Machine Reading for Precision Medicine

Hoifung Poon

Microsoft Research

Overview

Precision medicine

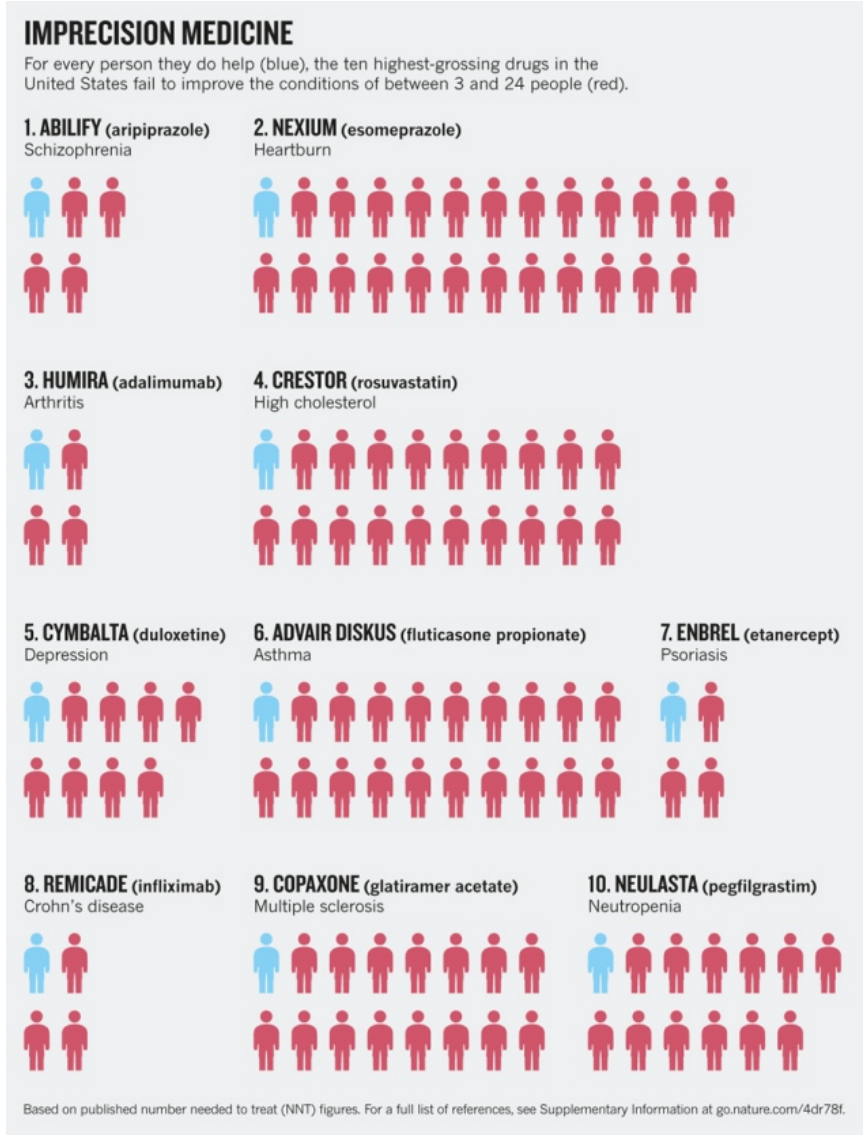
Machine reading

Self supervision

Novel neural architecture

Curation-as-a-Service (CaaS)

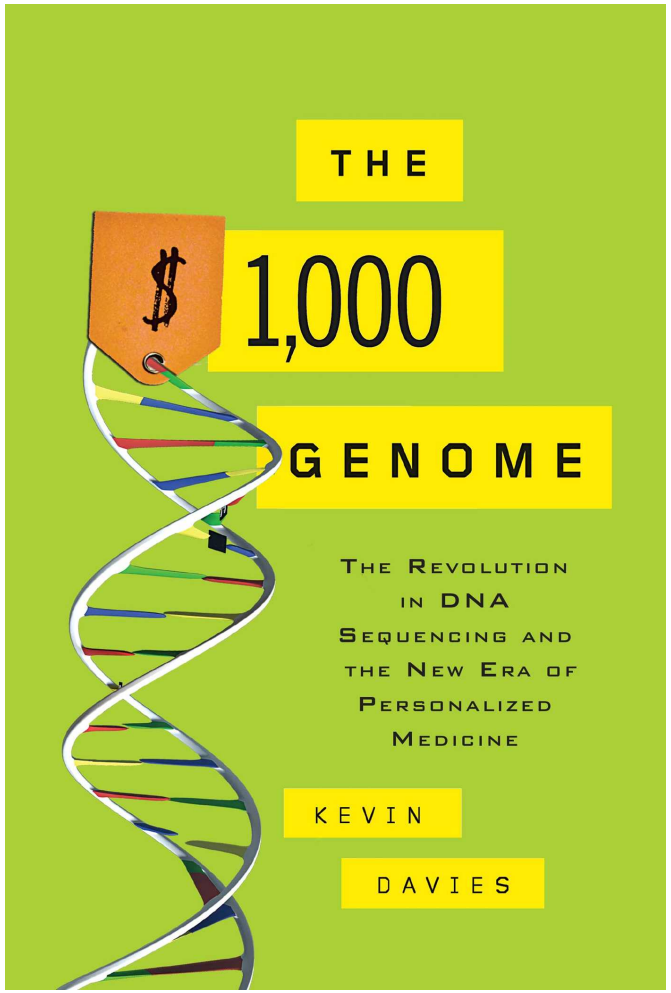
Medicine Today Is Imprecise



Top 20 drugs
80% non-responders

Wasted
1/3 health spending
$1 Trillion / year

Disruption: Big Data



Accenture study: 93% of US doctors using EMRs

May 14, 2013 IHQRE informatics, IHQRE Journal Club EHR, EMR, Meaningful Use

2009 – 2013: 40% → 93%

Key Scenario: Molecular Tumor Board

Problem: Hard to scale

U.S. 2018: 1.7 million new cases

902 cancer hospitals

Memorial Sloan Kettering

- Sequence: Tens of thousands
- Board can review: A few hundred

$200 rate X 10 experts X 3 hours X 1.7 m > $100 billion

OncoKB Team

OncoKB is developed and maintained by the Knowledge Systems group in the Marie Josée and Henry R. Kravis Center for Molecular Oncology at Memorial Sloan Kettering Cancer Center.

Design & Development

Debyani Chakravarty, PhD
Jianjiong Gao, PhD
Sarah Phillips, PhD
Hongxin Zhang, MSc
Ritika Kundra, MSc
Jiaojiao Wang, MSc
Ederlinda Paraiso, MPA
Julia Rudolph, MPA
David Solit, MD
Paul Sabbatini, MD
Nikolaus Schultz, PhD

Clinical Genomics Annotation Committee

Shrujal Baxi, MD, MPH
Margaret Callahan, MD, PhD
Sarat Chandarlapaty, MD, PhD
Alexandra Charen-Snyder, MD
Ping Chi, MD, PhD
Daniel Danila, MD
Mrinal Gounder, MD
James Harding, MD
Matthew Hellman, MD
Alan Ho, MD, PhD
Gopa Iyer, MD
Yelena Janjigian, MD
Thomas Kaley, MD
Maeve Lowery, MD
Antonio Omuro, MD
Paul Paik, MD
Michael Postow, MD
Dana Rathkopf, MD
Alexander Shoushtari, MD
Neerav Shukla, MD
Tiffany Traina, MD
Martin Voss, MD
Rona Yaeger, MD

Core Curators

Moriah Nissan, PhD
Lindsay Saunders, PhD
Tara Soumerai, MD
Fiona Brown, PhD
Tripti Shrestha Bhattarai, PhD
Kinisha Gala, BSc
Aphrothiti Hanrahan, PhD
Anton Henssen, MD
Phillip Jonsson, PhD
Iñigo Landa-Lopez, PhD
Eneda Toska, PhD

Quest Diagnostics

Feras M Abu Hantash, PhD
Andrew Grupe, PhD
Matthew Beer, BSc

Everyday

PubMed: 4000 new papers

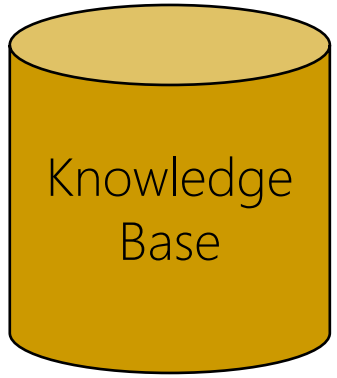
Expert can curate <10

Information Overload

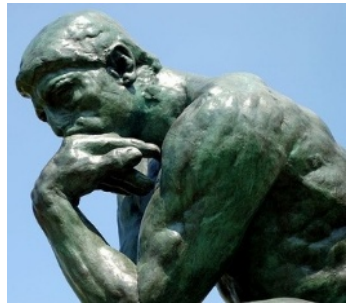
https://imgur.com/rwUE5

Project Hanover

Machine Reading



Decision Support



Unlock knowledge from text

Machine Reading

The deletion mutation on exon-19 of EGFR gene was present in 16 patients, while the L858E point mutation on exon-21 was noted in 10.

