +fat	s with chills (no	erview Map	All
history of <mark>vaginal ble</mark>	eding, s/p At	fib :	$\overline{Condition} \times$
hysterectomy <sup>®</sup> and c She also has a h/o <mark>af</mark> i		eds etoprolol tartrate	
PMH		itals ulse	
Medications	20 Ac	MR 016-06- ctive Medication list as rescription DICLOFENA	s/p Mechanical Fall s of : Medications - AC SODIUM [VOLTAREN] -
FH	20	016-06	. Apply thin film of gel to s/p Mechanical Fall
SH	an	-	atient is on chronic al fibrillation. She has been ast. Apixaban is not covered
ROS	Sh ho	ne states two days ago olding her warfarin an INR was 3.0.	s/p Mechanical Fall INR was 4.6. She has been d yesterday at

# Filling in Redundant Information

HPI	Edit Lock: yours
93 y/o F p/w nonproductive cough ,	fever , nausea , but no chills . She has a history of
an <mark>oophorectomy</mark> and type 2 diabet	es . She has mild <mark>hypertension</mark> and is on Coumadin
to treat this.	
РМН	
Medications	
FH	
SH	
ROS	

# Filling in Redundant Information

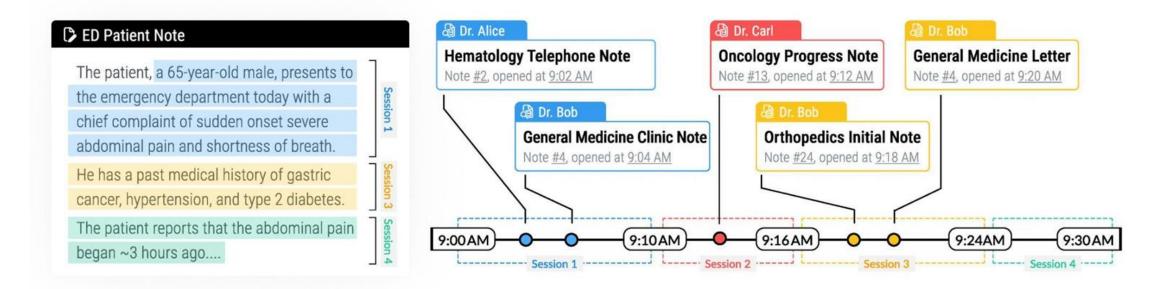
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to treat this.	
РМН	
oophorectomy, type 2 diabetes, hypertensio	n
Medications	
Coumadin	
FH	
SH	
ROS	
Constitutional:, fever, nausea, no chills 📃	
Head / Eyes: No diplopia	
ENT: no earache	
Resp:, nonproductive cough	
Cards: No chest pain	
Abd: No abdominal pain	

# **Deployment + Evaluation**

- We designed MedKnowts in a year-long iterative prototyping process with a clinician and their scribes across 1185 patients.
- We evaluated MedKnowts in a month-long deployment with four scribes across 234 patients.
- In a user questionnaire:
  - Would use frequently median 5/5
  - Quick learning curve median 5/5
  - Easy to use median 4.5/5

# Newer direction: leveraging EHR audit logs

We can use EHR audit logs to characterize the note writing process

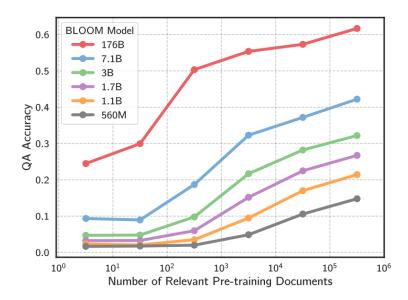


We can also use the signal from those audit logs to learn how to auto-surface notes (AUC of 0.963).

# With the advent of LLMs, what changes?

Bootstrapping/zero-shot performance at information extraction is **significantly better than before**, but still some critical gaps:

LLMs still struggle with the long tail:



*Figure 1.* Language models struggle to capture the long-tail of information on the web. Above, we plot accuracy for the BLOOM model family on TriviaQA as a function of how many documents in the model's pre-training data are relevant to each question.

