ICPE 2021 Symposium
New frontiers in computable phenotyping for medical product safety evaluation

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Sentinel

Improving Outcome Ascertainment by Applying Natural Language Processing and Machine Learning to Electronic Health Record Data: Identifying Anaphylaxis

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Overview

1. Motivation & objectives
2. Study design
    1. Study cohort
    2. Natural language processing (NLP)
    3. Structured data
    4. Machine learned-models
3. Results and implications

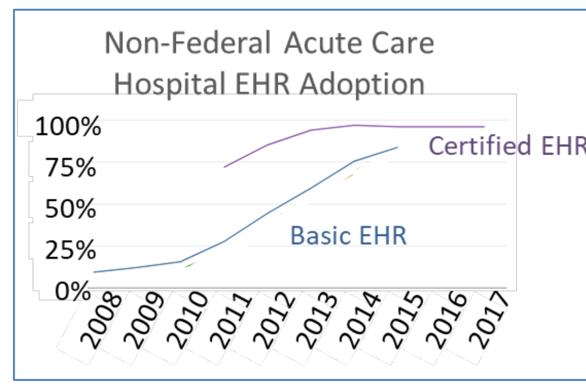
Motivation: Improving ARIA sufficiency

Existing algorithms …

- Rely on structured data (Dx, Px, Rx, demographics, …)
- Have good sensitivity
- Lack positive predictive value
  - <2/3 are true cases (Walsh et al. 2013)

A challenging outcome to model

- Rare (limited training data)
- "Rule-out" coding/mis-diagnosis
- Complex diagnosis
  - Ball et al. 2018: NLP of chart notes may help



EHR data = opportunity?

Objective: Improve outcome identification

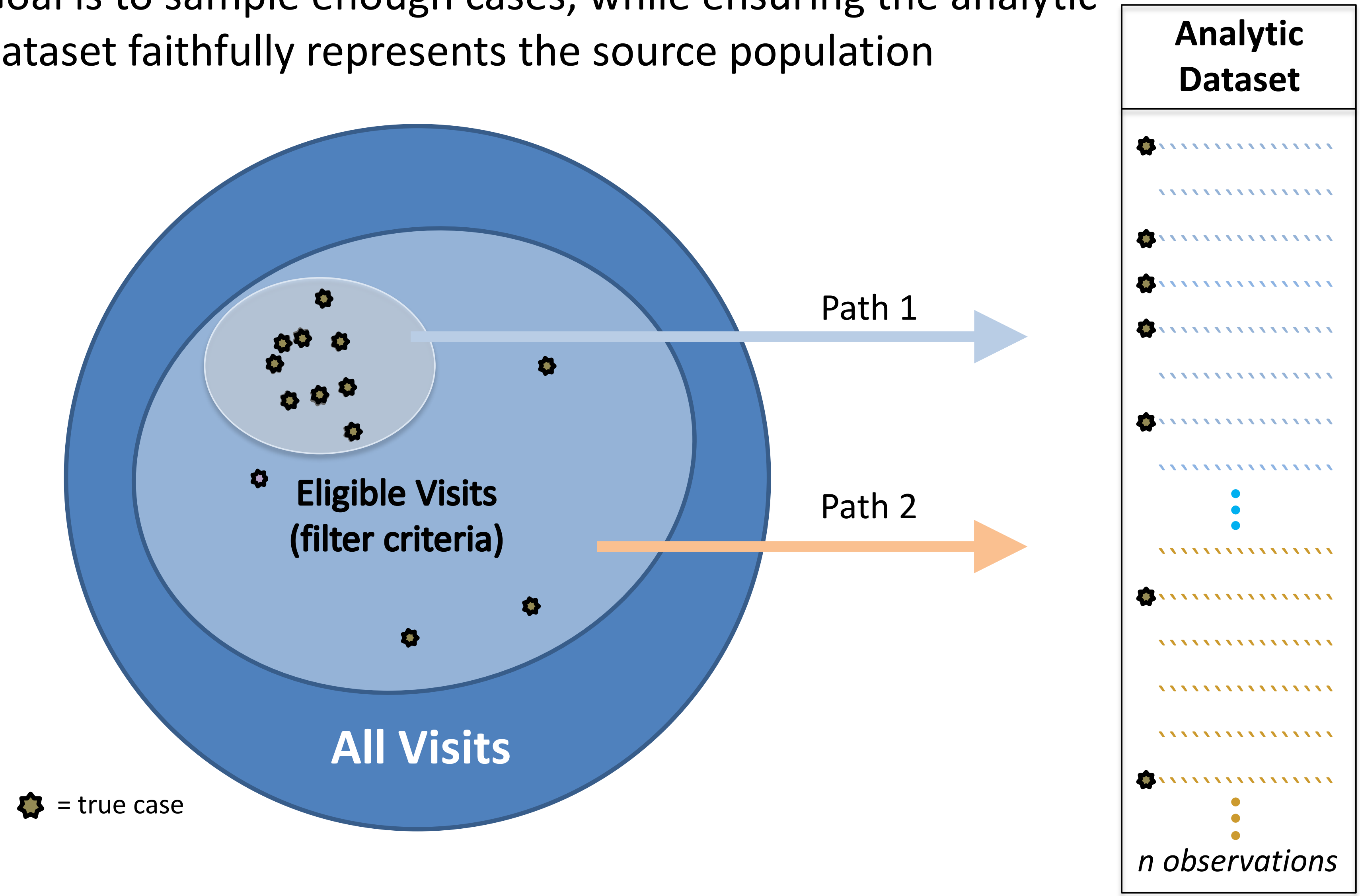
- Use **NLP**-extracted data to enrich covariates
  - Are clinical diagnostic criteria documented?
    - Organ system involvement (e.g., skin, respiratory, BP)
    - Clinical course (e.g., rapid onset)
  - Telltale utilization
    - Treatments (e.g., *multiple* epinephrine administrations)
    - Hospital admission “for observation”
  - Are competing explanations described?
- Use **machine learning** to better model “signal” in a rich set of covariates

Design: population, outcomes, covariates

- Study period: 10/2015 – 12/2018
- Population: Age ≥1-year
  - Kaiser Permanente Washington (KPWA)
  - Kaiser Permanente Northwest (KPNW)
- Eligibility
  - Anaphylaxis diagnosis (ED/inpatient or outpatient)
  - ≥12 months prior enrollment (*w/o anaphylaxis diagnosis*)
- Gold standard outcomes (clinician review)
- Covariates (manually engineered)
  - Structured: Demographics, Dx, Px, Rx, encounters
  - NLP-derived: Symptoms, clinical criteria, …

Stratified Random Sampling

Goal is to sample enough cases, while ensuring the analytic dataset faithfully represents the source population



Design: Gold standard creation

- KPWA:
  - Dual blind manual review by clinicians
  - Decisions recorded on spreadsheet
- KPNW
  - Dual blind manual review by non-clinician abstractors following a written protocol
  - Decisions, supporting documentation in REDCap
  - Difficult cases → clinician review

Design: Manual covariate curation

- Clinicians & informaticists reviewed/discussed charts

Nose: No rhinorrhea.
Mouth: Mild swelling
Neck: Nontender, supple, no lymphadenopathy
Lymphatic: No lymphadenopathy noted.
Cardiovascular: Normal heart rate, normal rhythm, no murmurs, no rubs, no gallops. Intact distal pulses, no tenderness, no cyanosis, no clubbing.
Respiratory: Normal breath sounds, no respiratory distress, no wheezing, no chest tenderness. No severe stridor, severe wheezing
Abdomen: Bowel sounds are present. Abdomen is soft, no tenderness, no masses, no rebound or guarding. No organomegaly. No hernia.
GU: No CVA tenderness. Bladder is nontender and not distended.
Skin: Erythema noted about the face and minimally to the hands
Back: No tenderness
Musculoskeletal: No tenderness to palpation or major deformities noted. No back or cervical spine tenderness. No edema.