All patients were treated with gefitinib and showed a partial response.

TREAT(Gefitinib, EGFR, L858E)

Challenge: Variations

TP53 inhibits BCL2.
Tumor suppressor P53 down-regulates the activity of BCL-2 proteins.
BCL2 transcription is suppressed by P53 expression.
The inhibition of B-cell CLL/Lymphoma 2 expression by TP53 …
……

negative regulation

532 inhibited, 252 inhibition, 218 inhibit, 207 blocked, 175 inhibits, 157 decreased, 156 reduced, 112 suppressed, 108 decrease, 86 inhibitor, 81 Inhibition, 68 inhibitors, 67 abolished, 66 suppress, 65 block, 63 prevented, 48 suppression, 47 blocks, 44 inhibiting, 42 loss, 39 impaired, 38 reduction, 32 down-regulated, 29 abrogated, 27 prevents, 27 attenuated, 26 repression, 26 decreases, 26 down-regulation, 25 diminished, 25 downregulated, 25 suppresses, 22 interfere, 21 absence, 21 repress ……

Challenge: Ambiguity

In eubacteria and eukaryotic organelles the product of this gene, peptide deformylase (PDF), removes the formyl group from the initiating methionine of nascent peptides. …… The discovery that a natural inhibitor of PDF, actinonin, acts as an antimicrobial agent in some bacteria has spurred intensive research into the design of bacterial-specific PDF inhibitors. …… In humans, PDF function may therefore be restricted to rapidly growing cells

Aliases for PDF Gene

- Peptide Deformylase (Mitochondrial) [2 3 5]
- Polypeptide Deformylase [4]
- EC 3.5.1.88 [4]
- PDF1A [4]

PDF Gene (Protein Coding) ★

Peptide Deformylase (Mitochondrial)

GCID: GC16M069328
GIFtS: 44

Challenge: Document-Level N-ary Relation

"We next expressed ALK F1174L, ALK F1174L/L1198P, ALK F1174L/G1123S, and ALK F1174L/G1123D in the original SH-SY5Y cell line."

(. . . 15 sentences and 2 figures . . .)

"The 2 mutations that were only found in the neuroblastoma resistance screen (G1123S/D) are located in the glycine-rich loop, which is known to be crucial for ATP and ligand binding and are the first mutations described that induce resistance to TAE684, but not to PF02341066."

Challenge: Annotation Bottleneck

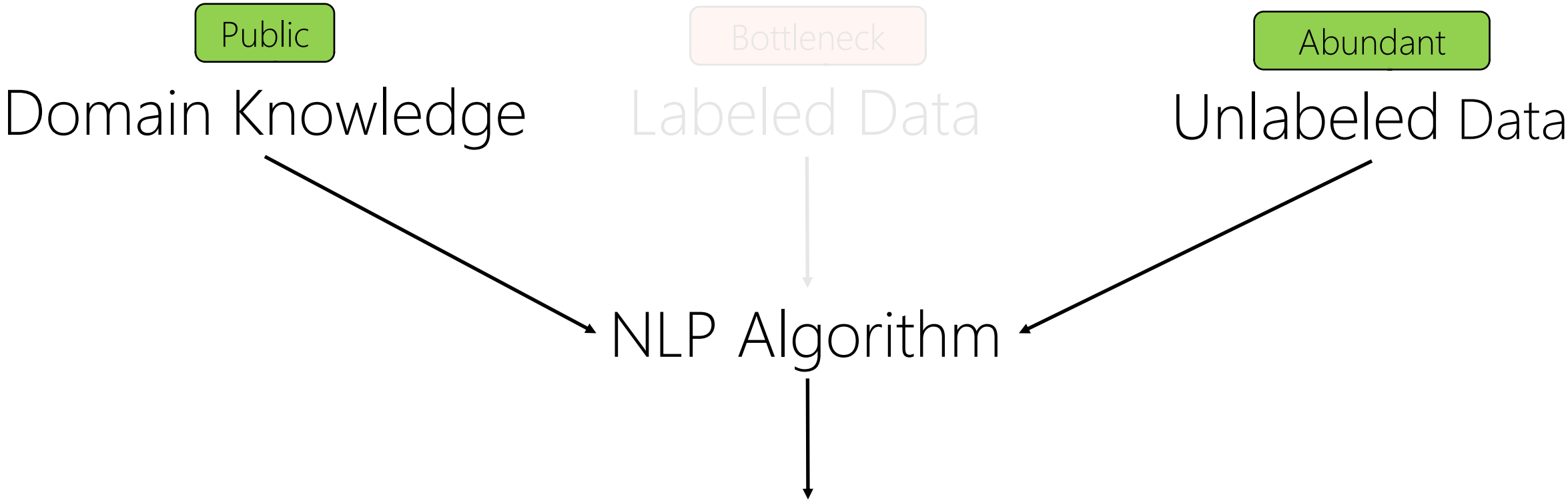
Deep learning requires many labeled examples

Hire experts to label: Not scalable

Crowdsource: Lack domain expertise

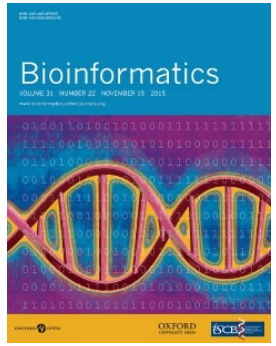
Self-Supervised Machine Reading

Self-Supervised Learning



Hanover: Self-Supervised Deep Learning

Gene Network



PSB 2015

NAACL HLT 2015

EMNLP 2015
CONFERENCE ON EMPIRICAL METHODS IN NATURAL LANGUAGE PROCESSING
LISBON

ACL 2016
AUGUST 7 – 12 | BERLIN, GERMANY

Molecular Tumor Board

EACL 2017

TACL 2017

EMNLP 2018

NAACL-HLT 2019

Open Science

PLOS BIOLOGY 2017

IJCAI ECAI 2018

Example: Distant Supervision

NCI Pathway KB

Regulation	Theme	Cause
Positive	A2M	FOXO1
Positive	ABCB1	TP53
Negative	BCL2	TP53
…	…	…

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Example: Joint Inference

In eubacteria and eukaryotic organelles the product of this gene, peptide deformylase (PDF), removes the formyl group from the initiating methionine of nascent peptides. …… The discovery that a natural inhibitor of PDF, actinonin, acts as an antimicrobial agent in some bacteria has spurred intensive research into the design of bacterial-specific PDF inhibitors. …… In humans, PDF function may therefore be restricted to rapidly growing cells.

Coreferent

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Apposition

Example: Joint Inference

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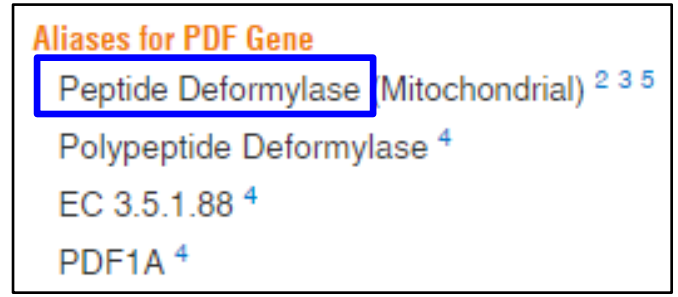

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Example: Data Programming

Case Histrogical type **EGFR** mutation status Brinkman index Treatment agent Response IL-8 (ng/mL) IL-10 (ng/mL) RANTES (pg/ml) 1 Ad Ex21 L858R 900 **gefitinib** PR 5.79 1.67 2 2 Ad Ex21 L858R 0 erlotinib PR 3.33 94.2 1.41 3 Ad Ex19 del 0 erlotinib PR 4.09 126 2.13 4 Ad Ex21 L858R 0 gefitinib PR 3.92 18.1 1.85 5 Ad Ex21 L858R + Ex19 del 370 erlotinib PR 21.9 1.23 2.11 6 Ad Ex19 del 0 erlotinib PR 7.05 1.37 2.56 7 Ad Ex19 del 0 gefitinib PR 4.82 1.59 2.02 8 Ad Ex21 L858R 1640 gefitinib PR 54.9 2.7 2.38 9 Ad negative 400 erlotinib SD 34.9 3.39 3.66 10 Ad negative 0 erlotinib SD 27.1 4.94 2.25 11 Ad unknown 1800 erlotinib SD NE NE NE 12 Sq Ex19 del 3840 gefitinib SD 12.6 1.1 1.98 13 Ad Ex19 del 30 erlotinib SD 5.27 0.69 2.66 14 Ad Ex19 del 0 erlotinib SD 10.5 0.85 2.5 15 Ad unknown 300 erlotinib SD 7.69 2.61 1.7 16 La negative 2080 erlotinib SD NE NE NE 17 Sq Ex21 L858R 750 erlotinib SD 11.6 56.3 3.06 18 Ad unknown 600 erlotinib SD 13.7 1.1 2.82 19 Ad Ex21 L858R 0 erlotinib SD 20.6 11.6 0.783 20 Ad Ex19 del 0 erlotinib SD 14.8 2.07 2.02 21 Ad Ex21 L858R + Ex19 del 0 gefitinib SD 3.04 1.3 1.76 22 Ad Ex19 del 200 gefitinib SD 10.9 1.59 1.91 23 Sq unknown 1560 erlotinib PD NE NE NE 24 Ad negative 1080 erlotinib PD 25.2 8.15 1.57 25 Ad unknown 0 erlotinib PD NE NE NE 26 Ad Ex18 **G719A** 2000 erlotinib PD 11.6 4.48 3.12 27 Ad unknown 1410 erlotinib PD NE NE NE 28 Ad Ex19 del 1000 gefitinib PD 9.44 2.25 2.89 29 Ad negative 1100 erlotinib PD 56.3 5.63 2.16 30 Ad negative 2000 erlotinib PD 15.6 0.85 0.292 31 Ad negative 825 erlotinib PD 8.27 1.59 2.13 32 Ad Ex21 L858R 0 erlotinib PD 5.34 7.05 1.7 33 Ad negative 1680 erlotinib PD 57.7 1.63 2.06