LLMs can be <u>"distracted" by irrelevant</u> <u>information</u> in ways that traditional methods may not be:

#### **Original Problem**

Jessica is six years older than Claire. In two years, Claire will be 20 years old. How old is Jessica now? **Modified Problem** 

Jessica is six years older than Claire. In two years, Claire will be 20 years old. <u>Twenty years ago, the age of</u> <u>Claire's father is 3 times of Jessica's age</u>. How old is Jessica now?

**Standard Answer** 24

## Takeaways: Re-imagining documentation



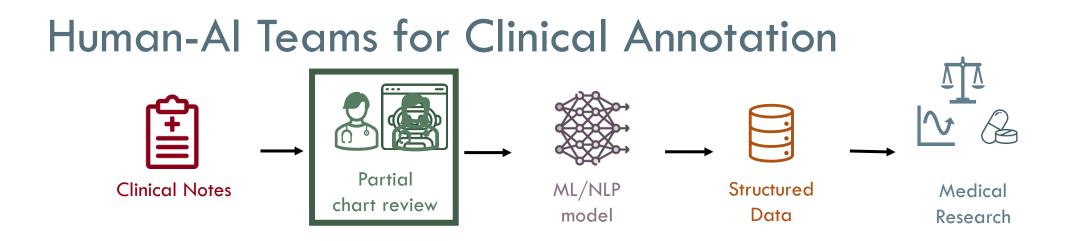
#### Via a redesign of the EHR, it is possible to simultaneously:

- Obtain cleaner data as a natural byproduct
- Reduce physician workload

These features can be integrated into live workflows via careful opt-in design

# Outline

- How can we leverage large language models?
- How can we incentivize cleaner clinical documentation?
- How can human-AI teams contribute?



#### Assessing the Impact of Automated Suggestions on Decision Making

Conference on Human Factors in Computing Systems (CHI), 2021.

Ariel Levy\*, Monica Agrawal\*, Arvind Satyanarayan, David Sontag

#### Clinical concept recognition

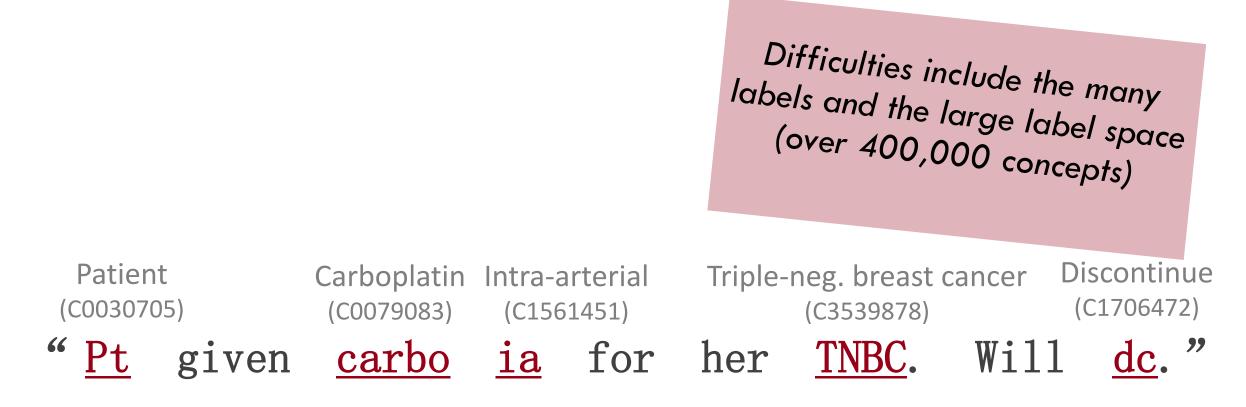
#### "Pt given carbo ia for her TNBC. Will dc."

