Harnessing Web Search Data as Complementary Signals for Pharmacovigilance

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With:
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Next Generation Surveillance
IOM
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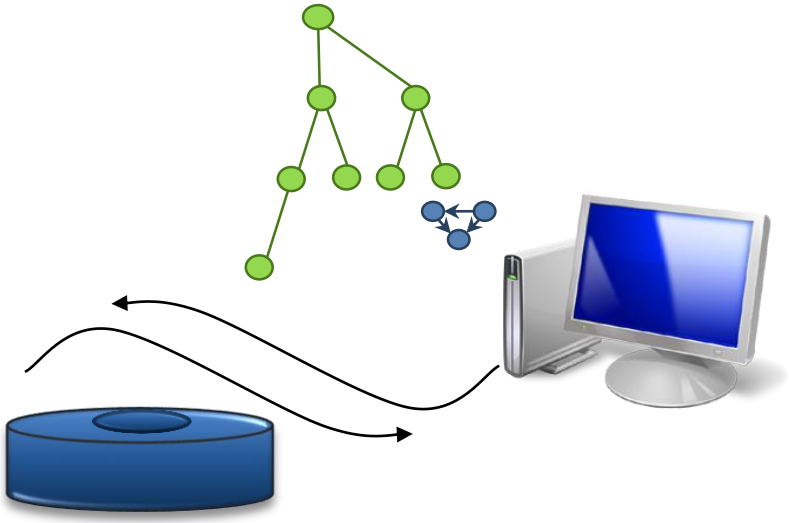
Web Search as Sensor

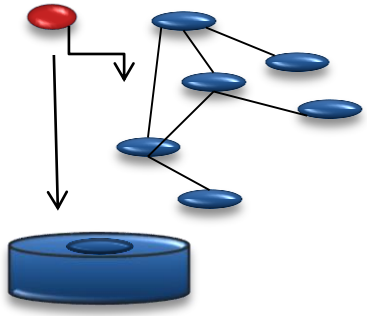
Insights & inferences from search logs

Epidemiology, diagnosis, illness, medications

Pew (2013): 70% online pursue health info.

80% health inquiries start at search





Online Behavioral Data as Sensors

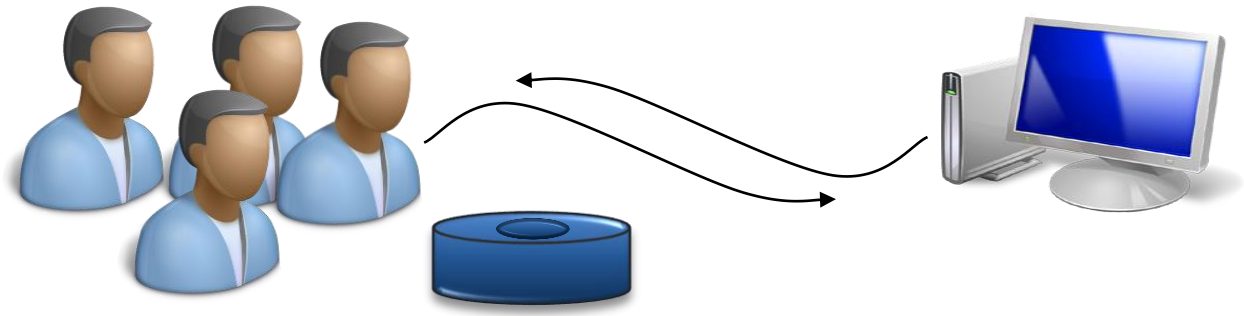
- Models of sensor error
- Detecting rare outcomes
- Models of users & reporting

e.g., detecting *experiential* vs. *exploratory* signals

Signals about Medications

→ Web search as sensor for ADRs?

1 in 250 of people query on top-100 drugs.



Signals about Medications

2011 finding (Tatonnetti, et al.):