Too many numbers → Unlikely to describe a relation

Probabilistic Logic

Distant Supervision $f_{KB}(X_i, Y_i) = \mathbb{I}[\texttt{In-KB}(X_i, r) \wedge Y_i = r]$

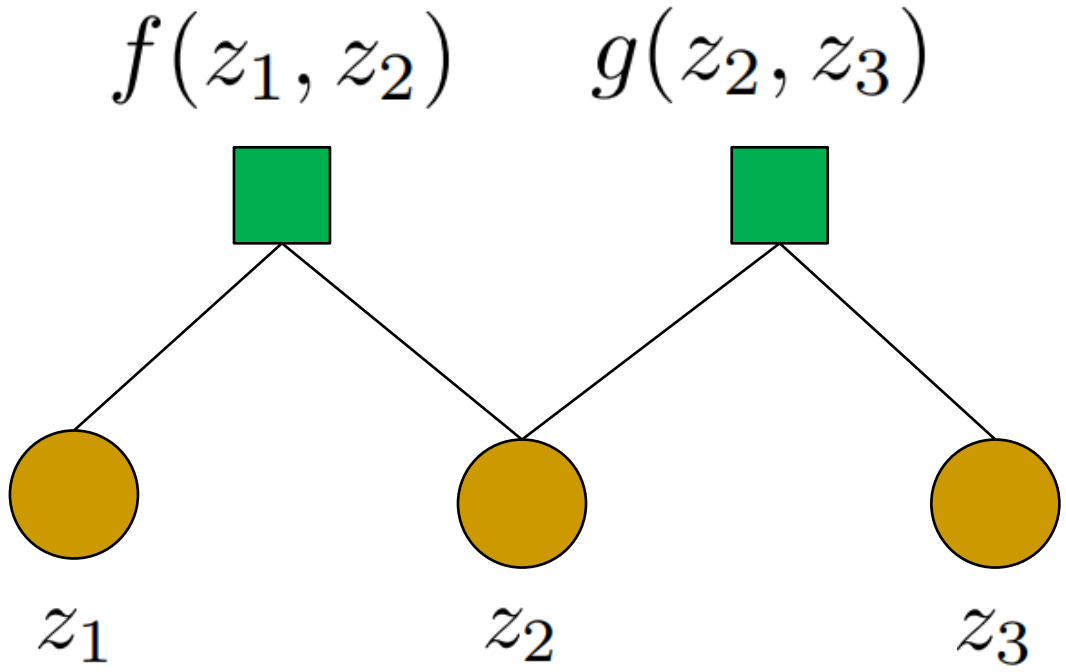
Data Programming $f_L(X_i, Y_i) = \mathbb{I}[L(X_i) = Y_i]$

Joint Inference $f_{\texttt{Joint}}(X_i, Y_i, X_j, Y_j) = \mathbb{I}[\texttt{Coref}(X_i, X_j) \wedge Y_i = Y_j]$

Probabilistic Logic

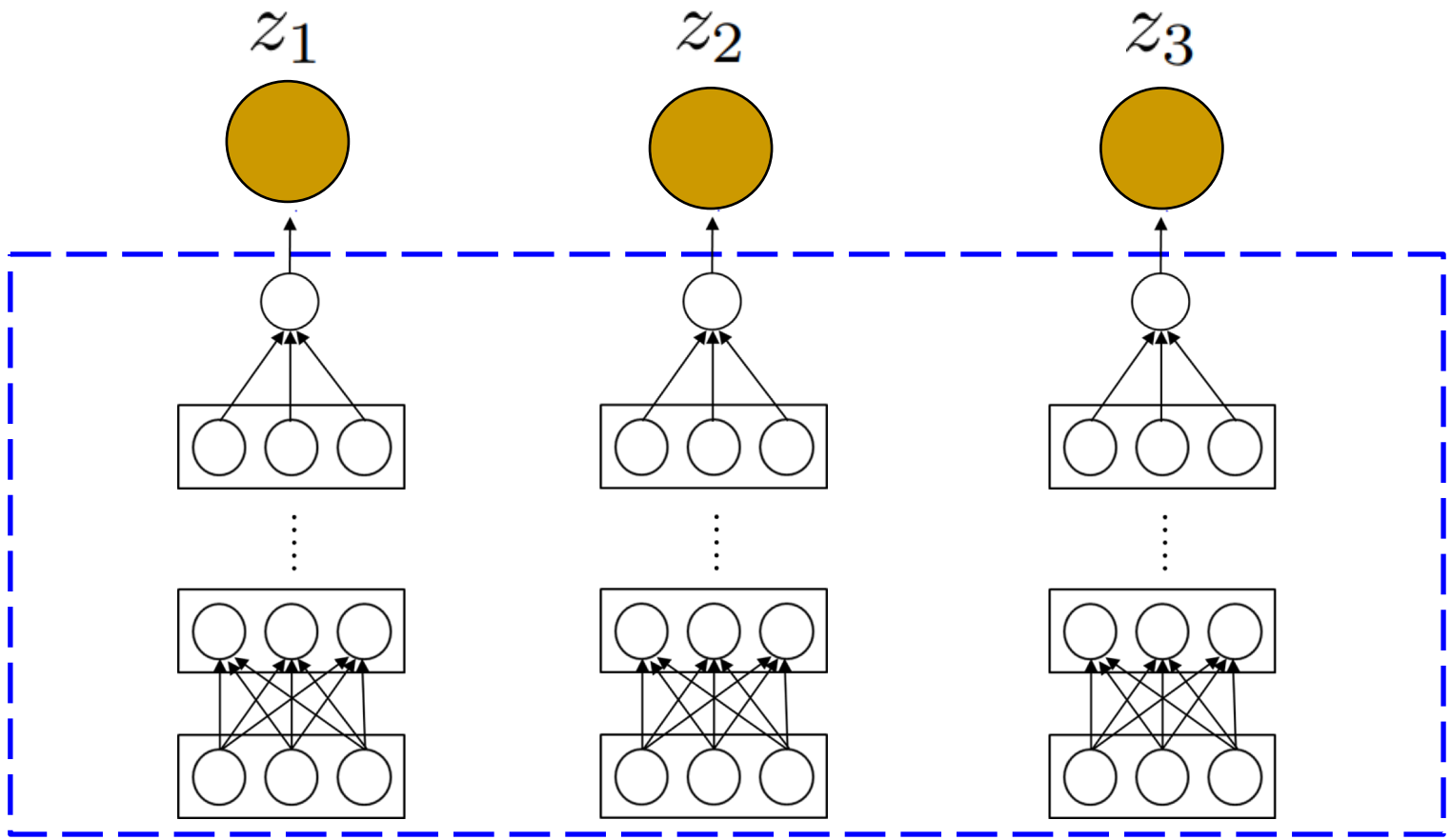
Factor

Variable



Probability $p(z_1, z_2, z_3) \propto \exp(w_f \cdot f(z_1, z_2) + w_g \cdot g(z_2, z_3))$