## Clinical concept recognition

D/C current? Prothrombin Patient? discontinue? time? Carbodome? Intra-arterial? carbo ia for 66 TNBC. Will her Pt given dc. Physical Intra-articular? Carboplatin? discharge? therapist? Doctor of

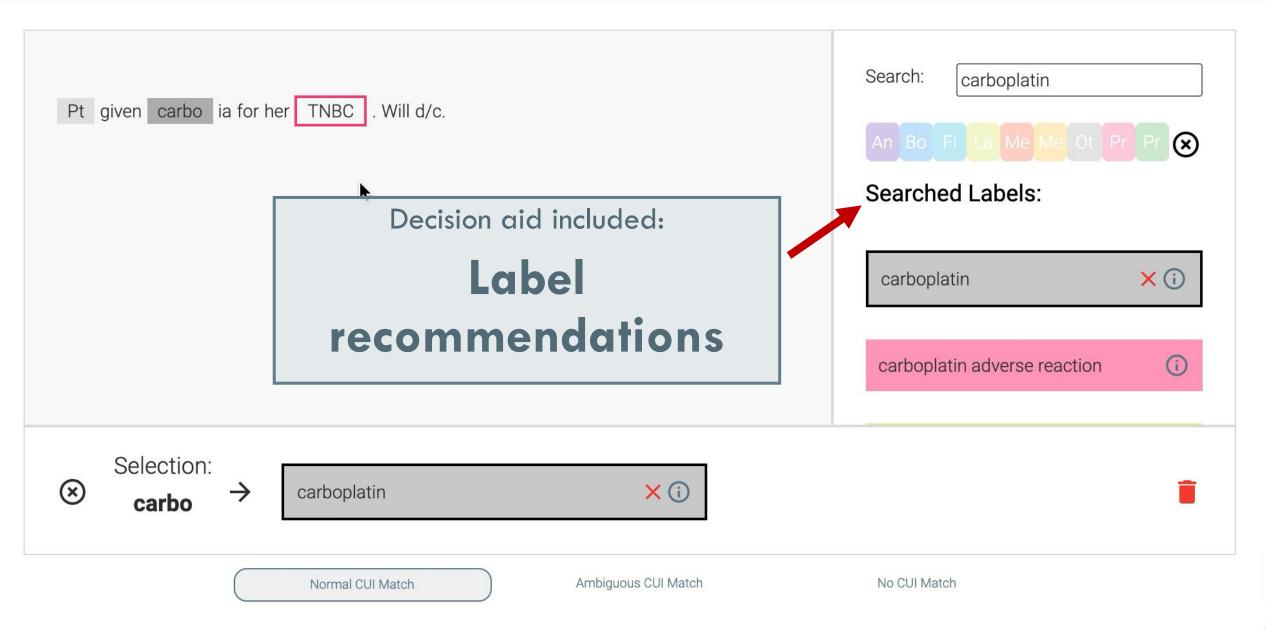
Chiropractic?