Paxil + Pravachol →  *Hyperglycemia*

Pravachol → ✕ *Hyperglycemia*

Paxil → ✕ *Hyperglycemia*

R. White, N. Tatonetti, N. Shah, R. Altman, E. Horvitz, JAMIA 2013

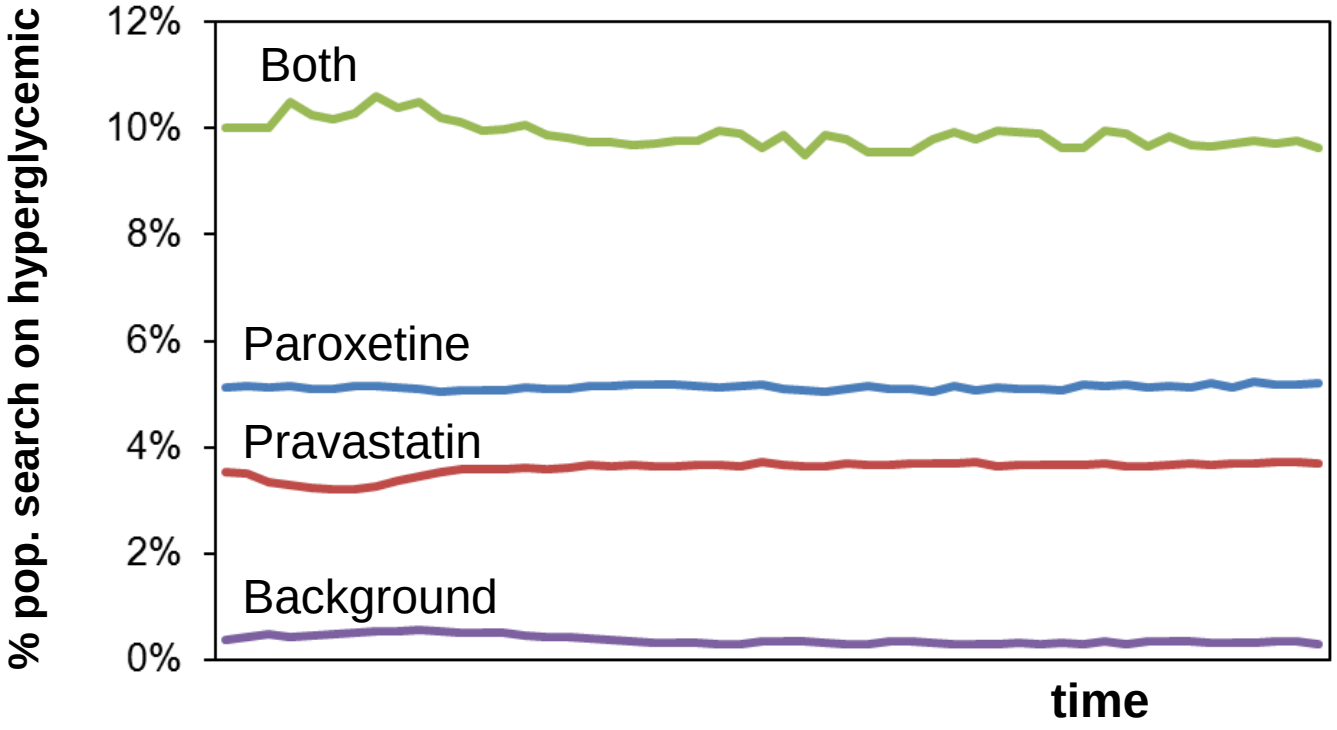
Terms Linked with Hyperglycemia

appetite increase	feet tingling	poor wound healing
blood glucose high	frequent urinating	short of breath
blood sugar high	frequent urination	shortness of breath
blood sugar increase	glucose high	skin tingling
blurred vision	heel tingling	sleepiness
blurry vision	high glucose	sleepy
breathing difficulty	high blood glucose	slow healing
breathing trouble	high blood sugar	slow wound healing
breathless	hunger	thirst
breathlessness	hungry	thirstiness
coma	hyperglycemia	thirsty
confused	hyperglycaemia	tingling feet
confusion	impotence	tingling heel
decreased libido	impotent	tingling skin
decreased sex drive	increase blood sugar	tired
decreased sexual desire	increased appetite	tiredness
dehydrated	increased urination	trouble breathing
dehydration	itchy skin	xerostomia
diabetes	labored breathing	
diabetic	light headed	
difficulty breathing	lightheaded	
dizziness	light-headed	
dizzy	lightheadedness	
drowsiness	loss in weight	
drowsy	loss of weight	
dry mouth	low sex drive	
dry skin	polydipsia	
erectile dysfunction	polyphagia	
fatigue	polyuria	
fatigued	poor healing	

Search Logs as Sensor

12 months of logs, 6 million people

- 82 million drug, symptom, condition queries
- Drug pairs: < day: 29.61%, < week: 41.90%, < month: 60.89%



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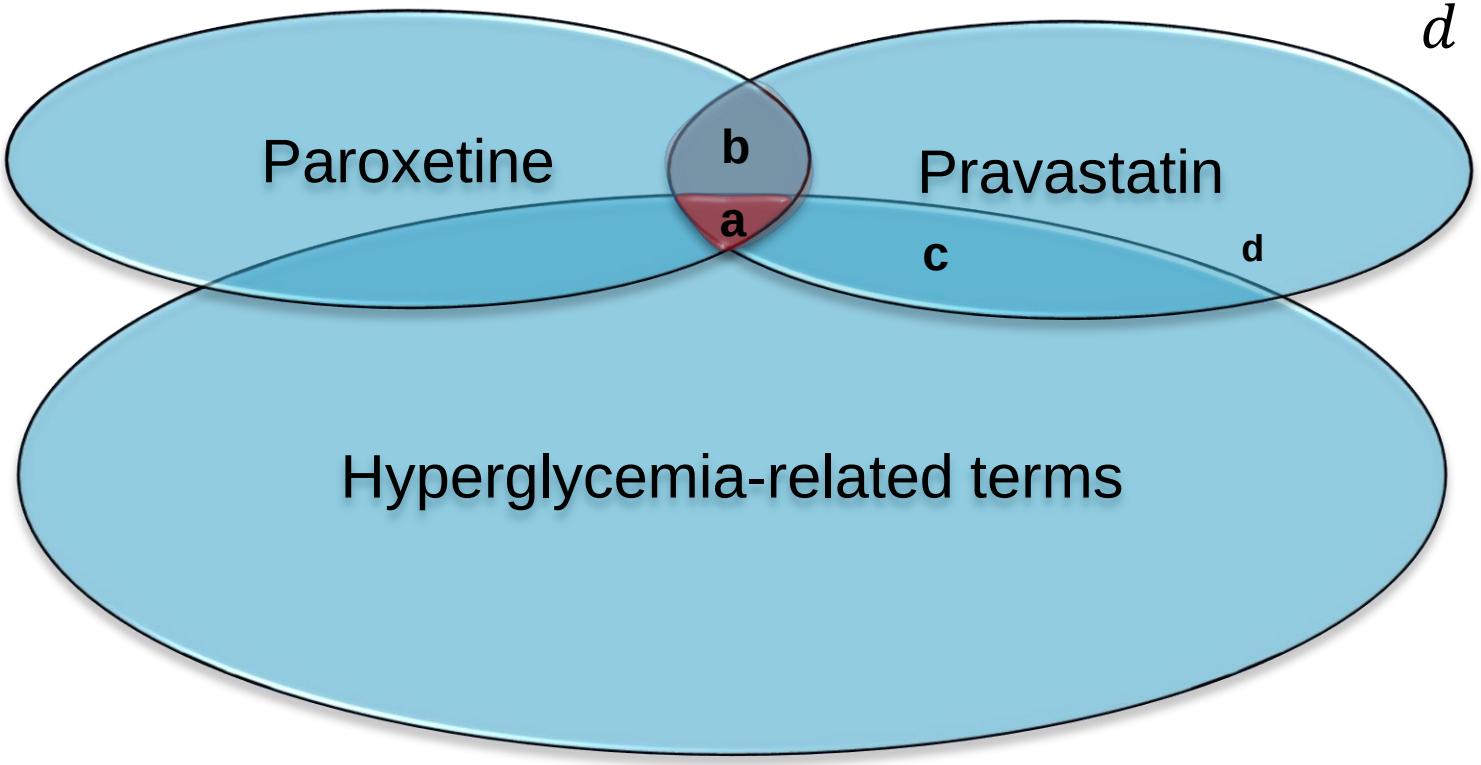
Web-Scale Pharmacovigilance