Pt after her CTA ABdomen she develop allergic /anaphylactic reaction in ED with nausea/vomting and tachycardia and hypotensive and she became hypoxic ,even so she had many ct with contrast without any reactions

She received multiple rounds of epinephrine , benadryl ,decadron ,pepcid

SHE FEEL MUCH BETTER NOW except some dizziness when she walk

- Curated structured and NLP covariates we judged *clinically relevant and feasible*
- *We did <u>not</u> use gold standard labels to curate covariates (due to small sample size)*

Design: Structured covariates

Manually curated from the Sentinel common data model

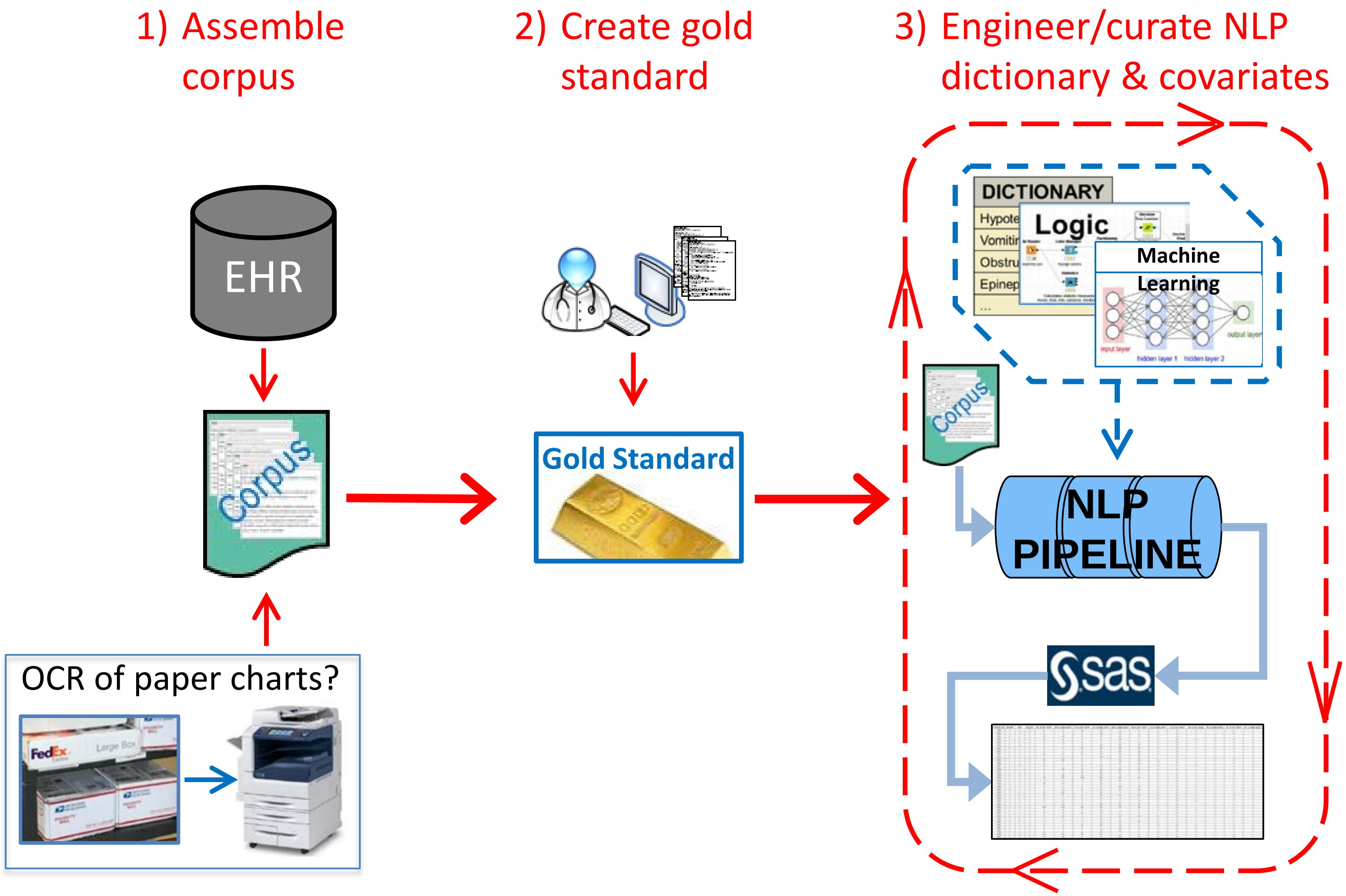
Anaphylaxis Structured Covariates	
Category	**Count**
Demographics (age, sex, race, enrollment history)	6
Care setting (ED, IP, outpatient)	6
History of allergic reaction/anaphylaxis	4
Exposures (e.g., imaging dye, immunotherapy)	3
Treatment (e.g., epinephrine, steroids, intubation, CPR)	10
Competing diagnoses (asthma, COPD, angioedema, infection)	11
Other (summer event, labs, immunology follow-up)	3
TOTAL:	43

Design: Covariate curation – NLP-derived

NLP definitions

- **NLP** – **Converts** information in **unstructured clinical text** to **structured data** using methods from computer science, artificial intelligence, and computational linguistics
- ***Manual* NLP** – Human curation of NLP dictionaries and NLP-derived covariates guided by domain-specific clinical knowledge, informatics expertise, and "gold standard" data
- ***Automated* NLP** – (semi)automated engineering of NLP dictionaries and covariates using "silver standard" data and data-driven approaches to algorithm development

Design: Covariate curation – NLP process



Design: Manual NLP process – dictionary

- 843 terms

  >50% “skin/mucosal”

- Concepts per chart:

  Median: 128

  Min: 9

  Max: 2,092

ID	CUI	TEXT	SOURCE	SOURCETYPE
3001	GI001	abd pain	GI	ABDOPAIN
6001	SM001	abdomen with erythema	GI	ABDOPAIN
3002	GI002	abdominal pain and shock	GI	ABDOPAIN
2001	BP001	acute hypotensive	BPREDUCED	HYPOTENSION
5001	RC001	acute hypoxic	RESPCOMP	HYPOXIA
5002	RC002	acute respiratory failure	RESPCOMP	RESPFAIL
5003	RC003	acute upper airway obstruction	RESPCOMP	AIRWAY
4001	OT001	admission diagnosis	OTHER	DIAGNOSIS
4002	OT002	admitting diagnosis	OTHER	DIAGNOSIS
5004	RC004	airway narrowing	RESPCOMP	AIRWAY CONSTRICTION
5005	RC005	airway obstruction	RESPCOMP	AIRWAY CONSTRICTION
6002	SM002	airway itch	SKINMUC	AIRWAY
6003	SM003	airway remains swolen	SKINMUC	ORALSWELL
6004	SM004	airway remains swollen	SKINMUC	AIRWAY
4003	OT003	alergic reacton	OTHER	ALLERGREACT
6005	SM005	all skin appears red	SKINMUC	RASH
4004	OT004	allergic reaction	OTHER	ALLERGREACT
4005	OT005	allergic reacton	OTHER	ALLERGREACT
4006	OT006	allergic to	OTHER	HYPO
4007	OT007	allergies	OTHER	HYPO
4008	OT008	allergy comment	OTHER	HYPO
2002	BP002	almost passed out	BPREDUCED	SYNCOPE
5006	RC006	altered mentation	RESPCOMP	ALTERED MENTATION
1001	AN001	anaphalytic shock	ANAPH	ANAPH SHOCK
1002	AN002	anaphylactic shock	ANAPH	ANAPH SHOCK
1003	AN003	anaphylaxis allergic shock	ANAPH	ANAPH SHOCK
4009	OT009	anaphylaxis	OTHER	ANAPH
2003	BP003	and hypotensive	BPREDUCED	HYPOTENSION
2004	BP004	and passed out	BPREDUCED	SYNCOPE
2005	BP005	and shock	BPREDUCED	SHOCK
6006	SM006	angioedema	SKINMUC	ANGIOEDEMA