### Clinical concept recognition

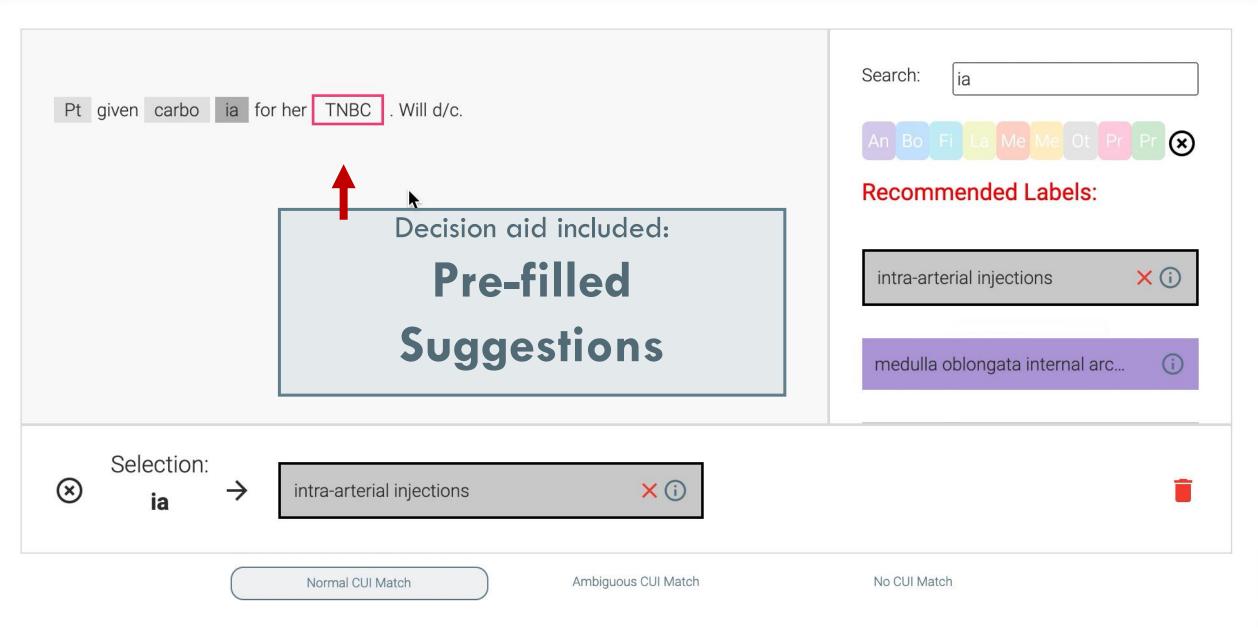


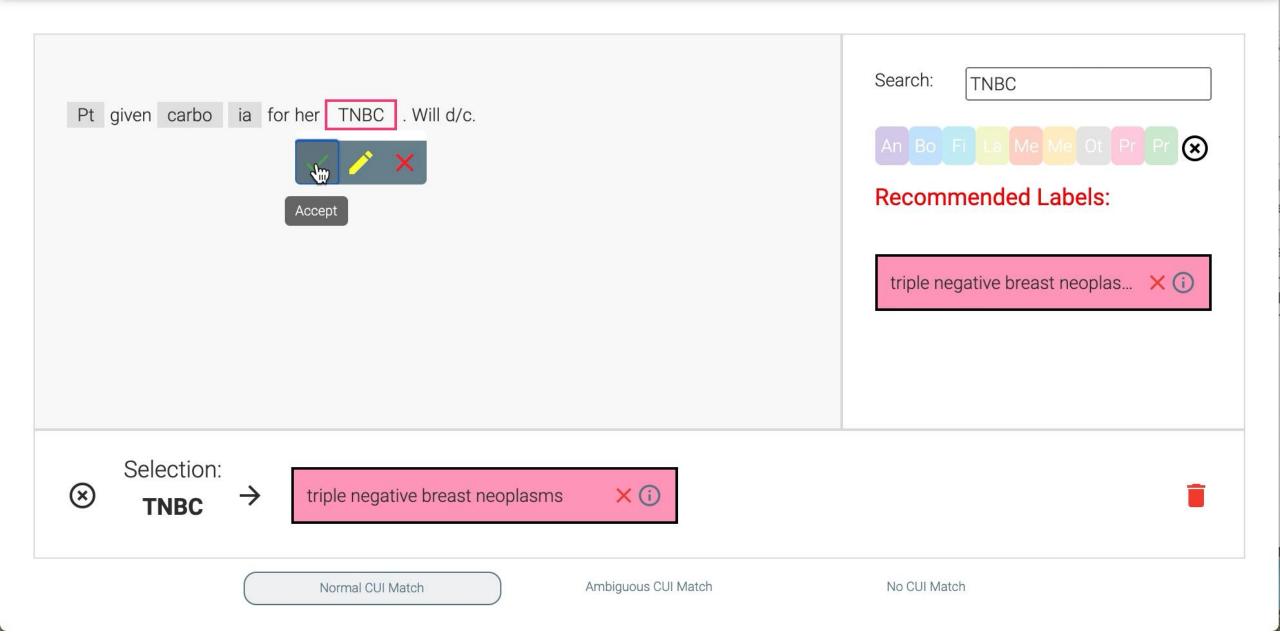
Pt given carbo ia for her TNBC	. Will d/c. We developed an annotation platform with built-in decision aid	Search: carboplatin     An Bo Fi La Me Me Ot Pr Pr 💓     Searched Labels:     carboplatin     (i)
Selection:	tin × i	
Normal C	JI Match Ambiguous CUI Match	No CUI Match

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# **Example Impact**

#### One Clinician Is All You Need–Cardiac Magnetic Resonance Imaging Measurement Extraction: Deep Learning Algorithm Development