Disproportionality analysis

- Reporting ratios (RR)--obs. vs. expected: $RR = \frac{\frac{a}{b}}{\frac{c}{d}}$

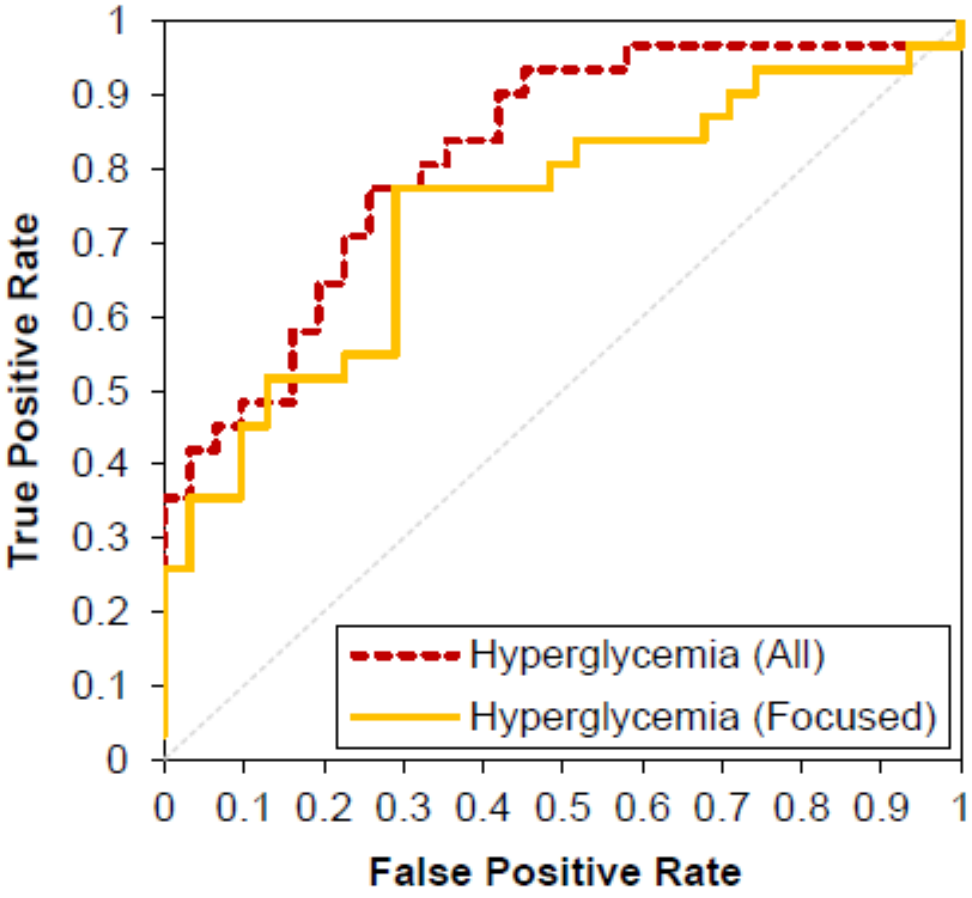


	a	*b*	*c*	*d*	*RR*	*95% CI (Lower, Upper)*	*p-value (one-tailed)*
Expected (pravastatin)	342	2716	2581	56302	2.747	2.438, 3.094	< 0.0001
Expected (paroxetine)	342	2716	3645	71243	2.461	2.189, 2.767	< 0.0001

Model of Sensor Error

Test on known interactions

- 31 true positives for hyperglycemia
- 31 true negatives for hyperglycemia



Label	*Drug 1*	*Drug 2*
TP	dobutamine	hydrocortisone
TP	dobutamine	triamcinolone
TP	dobutamine	prednisolone
TP	betamethasone	dobutamine
TP	glipizide	phenytoin
TP	dobutamine	methylprednisolone
TP	prednisolone	salmeterol
TP	salmeterol	triamcinolone
TP	betamethasone	terbutaline
TP	dexamethasone	dobutamine
TP	budesonide	salmeterol
TN	hydrochlorothiazide	tazobactam
TN	clindamycin	montelukast
TN	lamotrigine	nystatin
TN	methylprednisolone	rosuvastatin
TP	budesonide	formoterol
TN	loratadine	nystatin
TN	hydroxychloroquine	prochlorperazine
TN	labetalol	sertraline
TN	ciprofloxacin	vecuronium