Deep Learning

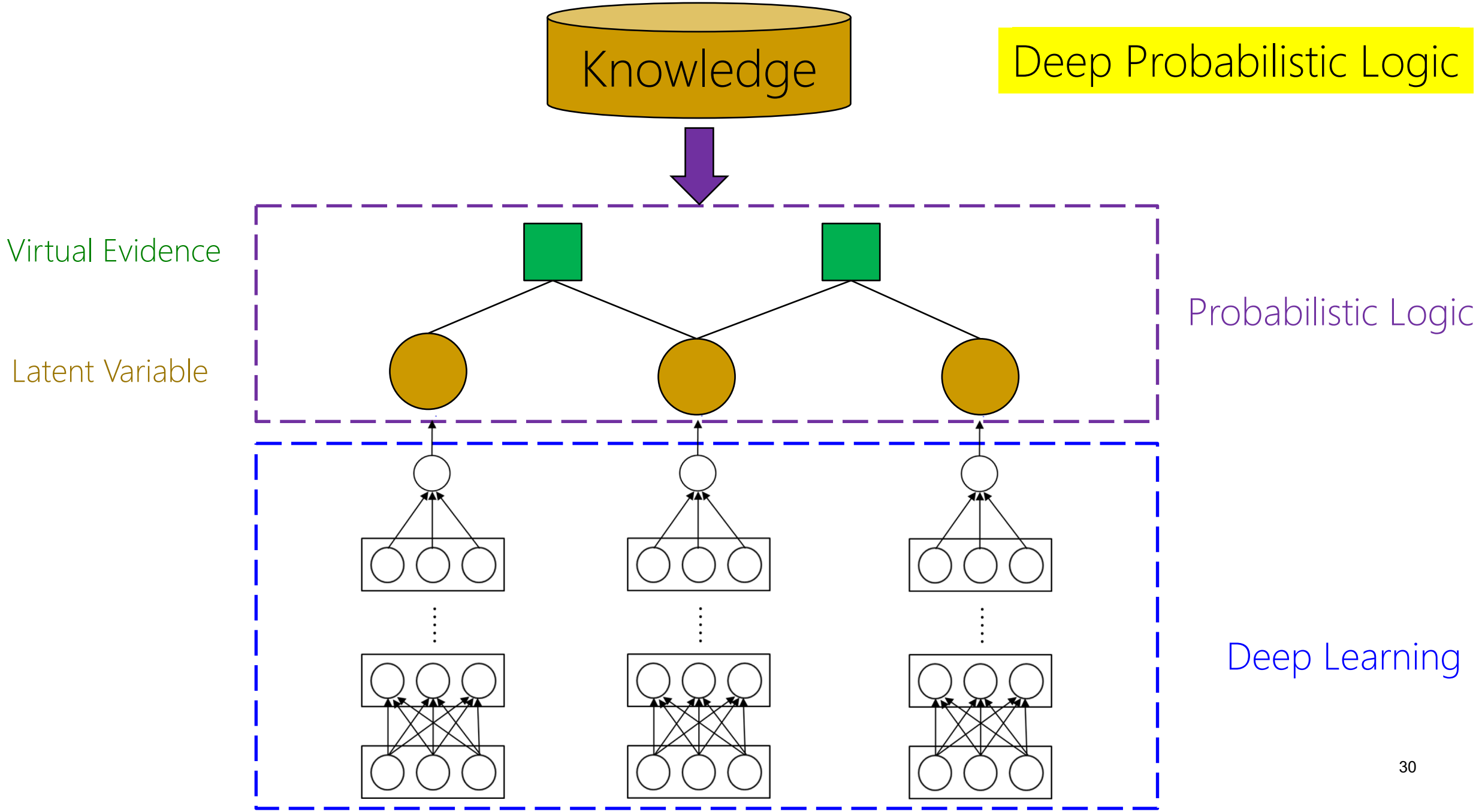


Variational EM

Marginal ~ $p(z_1, z_2, z_3)$

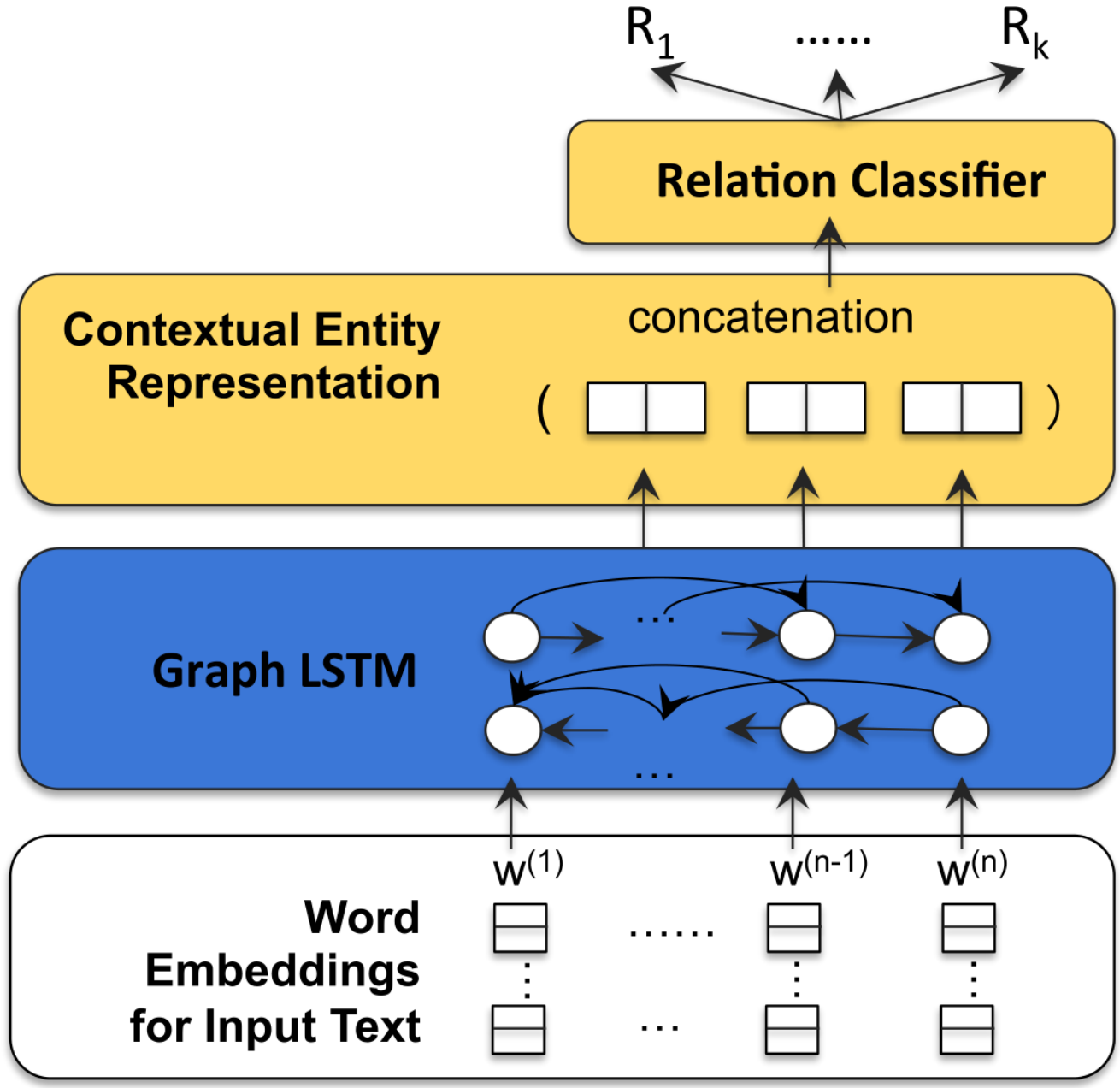
Probabilistic Labels

Deep Probabilistic Logic

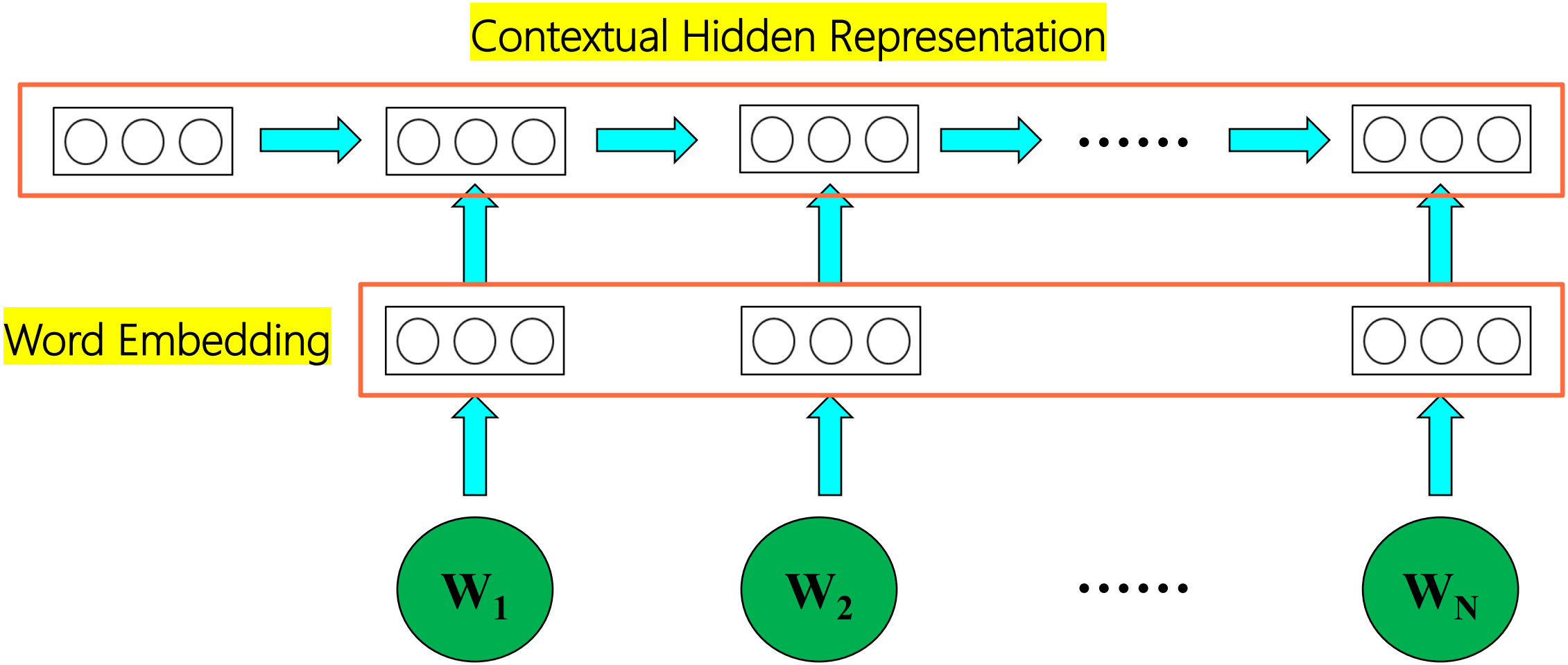


Novel Neural Architecture

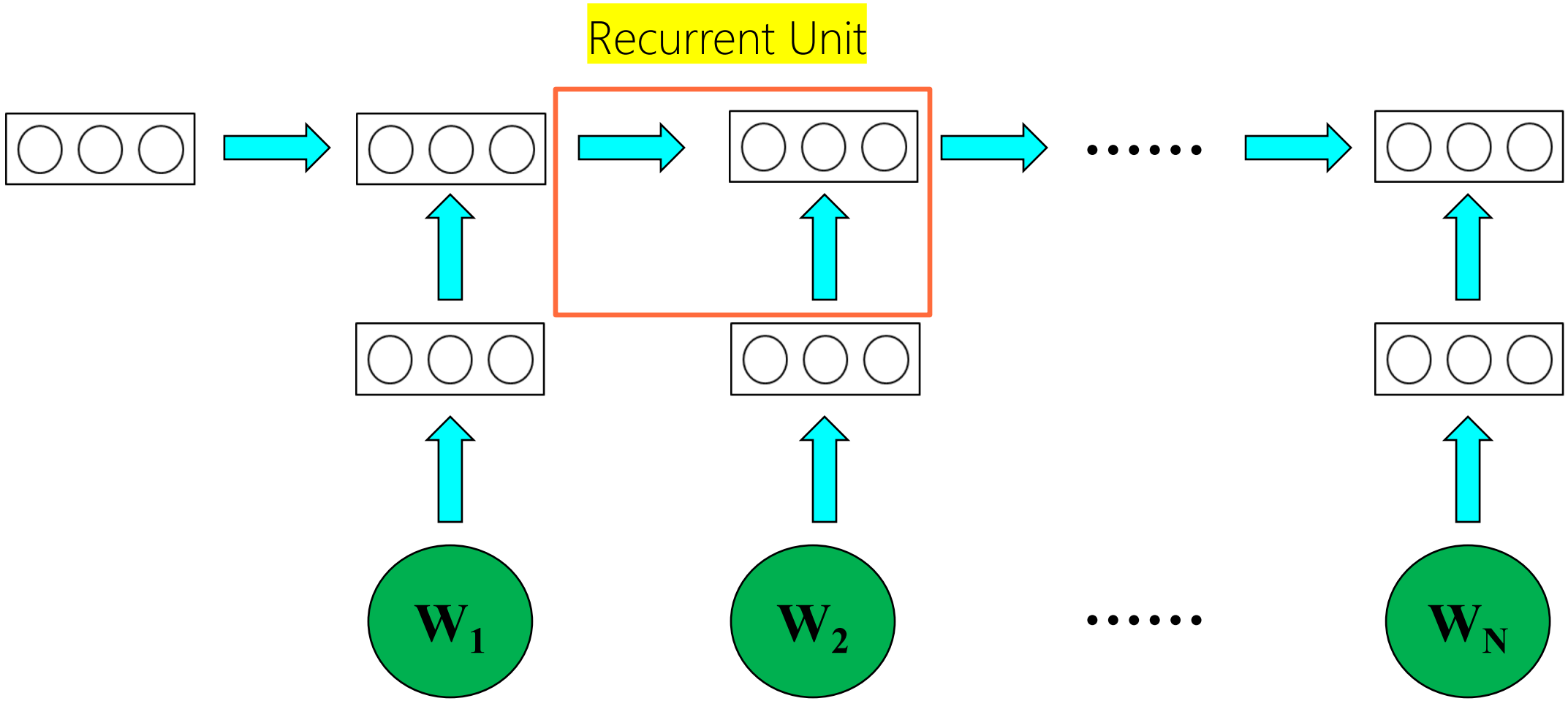