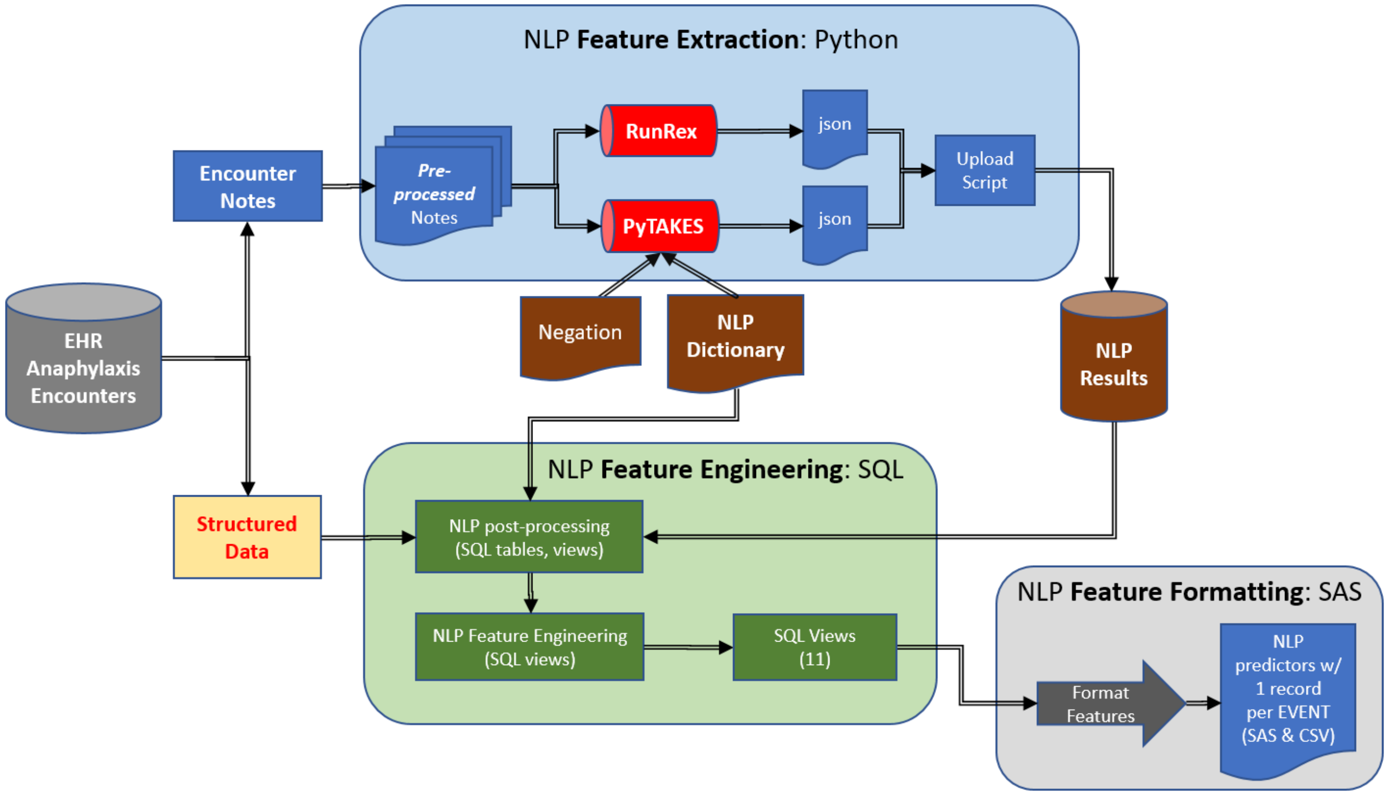
Design: Manual NLP process – dictionary

Anaphylaxis concepts in the NLP dictionary (N terms)			
• BRADYCARDIA (13)	• COARSE BREATH SOUND (4)	• ANGIOEDEMA (102)	• THROAT (4)
• CARDIACARRHYTH (8)	• DYSPHONIA (1)	• DIFFICULTY SWALLOWING (14)	• TINGLING (1)
• CARDIOCOLLAPSE (2)	• DYSPNEA (55)	• DYSPHAGIA (1)	• TINGLY SOFT TISSUE (14)
• COLLAPSE (2)	• HOARSENESS (7)	• EDEMA (4)	• URTICARIA (24)
• END ORGAN (2)	• HYPOXEMIA (6)	• ERYTHEMA (42)	• ALLERGREACT (5)
• HYPOTENSION (77)	• HYPOXIA (3)	• EYE SWELLING (33)	• ANAPH (5)
• PALPITATIONS (3)	• IMPENDING DOOM (2)	• FACIAL SWELLING (20)	• COMPLAINT (12)
• SHOCK (3)	• INTUBATION (6)	• FLUSH (38)	• DIAGNOSIS (8)
• SYNCOPE (30)	• LARYNGEAL OEDEMA (1)	• HIVES (68)	• DIFFERENTIAL (1)
• TACHYCARDIA (9)	• RESP COMPROMISE (3)	• ITCHING (14)	• HYPO (6)
• **ABDOPAIN (3)**	• RESP DISTRESS (2)	• ITCHY SOFT TISSUE (15)	• IMPRESSION (1)
• **VOMIT (1)**	• RESPFAIL (1)	• METALLIC TASTE (1)	
• AIRWAY (4)	• RONCHI (2)	• MOUTH (1)	
• AIRWAY CONSTRICTION (4)	• STRIDOR (3)	• MOUTHSWELL (4)	
• ALTERED MENTATION (1)	• TACHYPNEA (5)	• ORALSWELL (4)	
• APHONIA (3)	• THROAT CLOSURE (14)	• PRURITUS (15)	
• BREATH (6)	• THROAT TIGHTNESS (34)	• RASH (7)	
• BRONCHOSPASM (1)	• TIGHTNESS BREATHING (1)	• REACTION (1)	
• CHEST DISCOMFORT (2)	• VOICE QUALITY (1)	• SOFT TISSUE SWELLING (4)	
• CHEST TIGHTNESS (9)	• WHEEZE (8)	• SWELLING (31)	

• REDUCED BLOOD PRESSURE • GASTROINTESTINAL • RESPIRATORY COMPROMISE • SKIN/MUCOSAL
• OTHER

Design: Transportable NLP system

- Developed & applied at KPWA
- Transported to KPNW via GitHub
    - NLP system (Python), SQL queries, SAS code, documentation