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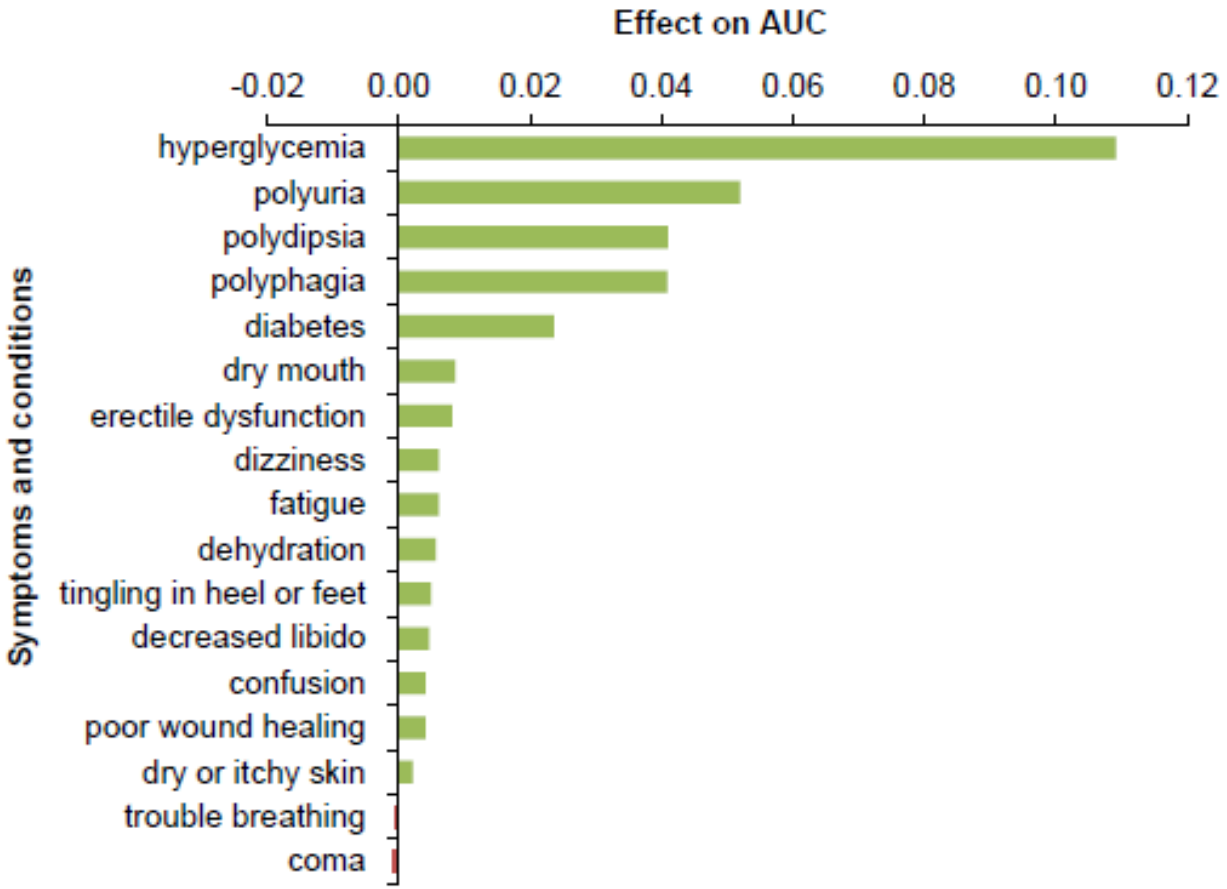
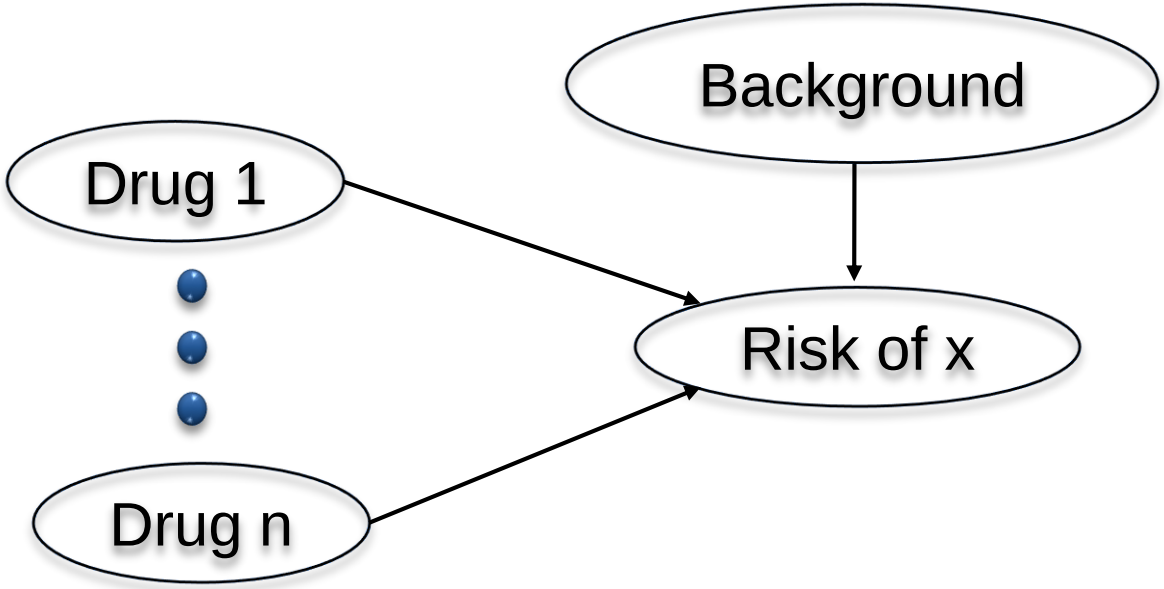


Models and Signals

e.g., Divergence from independent causal effects (DICE)



$$R = \frac{Observed\ x}{1-(\prod_{i=1}^{n} 1-x_i\ )(1-b)}$$

Toward Interactive Analytical Tools

Goals

Access & curation of data sets

Support multiple inferential models

Controls to define data filtering & signals

Controls to formulate experiments

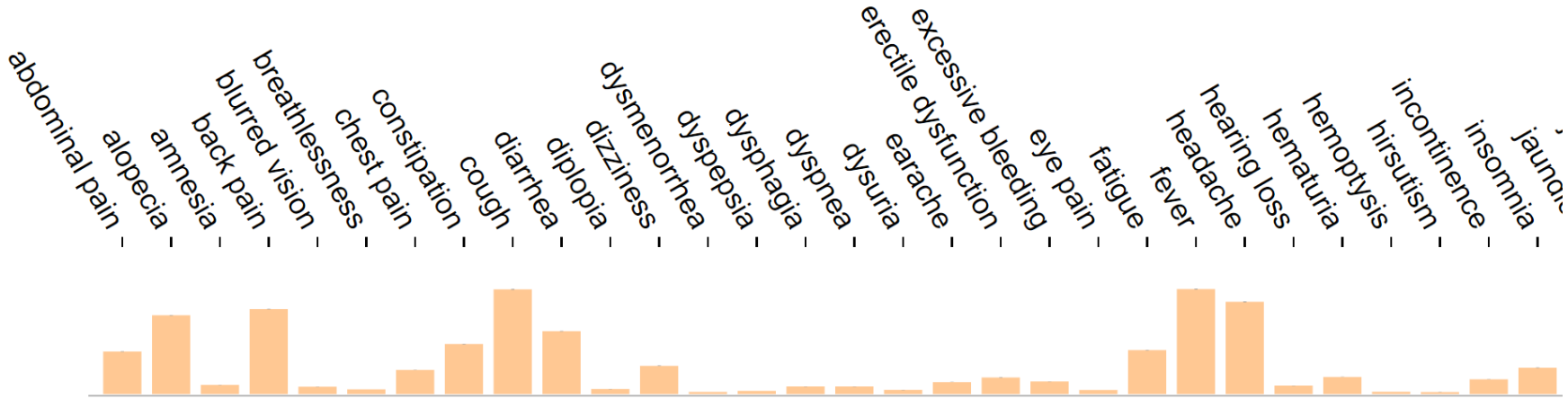
Tools for exploring, sweeping over parameters