Graph LSTM


R_1
.....
R_k
Relation Classifier
Contextual Entity Representation
concatenation
( )
Graph LSTM
...
...
$w^{(1)}$
$w^{(n-1)}$
$w^{(n)}$
Word Embeddings for Input Text
.....
...

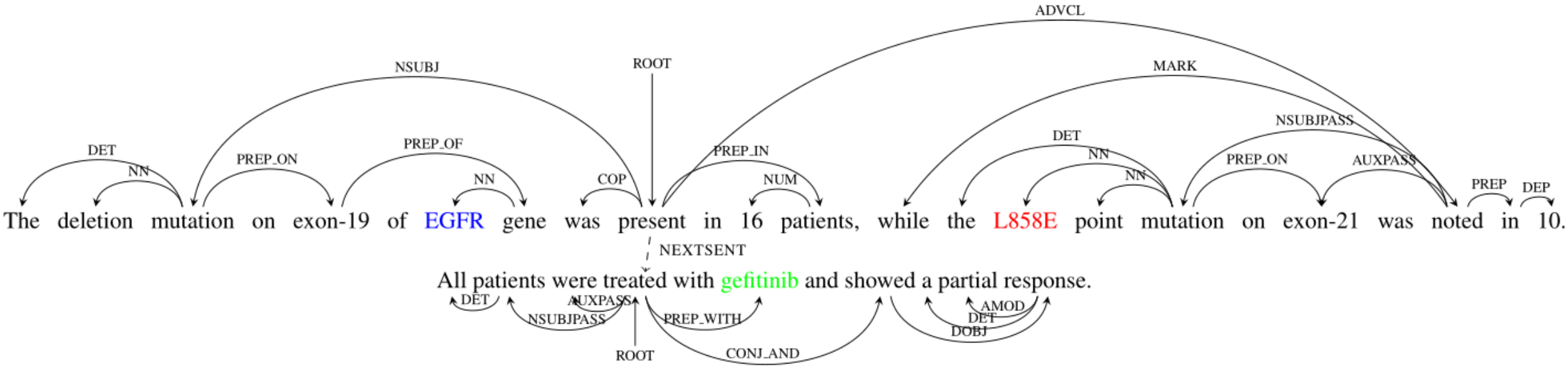
Recurrent Neural Network



Recurrent Neural Network



Why Graph?