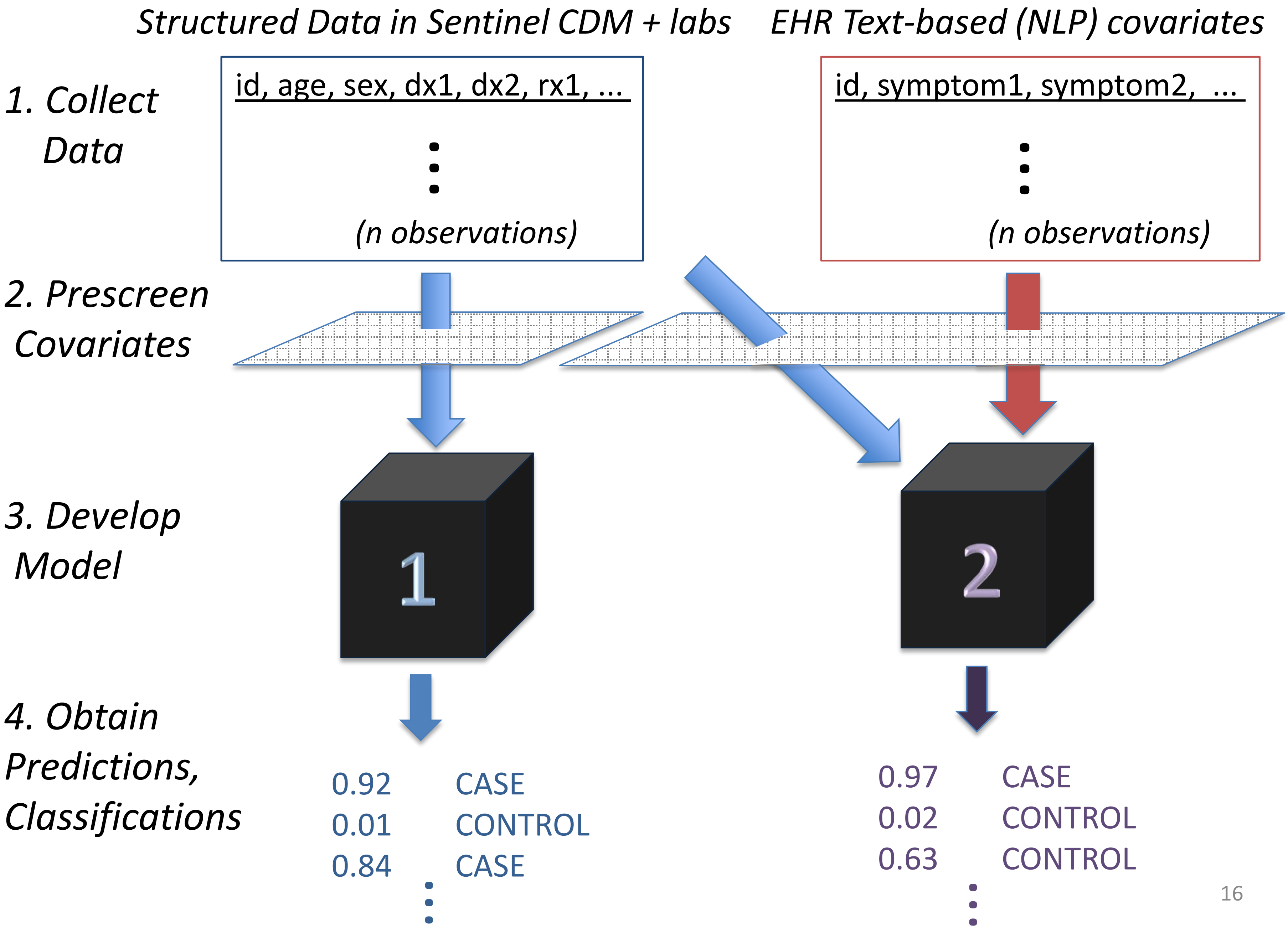


Design: NLP covariates

- 116 NLP covariates engineered for use in modeling (selected from >450 candidates):

Anaphylaxis NLP Covariates	
Category	**Count**
Symptoms (skin/mucosal, respiratory compromise, reduced BP)	10
Anaphylaxis concepts (e.g., wheezing, epinephrine, …)	66
Diagnostic criteria (e.g., skin/mucosal + [resp. comp. *or* ↓BP])	30
Explicit diagnoses of anaphylaxis	5
"Special features" (e.g., admitted to hospital for observation)	5
TOTAL:	116

Model Development

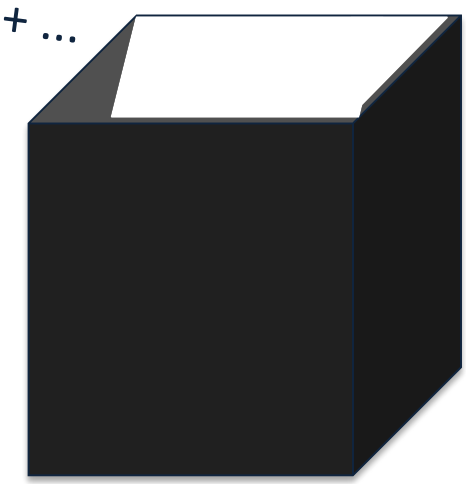


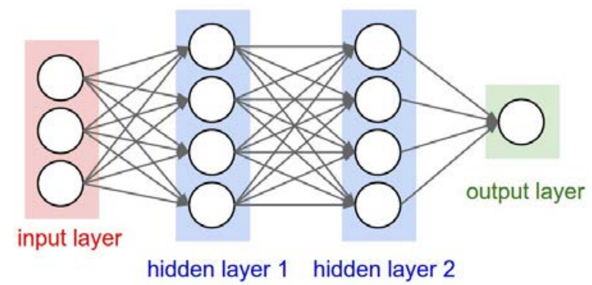
What’s in the box?

- Logistic regression
- Elastic net
- Bayesian Additive Regression Trees
- Neural network
- Boosted Trees

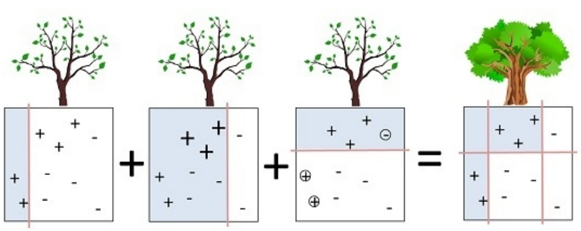
Super Learner
(a weighted combination)

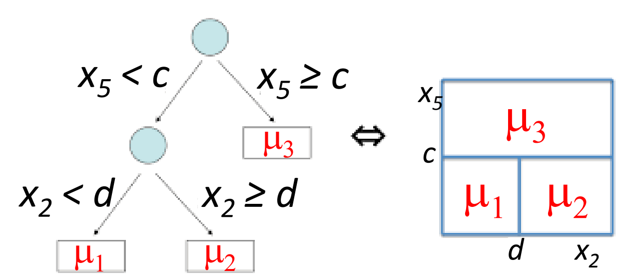
$\beta_0 + \beta_1 * age + \beta_2 * ICD10 + \ldots$





Boosted Regression Tree is a hierarchical and supervised machine learning method that combines weak learners (binary splits) to strong prediction rules that allow a flexible partition of the feature space.





75 Models

Algorithm	R package name	Notes on tuning parameters
1. Logistic regression	(base)	
2. Elastic net	glmnet	10-fold cross validation to select optimal alpha and lambda
3. Gradient boosting	xgboost	Variant 1: maximum tree depth = 2 Variant 2: maximum tree depth = 4
4. Bayesian Additive Regression Trees	dbarts	Variant 1: k = 2 (default), Variant 2: k=1 (reduced regularization prior)
5. Neural network (feed forward)	neuralnet	Variant 1: 1 hidden layer containing 1 node Variant 2: 1 hidden layer containing 3 nodes
6. Super Learner	SuperLearner	