Pulkit Singh <sup>1</sup> <sup>(b)</sup>; Julian Haimovich <sup>2, 3, 4</sup> <sup>(b)</sup>; Christopher Reeder <sup>1</sup> <sup>(b)</sup>; Shaan Khurshid <sup>2, 3, 5</sup> <sup>(b)</sup>; Emily S Lau <sup>3, 4</sup> <sup>(b)</sup>; Jonathan W Cunningham <sup>4, 6</sup> <sup>(b)</sup>; Anthony Philippakis <sup>1, 7</sup> <sup>(b)</sup>; Christopher D Anderson <sup>8, 9, 10</sup> <sup>(b)</sup>; Jennifer E Ho <sup>4, 11</sup> <sup>(b)</sup>; Steven A Lubitz <sup>2, 3, 4, 5</sup> <sup>(b)</sup>; Puneet Batra <sup>1</sup> <sup>(b)</sup>



Goal: Extraction of 21 Measurements from Cardiac MRI Reports Macro F1 score: 0.957 Clinician labeling time: ~11 hours for all training data Due to the ever-growing presence of automated decision aid, we build on past work to ask:

# How does domain expertise mediate the influence of decision aid?



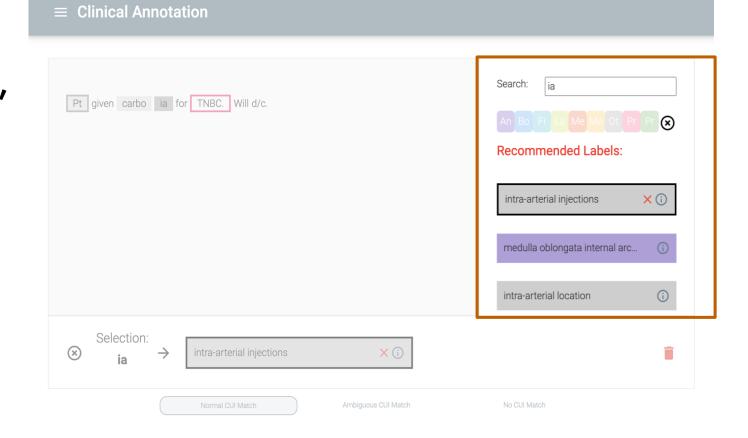
- In a task with a complex decision space
- Using objective measures of trust and agency
- Over an extended period of use to factor in fatigue

# **Study Overview**

- 18 clinicians from 9 institutions
- Study Novelties
  - Joint study of agency (what to label?) and trust (how to label?) using objective measures
  - Large space of 400k+ labels
  - $\sim 8$  hours of annotation per user
- Two stages
  - Stage 1: Label Recommendations
  - Stage 2: Pre-filled Suggestions

# **Stage 1: Label Recommendations**

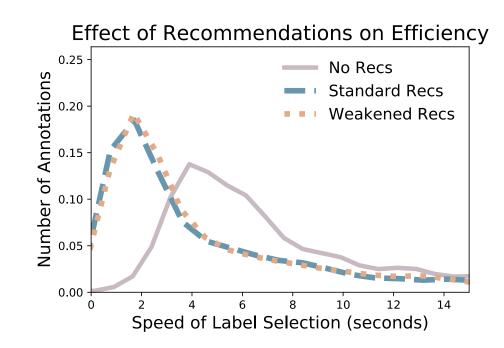
We analyze accuracy, speed, and search behavior, particularly where recommendations are inaccurate



## How does user behavior shift?

Users with full recommendations created **more annotations** (average of 12%) than those without any (p<0.02)

The median time to choose a label halves with recommendations: from 6 seconds to 3 seconds (p<0.05)



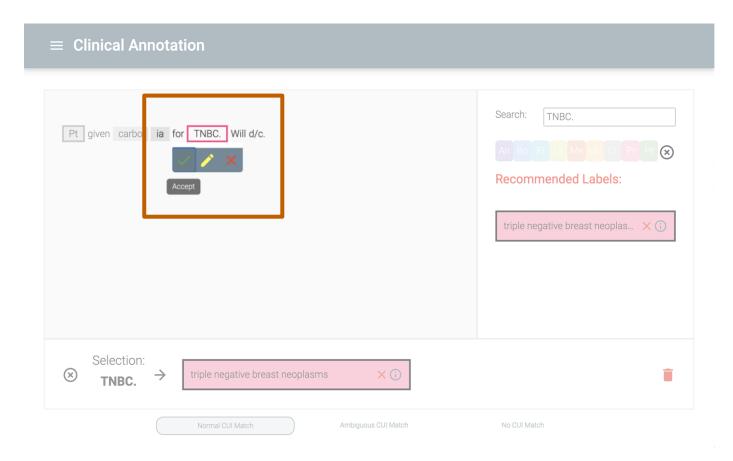
#### Do users search when needed, or misplace trust?