Exploit rich linguistic structures

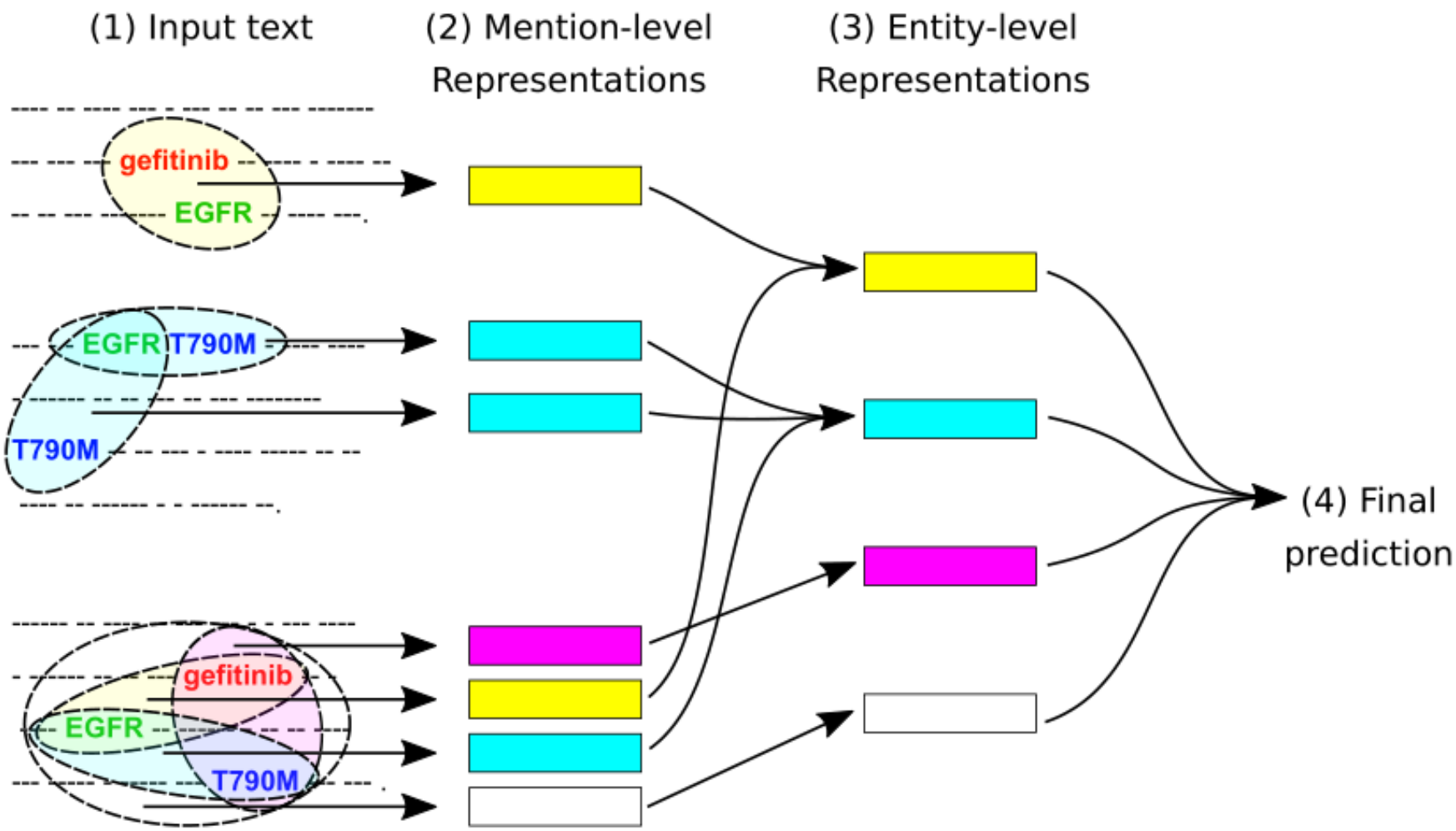
Document-Level Relation Extraction

"We next expressed ALK F1174L, ALK F1174L/L1198P, ALK F1174L/G1123S, and ALK F1174L/G1123D in the original SH-SY5Y cell line."

(. . . 15 sentences and 2 figures . . .)

"The 2 mutations that were only found in the neuroblastoma resistance screen (G1123S/D) are located in the glycine-rich loop, which is known to be crucial for ATP and ligand binding and are the first mutations described that induce resistance to TAE684, but not to PF02341066."

Multiscale Representation Learning



Graph LSTM

Distant supervision: GDKD + CIVIC

Cross-sentence triples extraction yield

Machine reading: 70 X manual curation

Graph helps, esp. if syntactic parses are good

Peng et al. "Cross-Sentence N-ary Relation Extraction with Graph LSTM", *TACL-17*.

Deep Probabilistic Logic

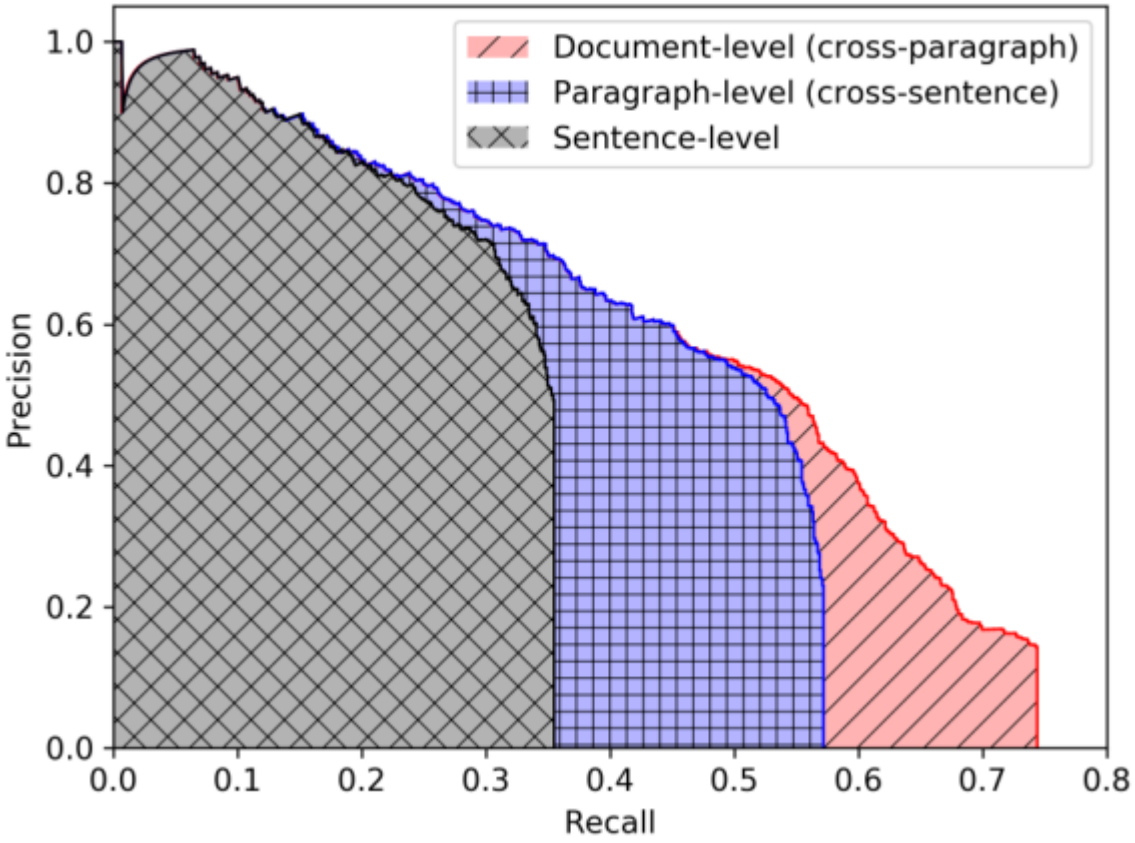
Distant Supervision + Data Programming + Joint Inference

Precision: +10 points (64% → 74%)

Recall: +25%

Wang & Poon. "Deep Probabilistic Logic: A Unifying Framework for Indirect Supervision", *EMNLP-18*.

Multiscale Representation Learning

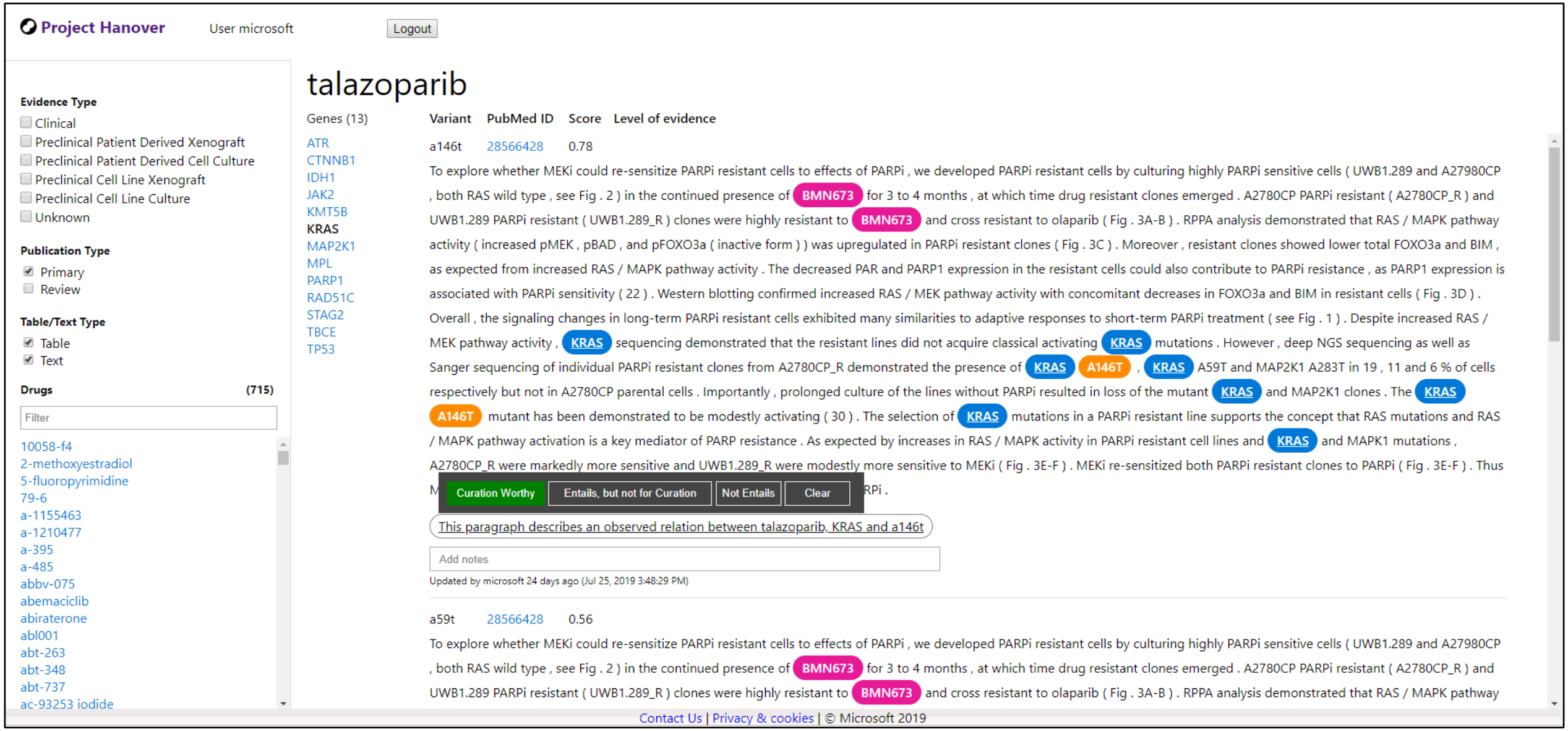


Improve AUC by absolute 8-13 points Compared to Wang & Poon 2018

Jia et al. "Document-Level n-ary Relation Extraction with Multiscale Representation Learning", *NAACL-19*.