BLAERS Prototype

Behavioral Log-Based Adverse Event Reporting System

BLAERS

Behavioral Log-based Adverse Event Reporting System



Generate background symptom spectrum

with A.Yates & R. White

BLAERS Prototype

Behavioral Log-Based Adverse Event Reporting System

BLAERS

Behavioral Log-based Adverse Event Reporting System

	Abilify	Accutane	Actonel	Adderall	Adipex	Advair	Allegra	Ambien	Amitiza	Arava	Aricept	Avodart	Boniva	Botox	Byetta	Carvedilol	Celebrex	Celexa	Chantix	Cialis	Cimzia	Ciprofloxacin	Claritin
Abilify								0.3833											OK	0.3833			
Accutane						0.3667									OK								0.3833
Actonel								OK															
Adderall																							
Adipex						0.7000	0.6333	0.6333			0.6167												0.8333
Advair		0.3667			0.7000		0.4500				0.6167												0.6000
Allegra					0.6333	0.4500		0.6333															0.5500
Ambien	0.3833		OK		0.6333		0.6333				0.6000				OK								0.7167
Amitiza															OK								
Arava																							
Aricept					0.6167	0.6167		0.6000															0.6500
Avodart																	OK						
Boniva																							
Botox																							
Byetta		OK						OK	OK														
Carvedilol																							
Celebrex												OK											
Celexa																							
Chantix	OK																						
Cialis	0.3833																						
Cimzia																							
Ciprofloxacin																							
Claritin		0.3833			0.8333	0.6000	0.5500	0.7167			0.6500												
Clomid																							
Coumadin					0.8333			0.7000			0.6500								OK	0.4500			0.7667
Crestor	0.3833				0.3833												0.4167						
Cyclobenzaprine																							
Cymbalta	0.3833						0.4667																

with R. White, A. Yates

BLAERS Prototype

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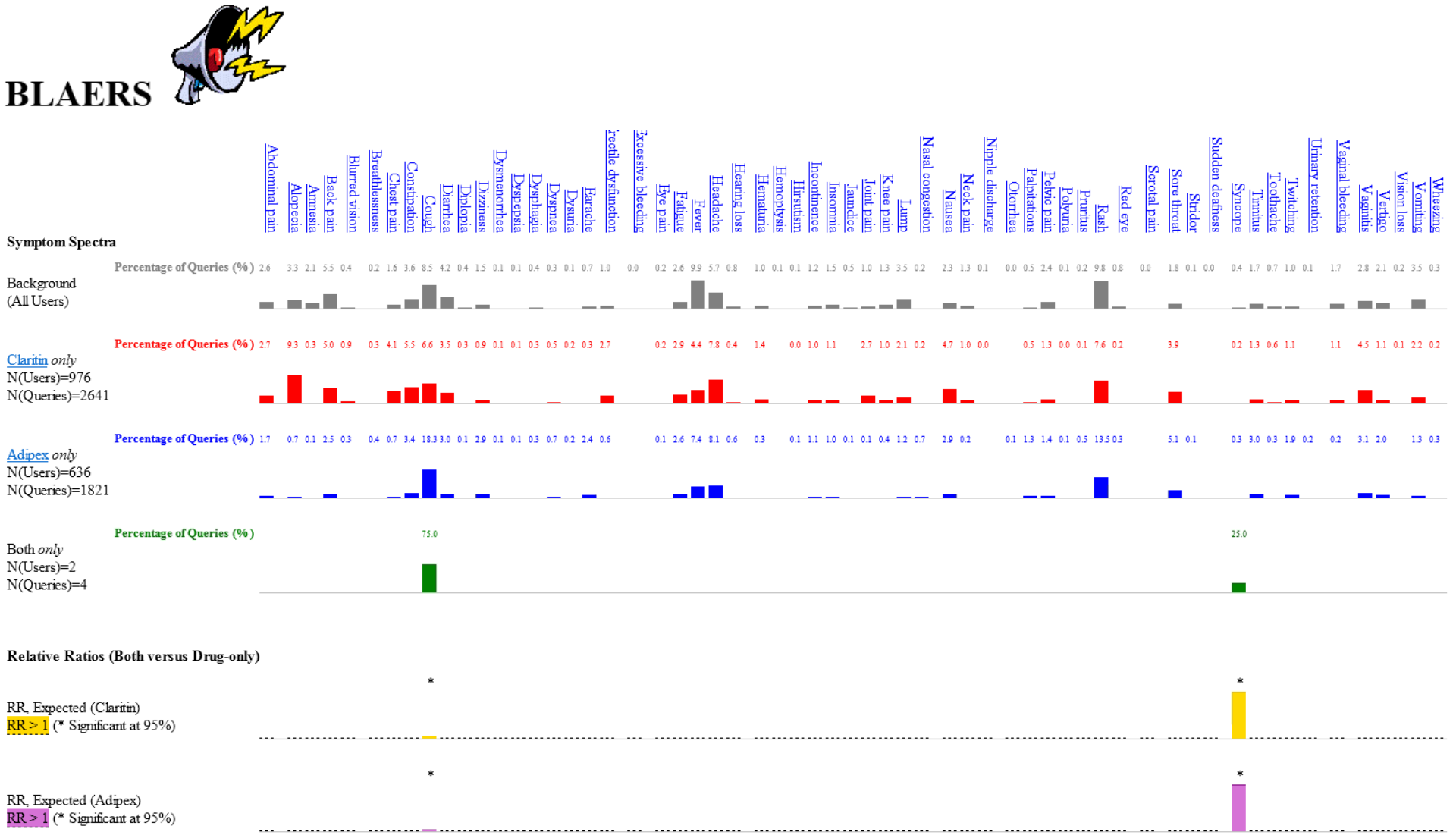