Yes, they generally search when the recommendation algorithm truly doesn't surface the correct answer.

However, they search less often when they may expect the correct answer to be surfaced.

# Stage 2: Pre-filled suggestions

We analyze accuracy and speed, particularly where suggestions are inaccurate, and additional annotation behavior



# Do users react appropriately?

#### Mostly. They:

- accept 99% of correct labels+spans
- accept only 17% of incorrect labels
- accept 33% of incorrect spans

Overall, they tend to have higher performance than users without pre-filled suggestions.

# Do users react appropriately?

There was large user variability in accepting of incorrect labels and spans – not correlated with their prior task performance

Providing label confidence made no discernable difference.

### What about agency for creating new annotations?

Users experience **loss of agency** in creating the new nontrivial annotations that don't come pre-filled: they made 12% fewer than in Stage 1

No such drop was observed in users without pre-filled suggestions, making the loss significant (p<0.01)

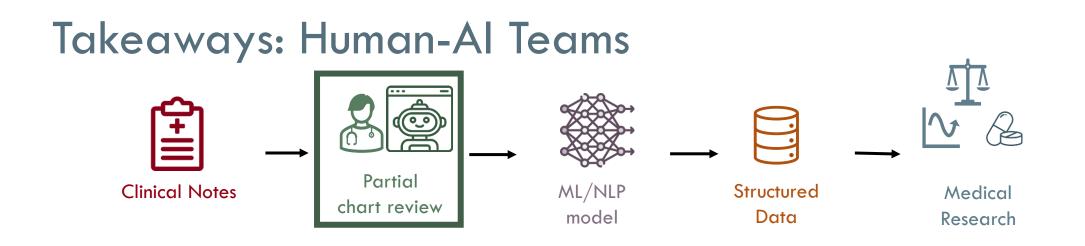
### What about agency for creating new annotations?

#### This loss of agency went unnoticed by users.

### What about agency for creating new annotations?



"[Pre-filled annotations] freed up mental bandwidth to spend more energy on unmarked text."



- With appropriate mental models, users properly modulated trust and mediated model errors.
- Users lost agency without noticing, highlighting the importance of objective measures.
- Both UIs and ML systems should consider such effects in their design

# Conclusion

A holy grail in ML for healthcare is **information extraction**. This would solve fundamental challenges **across healthcare**.

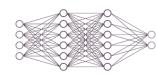
Core takeaways:

- 1. LLMs are getting us **much closer** to making ML-augmented information extraction possible, but has many challenges that need to be addressed, particularly for healthcare data (long tail, data availability, security & compliance, explainability/trust, etc.)
- 2. Rather than applying LLMs as a post-hoc bandaid to extract insights from clinical data, the true gamechanger is **collecting clean data at the point-of-care**, incentivized by ML-driven information retrieval.
- 3. ML for healthcare is a very **human problem** we need to design humancentered systems that understand the impact of introducing ML into workflows.

## CS329T: Projects & Datasets

Dataset	Description
Clinical Trial Matching	All FDA clinical trial eligibility criteria are freely available online.
<u>Medical Information Mart for</u> <u>Intensive Care (MIMIC)</u>	Vast dataset of de-identified structured & unstructured clinical data across ICU and ED.
PMC Patients	Patient summaries extracted from PubMed case reports; 167k+ patients.
Adverse Drug Event Corpus	Extracts all adverse drug events (ADEs) from a set of clinical notes.
Synthetic note generation	As in <u>here</u> , generate synthetic notes

# Any questions?



Leverage large language models.



Incentivize cleaner clinical documentation



Quantify the impact of human-AI teams

Beyond the talk: Reach out to us at <u>divya@layerhealth.com</u> / <u>monica@layerhealth.com</u>