Curation-as-a-Service (CaaS)

Assisted Curation



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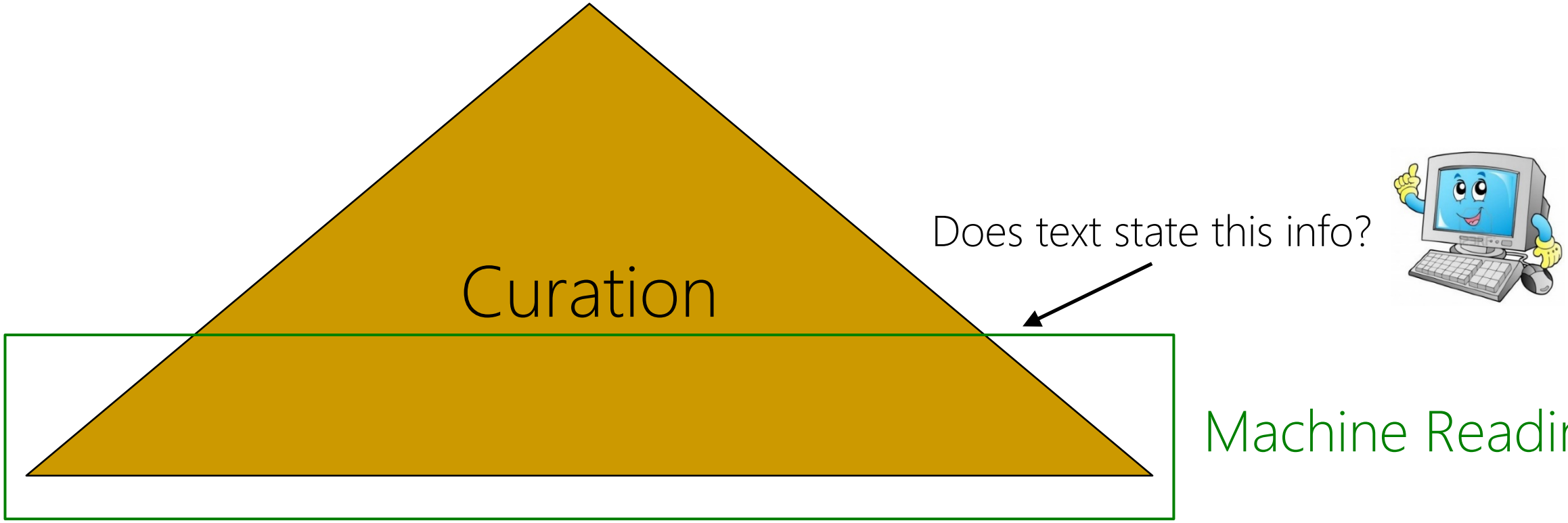
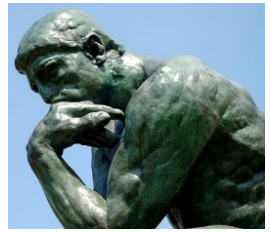
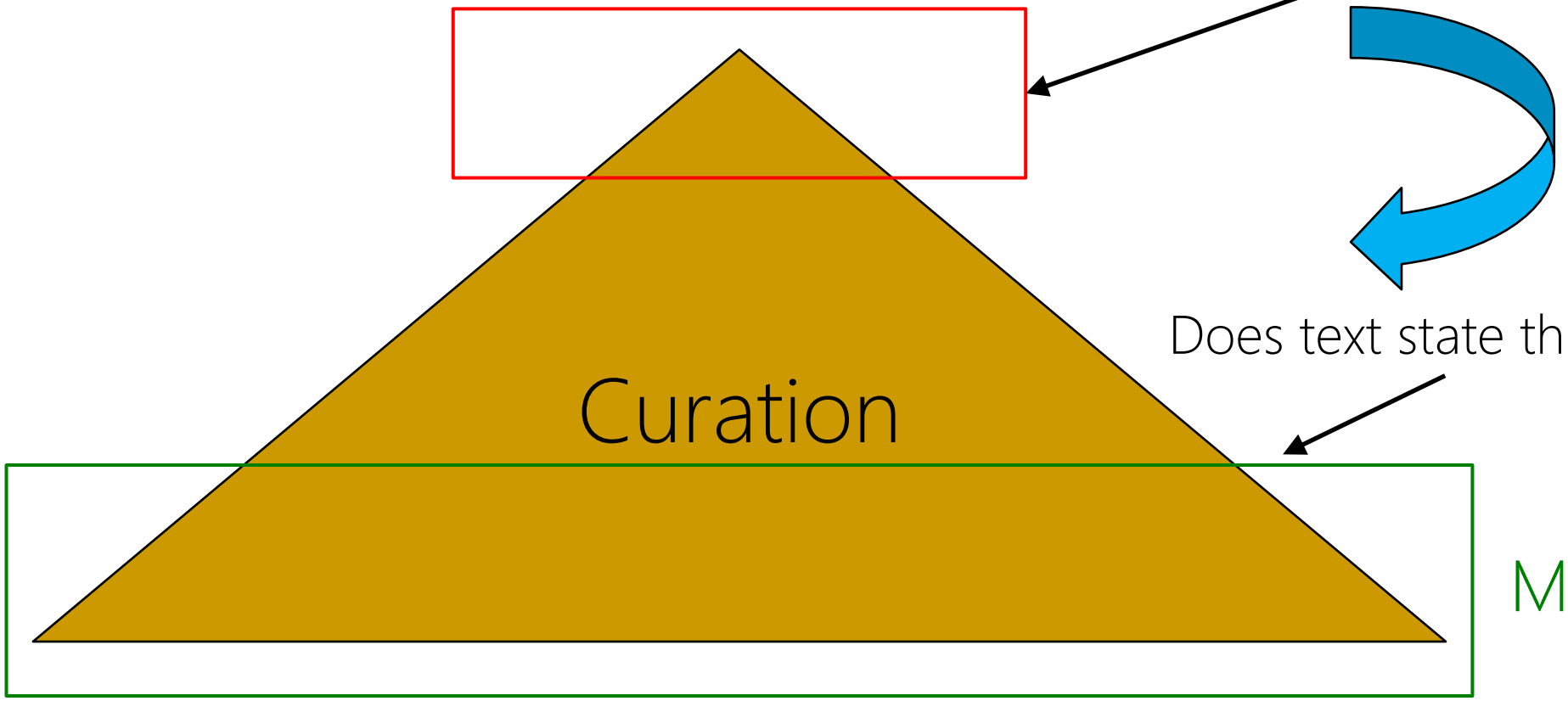


Goal: Empower curators with super speed

Assisted Curation



Do I trust this info?



Does text state this info?

Machine Reading

Goal: Empower curators with super speed

Curation-as-a-Service (CaaS)

Molecular tumor board

Cancer registry

Off-label drug use

Clinical trial matching

Synthetic control

Post-market surveillance

Molecular Tumor Board

DRUG	GENE	MUTATION	RESPONSE
gefitinib	EGFR	L858R	sensitive
erlotinib	EGFR	T790M	resistant
talazoparib	KRAS	A146T	resistant
		.....	