3 x (3 x 8 + 1) = 75

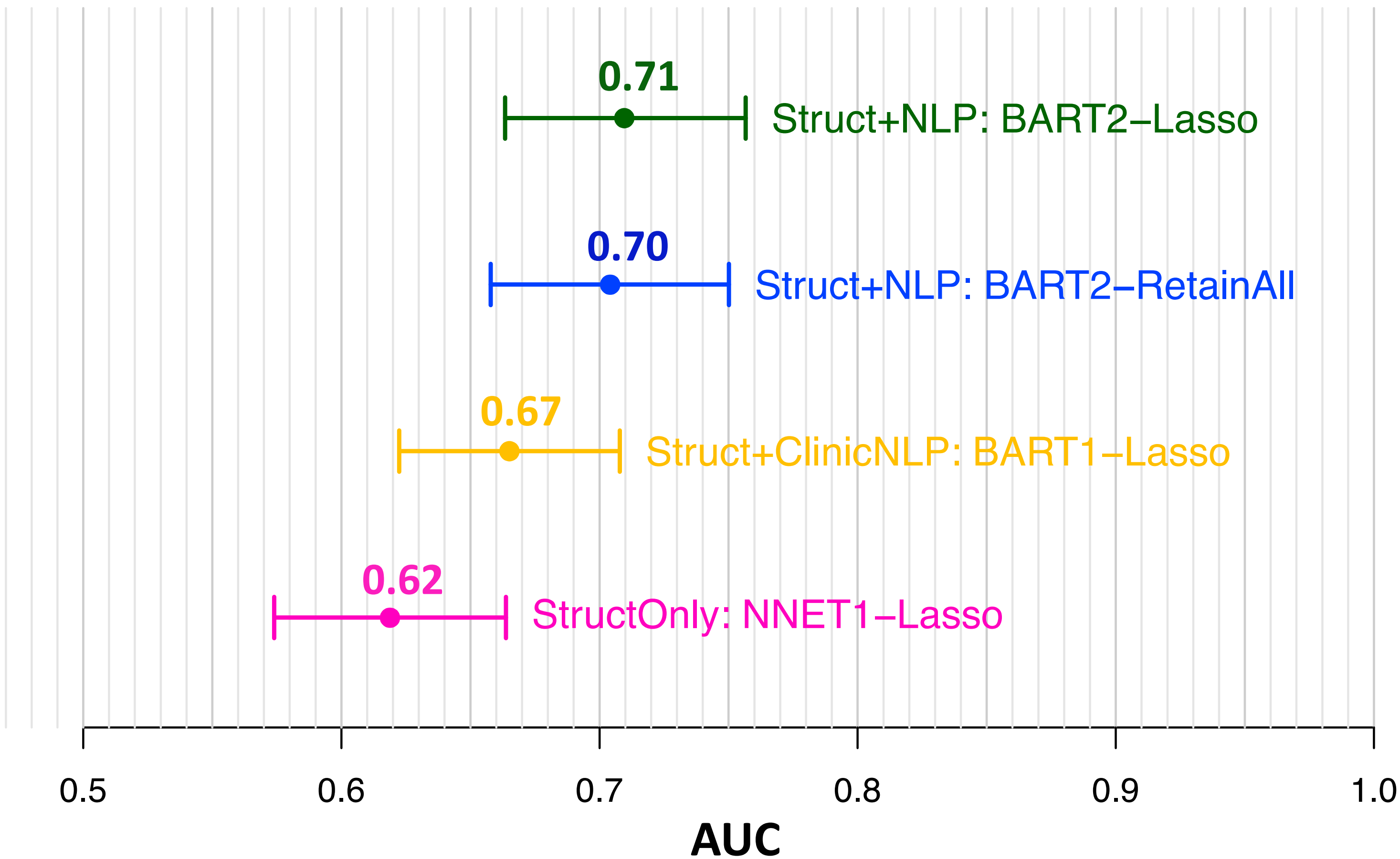
3	x (3	x 8	+ 1)	= 75
Datasets	Covariate Selection	Variants of six prediction algorithms	SL weighted combination	
structured data structured+NLP struct+clinicianNLP	none lasso clustering			

Results

Path	KPWA (n=239)		KPNW (n=277)	
	Cases	Controls	Cases	Controls
1	106 (65.8%)	55 (34.2%)	115 (70.6%)	48 (29.4%)
2	48 (61.5%)	30 (38.5%)	65 (57.0%)	49 (43.0%)
all	154 (64.4%)	85 (35.6%)	180 (65.0%)	97 (35.0%)

Results

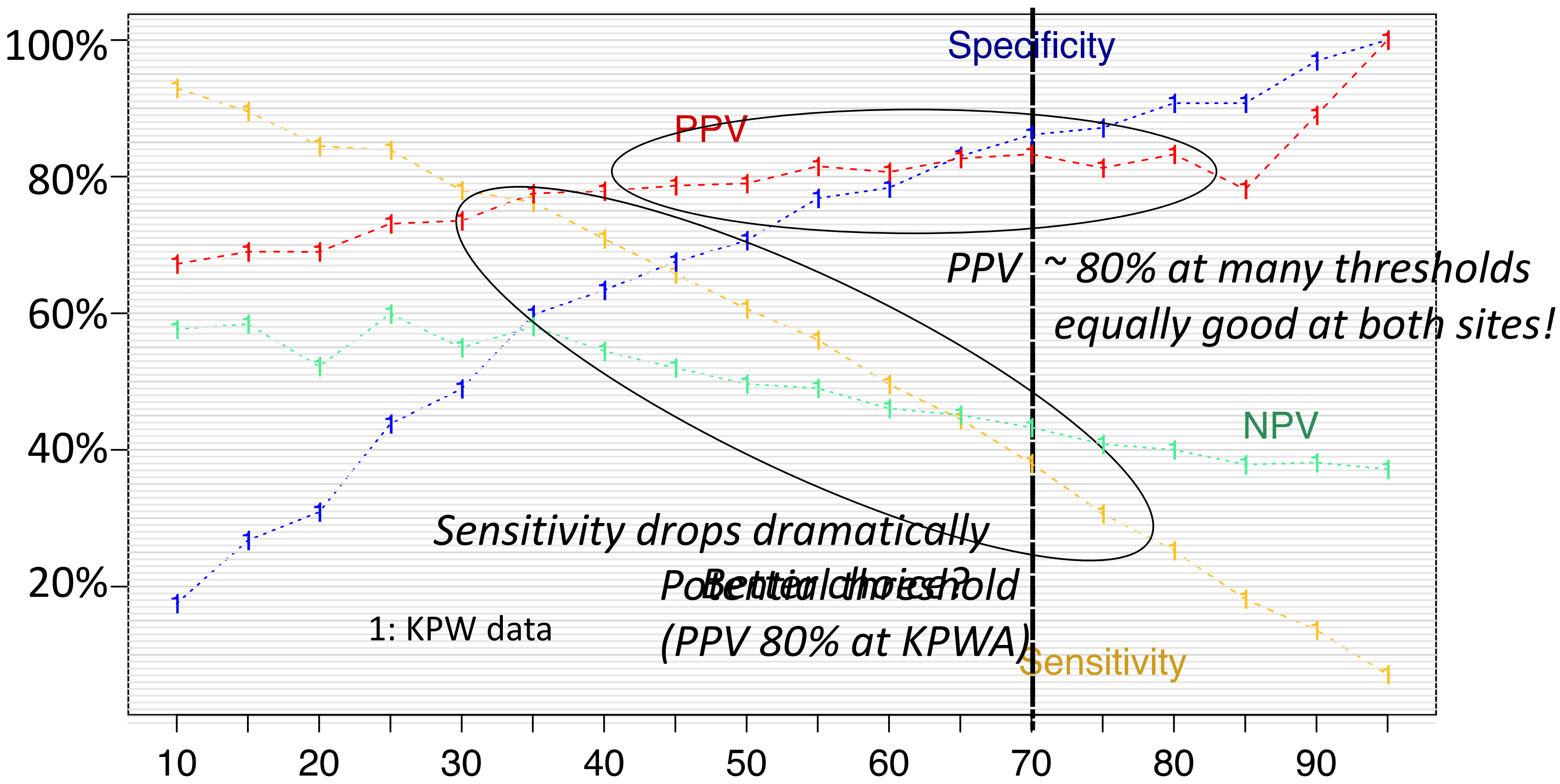
Cross-validated AUCs for best models for each KPWA data set