BLAERS Prototype

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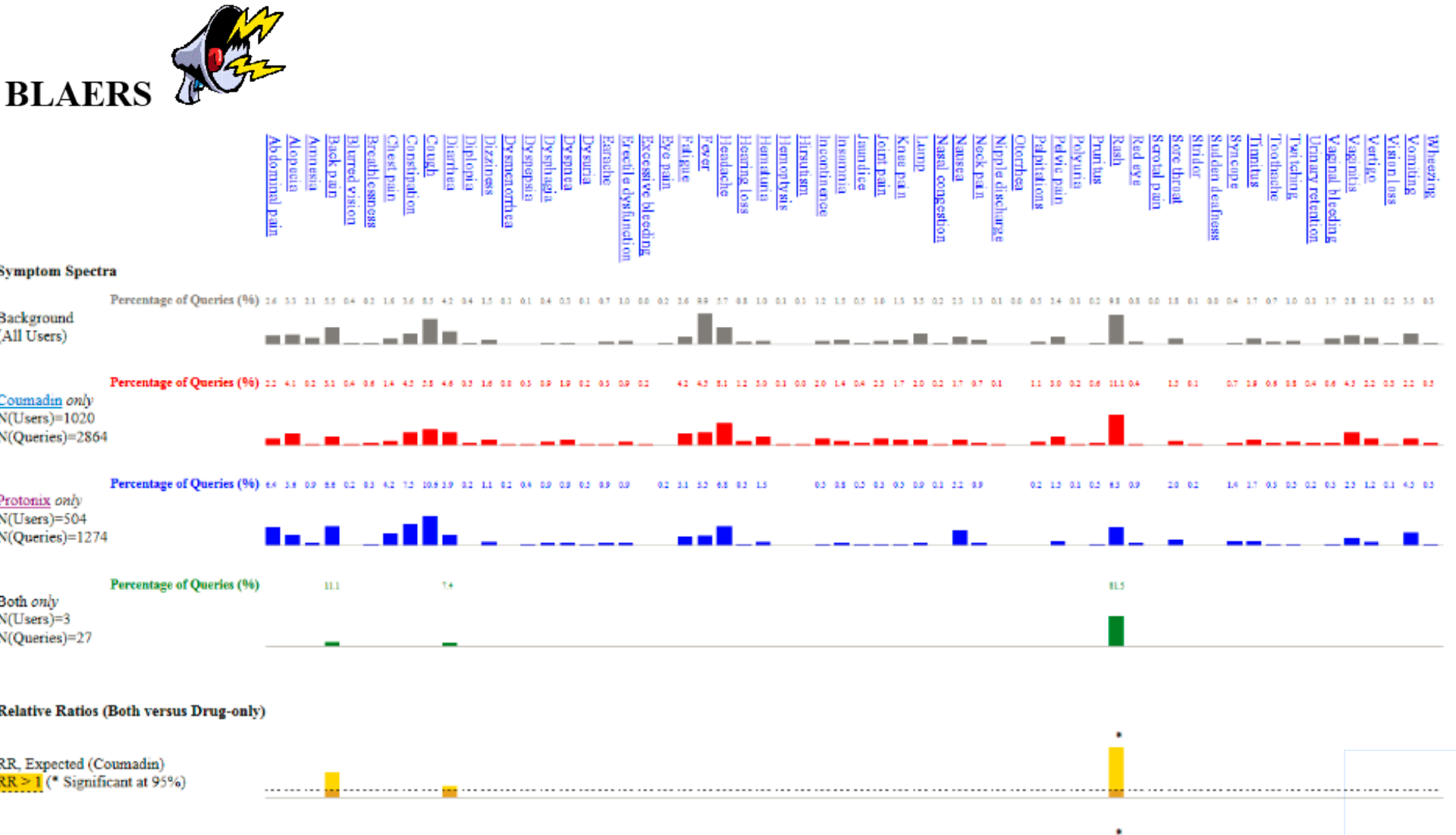


Study: Serious Rare Side Affects

Observational Medical Outcomes Partnership (OMOP)

OMOP gold-standard drug safety test set

181 drugs: *NSAIDs, antibiotics, antidepressants, ACE inhibitors, beta blockers, antiepileptics, glucose-lowering drugs*

Four outcomes:

- Acute myocardial infarction
- Acute renal failure
- Acute liver injury
- Upper gastrointestinal bleeding

Most significant drug safety outcomes

R. White, R. Harpaz, N. Shah, W. DuMouchel, E. Horvitz. Nature CPT, 2014

Study: Serious Rare Side Affects

Observational Medical Outcomes Partnership (OMOP)

18 months of Internet search logs (2011-2013)

80 million users with web browser add-on (consented)

Users' search queries on Google, Bing, and Yahoo!

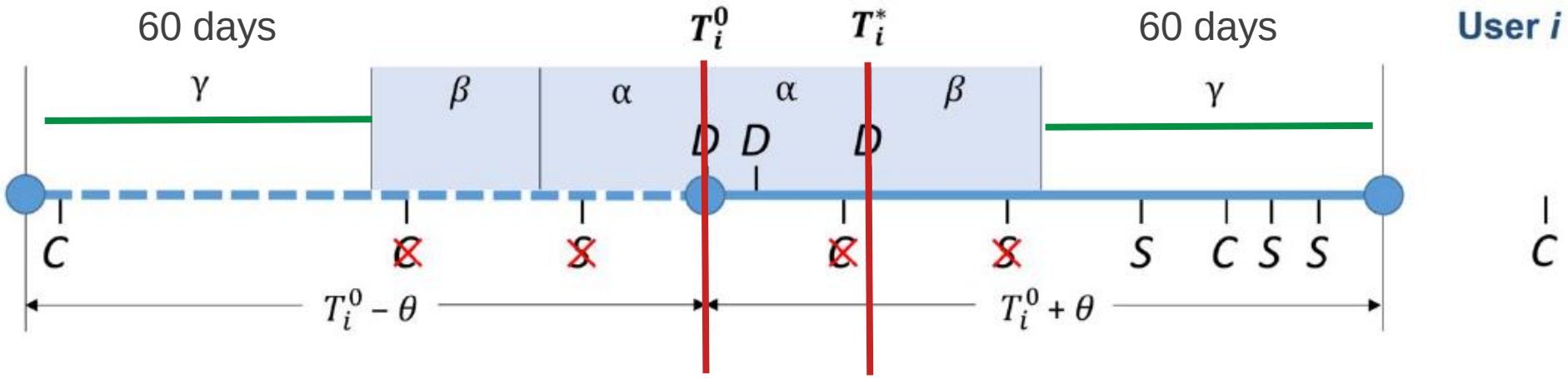
Anonymous identifier for instance of browser