Goal: Democratize cutting-edge cancer care

EMR: 60-80% In Unstructured Text

Wolters Kluwer: Health Language Blog

```
1,23224,174680,2147-12-05,,,"Discharge summary","Report",,"","Admissi
on Date:  [**2823-9-29**]              Discharge Date:   [**2823-10-1
7**]

Date of Birth:  [**2768-10-11**]             Sex:   F

Service: SURGERY

Allergies:
Patient recorded as having No Known Allergies to Drugs

Attending:[**First Name3 (LF) 1**]
Chief Complaint:
headache and neck stiffness

Major Surgical or Invasive Procedure:
central line placed, arterial line placed

History of Present Illness:
54 year old female with recent diagnosis of ulcerative colitis
on 6-mercaptopurine, prednisone 40-60 mg daily, who presents
with a new onset of headache and neck stiffness. The patient is
in distress, rigoring and has aphasia and only limited history
is obtained. She reports that she was awaken 1AM the morning of
[**2823-9-28**] with a headache which she describes as bandlike. She
states that headaches are unusual for her. She denies photo- or
phonophobia. She did have neck stiffness. On arrival to the ED
at 5:33PM, she was afebrile with a temp of 96.5, however she
later spiked with temp to 104.4 (rectal), HR 91, BP 112/54, RR
24, O2 sat 100 %. Head CT was done and relealved attenuation
within the subcortical white matter of the right medial frontal
lobe. LP was performed showing opening pressure 24 cm H2O WBC of
316, Protein 152, glucose 16.  She was given Vancomycin 1 gm IV,
Ceftriaxone 2 gm IV, Acyclovir 800 mg IV, Ambesone 183 IV,
Ampicillin 2 gm IV q 4, Morphine 2-4 mg Q 4-6, Tylenol 1 gm ,
Decadron 10 mg IV.  The patient was evaluated by Neuro in the
ED.
```

Real-World Evidence

What if we can unlock valuable info in EMRs?

Diagnoses
Treatments
Outcomes
……

Only 3% cancer patients enroll in clinical trials

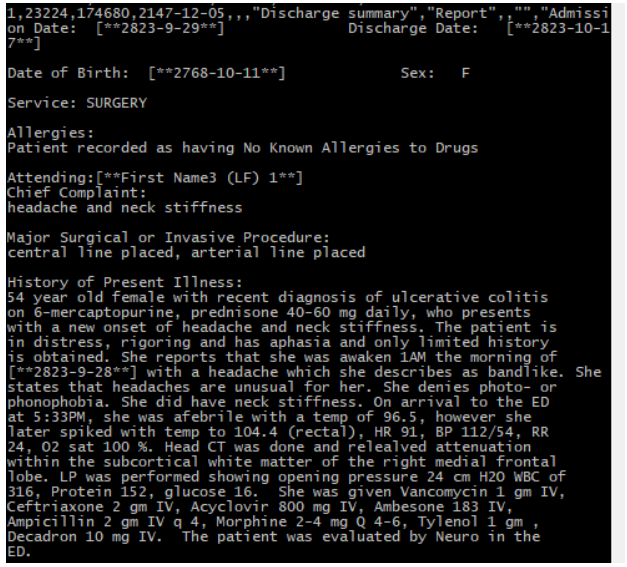
Goal: Make every patient count

Cancer Registry

Stakeholder: Providers

Required by law: report basic cancer info

Manual: slow & tedious



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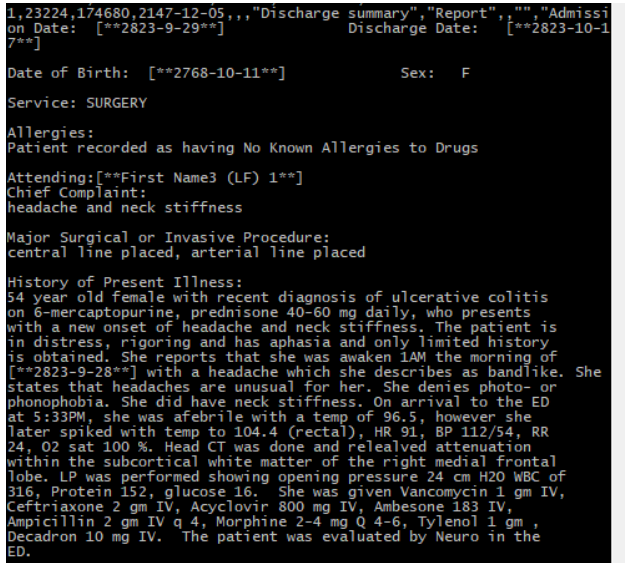
ATTRIBUTE	VALUE
Site	Large intestine (C180)
Morphology	Glassy cell (8015)
Staging	IIA (T2 N0 M0)

Off-Label Drug Use

Stakeholder: providers, oncologists

Standard of care often fails

N-of-one trials → Find patients like X



1,23224,174680,2147-12-05,,,"Discharge summary","Report","","Admission Date: [**2823-9-29**] Discharge Date: [**2823-10-17**]

Date of Birth: [**2768-10-11**] Sex: F

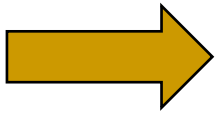
Service: SURGERY

Allergies:
Patient recorded as having No Known Allergies to Drugs

Attending:[**First Name3 (LF) 1**]
Chief Complaint:
headache and neck stiffness

Major Surgical or Invasive Procedure:
central line placed, arterial line placed

History of Present Illness:
54 year old female with recent diagnosis of ulcerative colitis on 6-mercaptopurine, prednisone 40-60 mg daily, who presents with a new onset of headache and neck stiffness. The patient is in distress, rigoring and has aphasia and only limited history is obtained. She reports that she was awaken 1AM the morning of [**2823-9-28**] with a headache which she describes as bandlike. She states that headaches are unusual for her. She denies photo- or phonophobia. She did have neck stiffness. On arrival to the ED at 5:33PM, she was afebrile with a temp of 96.5, however she later spiked with temp to 104.4 (rectal), HR 91, BP 112/54, RR 24, O2 sat 100 %. Head CT was done and relealved attenuation within the subcortical white matter of the right medial frontal lobe. LP was performed showing opening pressure 24 cm H2O WBC of 316, Protein 152, glucose 16. She was given Vancomycin 1 gm IV, Ceftriaxone 2 gm IV, Acyclovir 800 mg IV, Ambesone 183 IV, Ampicillin 2 gm IV q 4, Morphine 2-4 mg Q 4-6, Tylenol 1 gm , Decadron 10 mg IV. The patient was evaluated by Neuro in the ED.



Diagnoses
Treatments
Outcomes
.....

Clinical Trial Matching

Marty Tenenbaum
Late-stage melanoma (late 1990s)
Initial prognosis: 6 months
Saved by Phase III trial of Canvaxin

20% cancer trials failed due to insufficient patients

Clinical Trial Matching

Stakeholder: CROs, Providers

Currently, rely on manual word-of-mouth

Structured Patient Info

Structured Eligibility Criteria

Match?

Scenario: Drug Development

Average cost of an FDA-approved drug		Annual number of FDA-approved drugs		Per Year
$2.5-10 billion	×	~50	=	$125-500 billion

Phase-3 Trial

Case: New drug

Control: Standard-of-care

Thousands of patients
Cost hundreds of million per trial

Can we get this for free?

Synthetic Control

Stakeholder: Pharma, Providers

EMR: Standard of care ⇒ Virtual control arm

Case study: Flatiron

- Demonstrated efficacy in pivotal study with Pfizer
- Acquired by Roche for $2B in 2018
- Manual curation by hundreds of abstracters; 2-3 hours per patient

Can we speed up curation by 10X?

Post-Market Surveillance

Stakeholder: Pharma, Providers

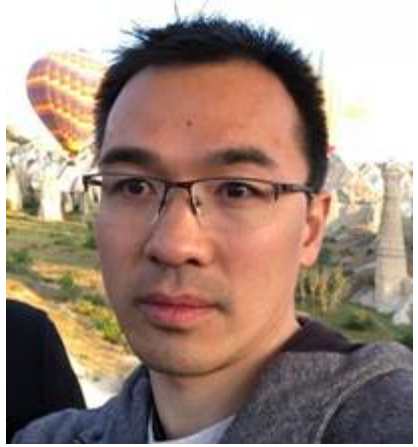
Assess drug performance in real population

FDA favors more conditional approval + PMS

Phase-5 trials: often cost more than 1-3 combined

Goal: Make drug development sustainable

Hanover Team



Cliff Wong

Tristan Naumann

Rajesh Rao

Collaborators

JAX: Susan Mockus, Sara Patterson

Fred Hutchinson: Christopher Li, Kathi Malone

Knight Cancer Institute: Brian Druker, Jeff Tyner, Steve Kurtz

U. Chicago: Andrey Rzhetsky

UCSC: Max Haeussler

MSR: Chris Quirk, Ravi Pandya, Bill Bolosky, Lucy Vanderwende, Robin Moeur, Curtis von Veh, Tony Carbary

Interns: Maxim Grechkin, Ankur Parikh, Victoria Lin, Sheng Wang, Stephen Mayhew, Daniel Fried, Violet Peng, Hai Wang, Robin Jia

Publications

EMRs

Clinical Trials

Precision Cancer Treatment

Structured Patient Info

Structured Eligibility

Molecular Tumor Board

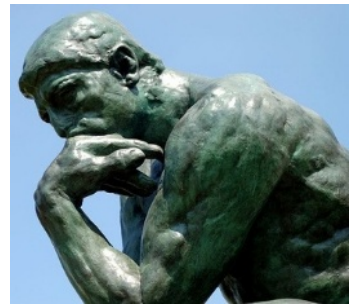
Real-World Evidence

Clinical Trial Matching

Machine Reading

Knowledge Base

Decision Support



Deep Probabilistic Logic

Feedback Loop

http://hanover.azurewebsites.net