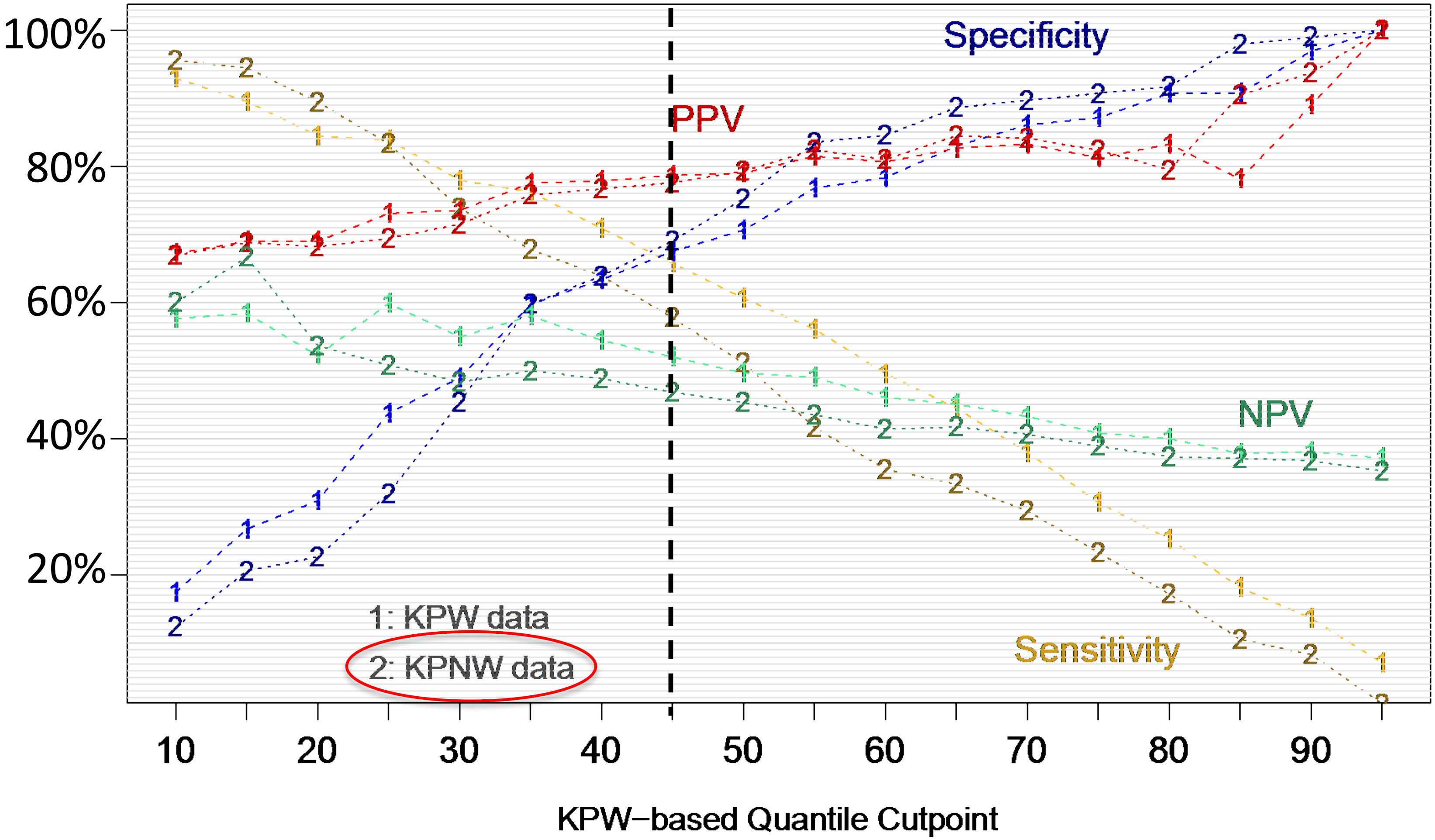
Results

- Two versions of Bayesian Additive Regression Trees combining structured data with NLP-derived covariates were nearly identical
- BART2-RetainAll generalized best to KP Northwest external validation set
  - cvAUC at KPWA = 0.70, cvAUC at KPNW = 0.67
  - Next step: Choose a prediction risk threshold for classification
    - if risk >= *threshold*, classify as a case, otherwise a control
    - most interested in high positive predictive value (PPV), high sensitivity (% cases identified)

Results: Performance Metrics



Results: Performance Metrics



Implications

- NLP-derived covariates derived from EHR data improve algorithm performance
- Machine-learning models are well-suited to this type of data
- Next steps:
  – Explore two-stage models (to correct classification errors)
  – Explore modeling all data (KPWA 239 + KPNW 277 = 516)
  – Explore (semi)automated NLP approaches

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** Study team members listed alphabetically*

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Questions & Discussion

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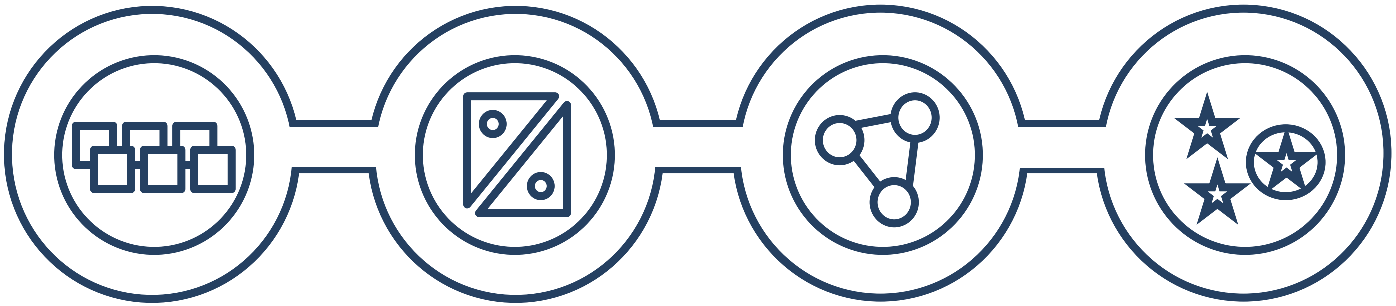
Extra Slides

Priorities	Goals	Initiatives	Outputs
Establishing data infrastructure	Establishing a Sentinel electronic health record (EHR) network requires determining where to source and how to structure the data, as well as implementation of robust governance, harmonization, and quality assurance (QA) processes.	• Horizon scan of EHR databases • Adding unstructured data to the Sentinel common data model • Assessment and validation of source data mappings to improve the reliability and reproducibility of real-world data sources • Harmonizing EHRs from heterogenous systems • Developing and integrating approaches to identifying date and cause of death • FHIR implementation preparedness	• EHR data partners • Set of necessary EHR data elements • EHR common data model • Data governance process • Data harmonization and QA strategy • Data quality metrics • Sentinel death index • FHIR strategy
	Frameworks and tools are needed for extracting critical information from EHR data to enable and enhance EHR-based computable phenotyping and to support EHR-based descriptive, inferential, and detection queries in Sentinel.	• Extending machine learning methods development in Sentinel: follow-up analyses for anaphylaxis algorithm and formalization of a general phenotyping algorithm • Scalable automated natural language processing- (NLP-) assisted chart abstraction • Advancing scalable NLP approaches for unstructured EHR data • Improving probabilistic phenotyping of incident outcomes through enhanced ascertainment with NLP	• Computable phenotyping framework • NLP tools for cohort identification, exposure assessment, covariate ascertainment, and outcome identification • Chart review automation approaches • Automated feature extraction tool to improve confounding control in EHR data • NLP-assisted chart abstraction tool
	Developing, evaluating, and implementing advanced epidemiologic and statistical methods will enable Sentinel to make best use of EHR data to increase Active Risk Identification and Analysis (ARIA) sufficiency and expand the acceptance and use of real-world data for regulatory decision-making.	• Empirical evaluation of the causal inference effects of utilizing best practices for pharmacoepidemiologic studies • Enhancing causal inference in the Sentinel system: an evaluation of targeted learning and propensity scores • Approaches for handling missing laboratory data • Subset calibration for detecting and correcting for bias • Development of performance metrics and reporting standards • Advancing distributed regression in Sentinel	• Causal inference design and analysis framework • Super learner, target maximum likelihood estimation, complex treatment strategy analysis, missing data, subset calibration, and distributed regression tools • Inferential query performance metrics and reporting standards
	Building safety signal detection approaches for specific use cases and in EHR data, in general, will substantially enhance Sentinel's capabilities for ensuring medical product safety but requires special design and analytic methods.	• Evaluation of existing approaches to EHR-based signal detection • Empirical comparison of EHR-based approaches to signal detection in Sentinel • Developing and advancing EHR-based signal detection methods • Advancing methods for safety signal detection for pregnancy and birth outcomes • Developing and evaluating a cancer signal detection tool	• Methodological framework for EHR-based signal detection • General safety signal detection tool for EHR data • Enhanced methods for signal detection for pregnancy and birth outcomes • Tool for cancer safety signal detection

slide courtesy of Joshua Gagne



Data infrastructure

- Data partners
- Data elements
- Governance
- Harmonization
- Data quality assurance