R. White, R. Harpaz, N. Shah, W. DuMouchel, E. Horvitz. Nature CPT, 2014

Trial Design

Self-controlled design: each searcher serves as own control

Query rate ratio (QRR): queries on conditions & symptoms after vs. before drug query, with exclusion period

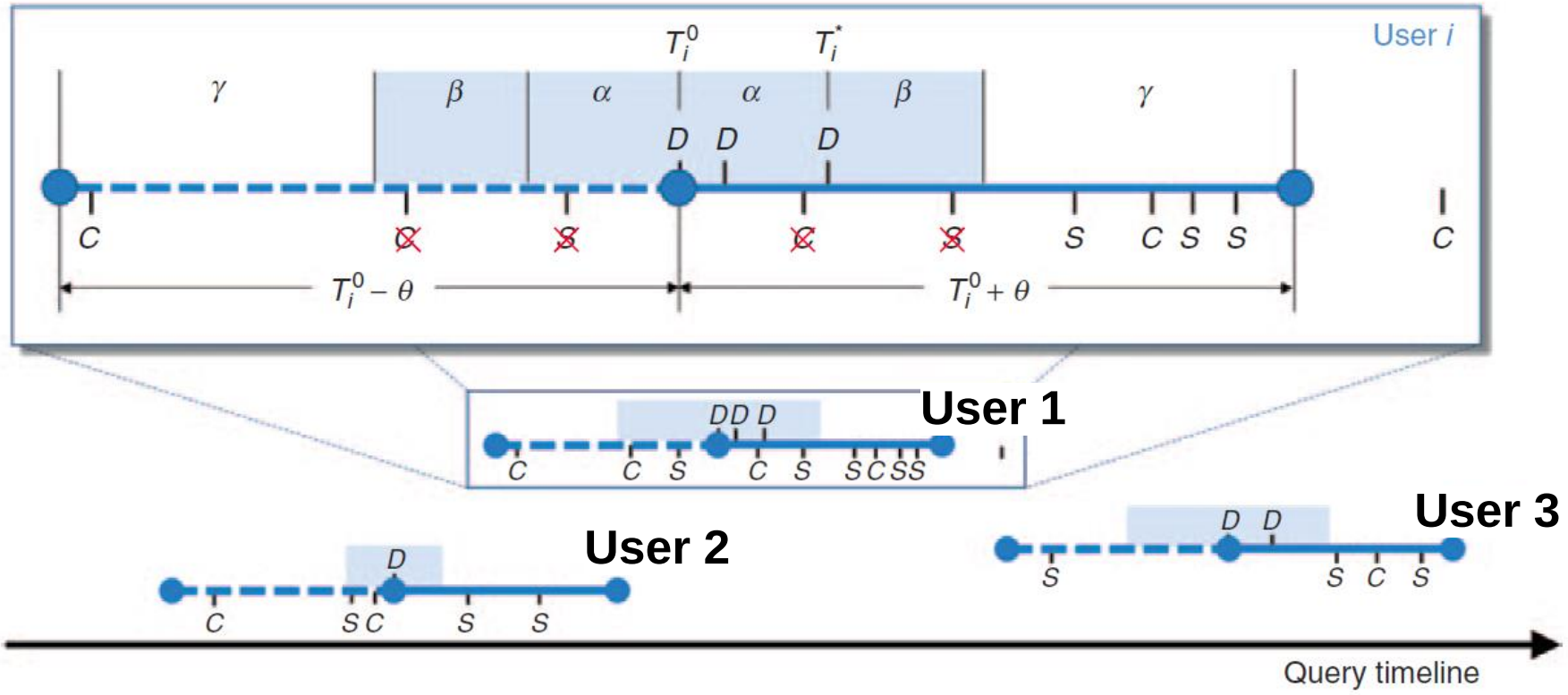


D: query for drug of interest
C: query for condition of interest
S: query for a symptom of *C*
✕: ignored *C* or *S*

$\alpha = T_i^* - T_i^0$
β = 7 days
γ = 60 days
$\theta = (\alpha + \beta + \gamma)$

surveillance window post T_i^0
surveillance window pre T_i^0
exclusion period $[T_i^0 - (\alpha + \beta), T_i^0 + (\alpha + \beta)]$

Trial Design



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Statistics of rare events

Concern: High sampling variability when baseline & observed frequencies very small