Feature engineering

- Natural language processing
- Automated feature extraction
- Computable phenotyping

Causal inference

- Target trial design
- Advanced, semi-automated analytics
- Subset calibration
- Distributed methods

Detection analytics

- Methodological framework
- Statistical methods
- Cancer outcomes
- Pregnancy and birth outcomes

slide courtesy of Joshua Gagne

Variable Importance (struct. + all NLP)

Top 5 structured:

1. Number of prior years with allergic reaction diagnoses (-)
2. Allergic reaction diagnosis in the prior year (-)
3. Same-day exposure to any imaging procedure (-)
4. Prescription for antihistamines @discharge (-)
5. Prescription for corticosteroids @discharge (-)

Top 5 NLP-derived:

1. ≥2 affirmative mentions of hypotension
2. Any description of respiratory compromise and reduced BP near a mention of either anaphylaxis as a diagnosis, epinephrine administration, suddenness of onset, or admission for observation
3. ≥2 affirmative mentions of skin/mucosal involvement and either respiratory compromise or reduced blood pressure near anaphylaxis as a diagnosis
4. ≥2 affirmative mentions of wheezing
5. any description of skin/mucosal involvement and reduced blood pressure near a mention of either anaphylaxis as a dx, epinephrine administration, suddenness of onset, or admission for observation

NLP dictionary: 2. Exploratory query

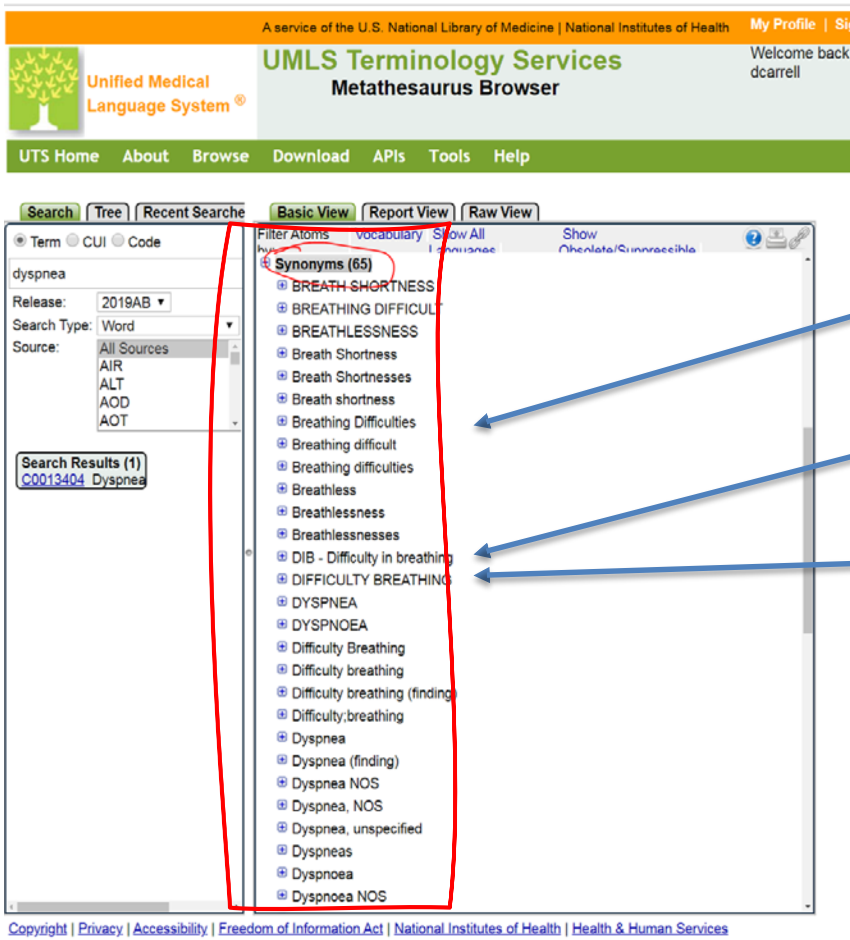
- Use relational database full-text indexing
- Find Synonyms of “dyspnea”
  - Known: “shortness of breath” and “trouble breathing”
  - Review notes with breath
    - 208 strings yield 5 new terms

Before_Term	Term	After_Term
was closing and wheezing and difficulty	breath	ing. She has some mild reactive airway d
and throat swelling. Having difficulty	breath	ing and a hard time swallowing saliva. W
rhythm. RESP: Clear to auscultation.	breath	ing comfortably. Jerico endorses feel
like this before. Feels like she cannot	breath	. Cannot swallow. Has not taken anything
omplaint: Allergic Reaction; Edema; and	breath	ing Problems HISTORY AND PHYSICAL E
tightening and it was a little hard to	breath	e so comes here for evaluation where she
ing Swelling around eyes, tears, no	breath	ing problems • Lovastatin • Sulfa (
en he began to cry and said he couldn't	breath	. He sent Mom a picture of his face- she
the first time. Pt apparently stopped	breath	ing briefly, was given epinephrine and a

NLP dictionary: 3. Synonyms

UMLS: Unified Medical Language System – Metathesaurus

“Dyspnea”



“breathing difficulties”

“DIB”

“difficulty in breathing”

…

NLP dictionary: Clinical knowledge sources

- 1st step in Yu and colleagues 2015 JAMIA paper "AFEP"


Toward high-throughput phenotyping: unbiased automated feature extraction and selection from knowledge sources

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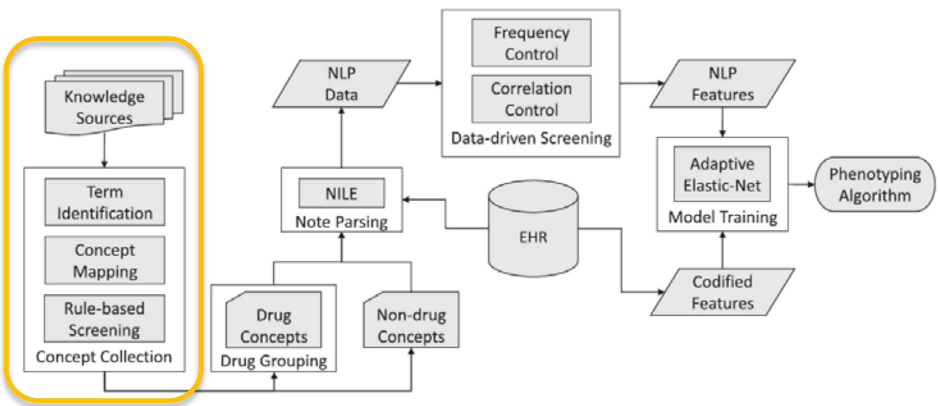
PUBLISHED ONLINE FIRST 30 April 2015

Sheng Yu[1,2,3,*], Katherine P Liao[2,3], Stanley Y Shaw[4], Vivian S Gainer[5], Susanne E Churchill[5], Peter Szolovits[6], Shawn N Murphy[4,5], Isaac S Kohane[3,7], Tianxi Cai[8]



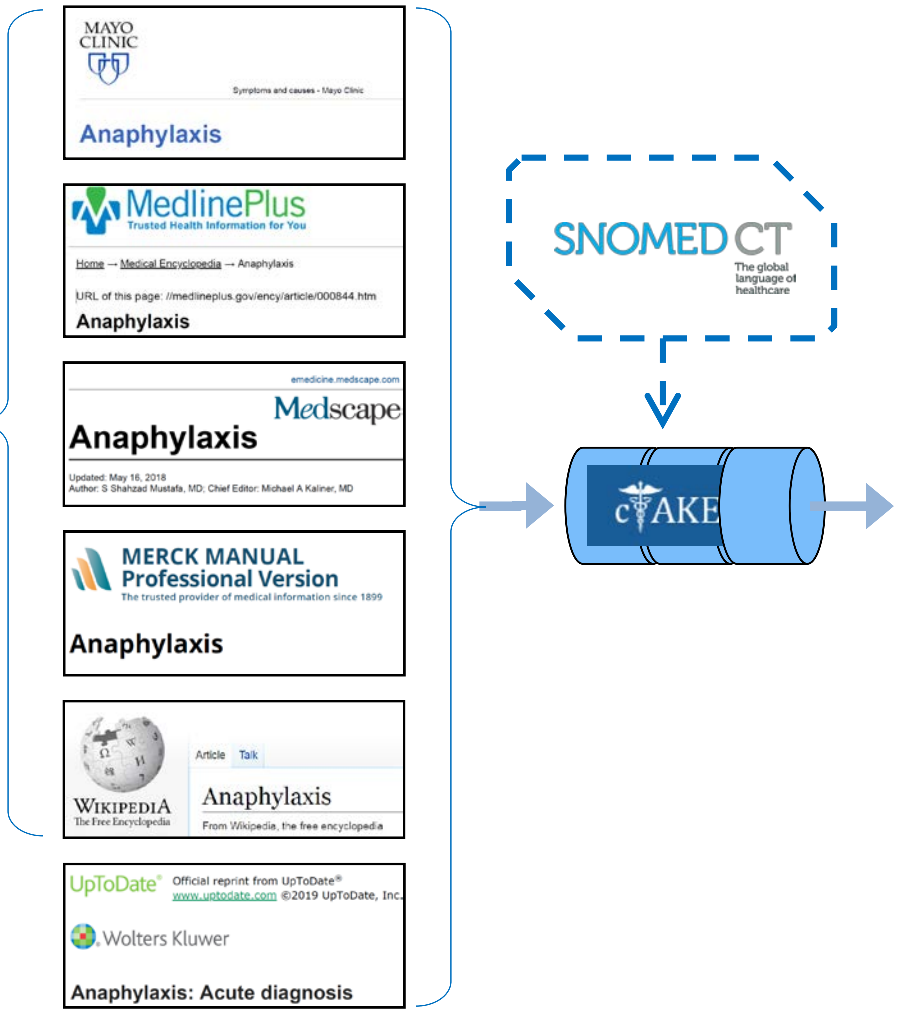
- Important terms will appear in ≥3 clinical knowledge base articles

Yu et al. Toward high-throughput phenotyping: unbiased automated feature extraction and selection from knowledge sources JAMIA 2015;22:993–1000.

NLP dictionary: Clinical knowledge sources

5 clinical knowledge base articles on the topic anaphylaxis

(+ UpToDate)



	Source	CUI_Code	Term
1	SNOMEDCT_US	C0663655	abacavir
2	SNOMEDCT_US	C0000726	Abdomen
3	SNOMEDCT_US	C1122087	adalimumab
4	SNOMEDCT_US	C0001443	Adenosine
5	SNOMEDCT_US	C3536832	Air
6	SNOMEDCT_US	C0001927	Albuterol
7	SNOMEDCT_US	C0002055	Alkalies
8	SNOMEDCT_US	C0002092	Allergens
9	SNOMEDCT_US	C0002508	Amines
10	SNOMEDCT_US	C0002575	Aminophylline
11	SNOMEDCT_US	C0002667	Amphetamines
12	SNOMEDCT_US	C0002771	Analgesics
13	SNOMEDCT_US	C0002792	anaphylaxis
14	SNOMEDCT_US	C0002932	Anesthetics
15	SNOMEDCT_US	C0002994	Angioedema
16	SNOMEDCT_US	C0003018	Angiotensins
17	SNOMEDCT_US	C0003232	Antibiotics
18	SNOMEDCT_US	C0003241	Antibodies
19	SNOMEDCT_US	C0003320	Antigens
20	SNOMEDCT_US	C0003360	Antihistamines
21	SNOMEDCT_US	C0003445	Antitoxins
22	SNOMEDCT_US	C0003450	Antivenin
23	SNOMEDCT_US	C0003467	Anxiety
24	SNOMEDCT_US	C0003483	Aorta
25	SNOMEDCT_US	C0003564	Aphonia
26	SNOMEDCT_US	C0233485	apprehension
27	SNOMEDCT_US	C0003842	Arteries
28	SNOMEDCT_US	C0004044	Asphyxia
29	SNOMEDCT_US	C0004057	Aspirin
30	SNOMEDCT_US	C1510438	Assay
31	SNOMEDCT_US	C0004096	Asthma
32	SNOMEDCT_US	C0231221	Asymptomatic
33	SNOMEDCT_US	C0392707	Atopy
34	SNOMEDCT_US	C0004259	Atropine
35	SNOMEDCT_US	C0004268	Attention
36	SNOMEDCT_US	C0004271	Attitude
37	SNOMEDCT_US	C0004398	Autopsy
38	SNOMEDCT_US	C0004521	Aztreonam
39	SNOMEDCT_US	C0004827	Basophils
40	SNOMEDCT_US	C0005558	Biopsy
41	SNOMEDCT_US	[illegible]	[illegible]

367 unique SNOMED terms

90 terms appear in ≥3 sources

NLP dictionary: Clinical knowledge sources

90 terms in the Standard Nomenclature of Medicine, Clinical Terms (SNOMED CT) appeared in at least 3 anaphylaxis knowledge base articles on anaphylaxis.				
Appearing in 5-6 articles		**Appearing in 4 articles**	**Appearing in 3 articles**	
Allergens	Blood	Angioedema	Air	Lung
Anaphylaxis	~~Cells~~[1]	Anxiety	Albuterol	Muscle
~~Diagnosis~~[1]	Dizziness	Atopy	Antigens	omalizumab
Diarrhea	Dyspnea	Basophils	Arteries	Ovum
~~Disease~~[1]	Exercise	Coughing	Asphyxia	Oxygen
Epinephrine	Heart	Edema	Autopsy	Panic
Hypersensitivity	Histamine	Esthesia	Chest	Proteins
Shock	Hypotension	Flushing	~~Complication~~[1]	receptor
Skin	Injection	Glucagon	Confusion	Redness
Urticaria	Latex	Hoarseness	Congestion	Seizures
Venoms	Nausea	Mastocytosis	Extravasation	~~Services~~[1]
Vomiting	Obstruction	Nose	Eye	~~Source~~[1]
Wheezing	Pain	Opioids	~~Gold~~[2]	Uterus
Abdomen	Palpitations	Rhinorrhea	Headache	Vaccines
Antibiotics	Pruritus	Stridor	Immunoglobulins	Vancomycin
Antibodies	Swelling	Tachycardia	Immunotherapy	Vasodilation
Antihistamines	Syncope	Tryptase	Lactams	Veins
Aspirin	Tongue		Larynx	
Asthma			Lightheadedness	
37 terms (13 in 6 and 24 in 5)		17 terms	36 terms	

[1] Terms unlikely to be useful for distinguishing anaphylaxis cases from non-cases.

[2] “Gold” is an author name appearing in 3 bibliographies (N Engl J Med 2008; 358:28).

NLP: Feature engineering (manual)

Diagnostic criteria for anaphylaxis (Sampson/NIAID 2006)

Sampson Criterion	**Clinical criteria**	**NLP Features**
#1	Skin/mucosal involvement (SM), *plus either:* Respiratory compromise (RC) *or* Reduced blood pressure (BP)	SM+RC SM+BP
#2	Exposure to a likely allergen *for that patient*[1] *plus any 2:* Skin/mucosal involvement (SM) *or* Respiratory compromise (RC) *or* Reduced blood pressure (BP) *or* Gastrointestinal symptoms (GI)	~~SM+RC~~[2] ~~SM+BP~~[2] SM+GI RC+BP RC+GI BP+GI
#3	Exposure to a known allergen *for that patient*[1] *plus:* Reduced blood pressure (BP)	None[3]

1. Allergen exposure not operationalized because too difficult to do accurately via NLP.
2. This combination not included in criterion #2 because already in criterion #1.
3. Not operationalized because w/o allergen exposure reduced BP is non-specific.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – second national Institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. J Allergy Clin Immunol. 2006;117:391–397