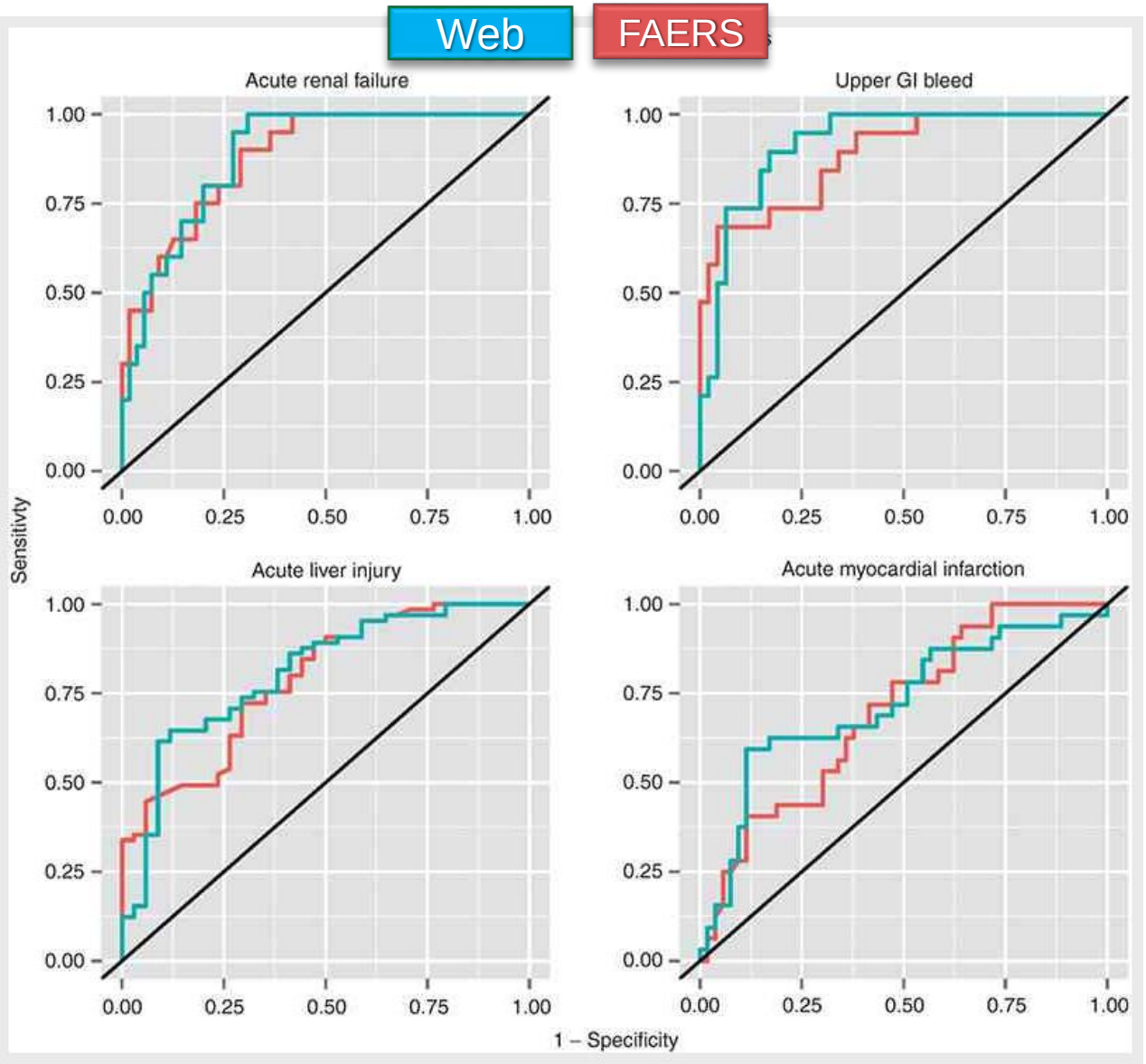
Empirical Bayes

Assume observed counts drawn from Poisson distribution with unknown mean.

Estimate parameters of distribution from data.

Multi-item Gamma Poisson Shrinker
(DuMouchel & Pregibon, 2001)

AERS & Search on OMOP



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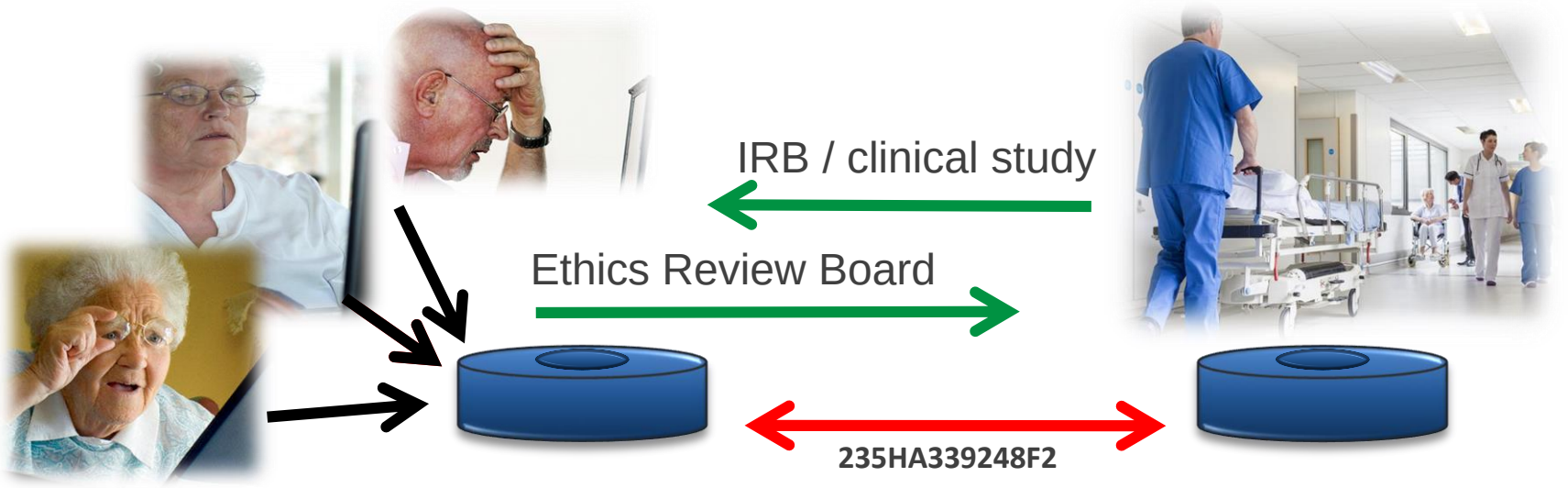
Complementarity of Signals

	FAERS	Search	Together
Acute Renal Failure	0.88	0.88	0.93
Upper GI Bleed	0.89	0.92	0.92
Acute Liver Injury	0.79	0.81	0.86
Acute Myocardial Infarction	0.70	0.73	0.75
Average	0.81	0.83	0.86

AUC improvements statistically significant ($p<0.05$)

R. White, R. Harpaz, N. Shah, W. DuMouchel, E. Horvitz. Nature CPT, 2014

Direction: Bridge Online & Traditional Health Data



Survey on Breast Cancer and the Web

Microsoft Research

You can help us to understand how people diagnosed with breast cancer make use of the Web to find information and support. The overarching goal of the study is to make search engines better at providing accurate information and support

Survey information about your diagnosis, relevant medical history, and questionnaire responses about how you use the Web for finding and sharing medical information.

Your **search history** from past 18 months, including new queries in the next 18 months (36 total), using the Bing search engine. This will allow us to understand what cancer-related information you searched for and when.

Directions

Opportunity to harness online behavioral signals as wide-scale sensor array

Complements signals from spontaneous reporting systems & health records data.

Intriguing analytical challenges & directions

Promising area for more intensive effort and investment.