Multimodal Drug Safety

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Rave Harpaz
Senior Research Scientist, Oracle Health Sciences

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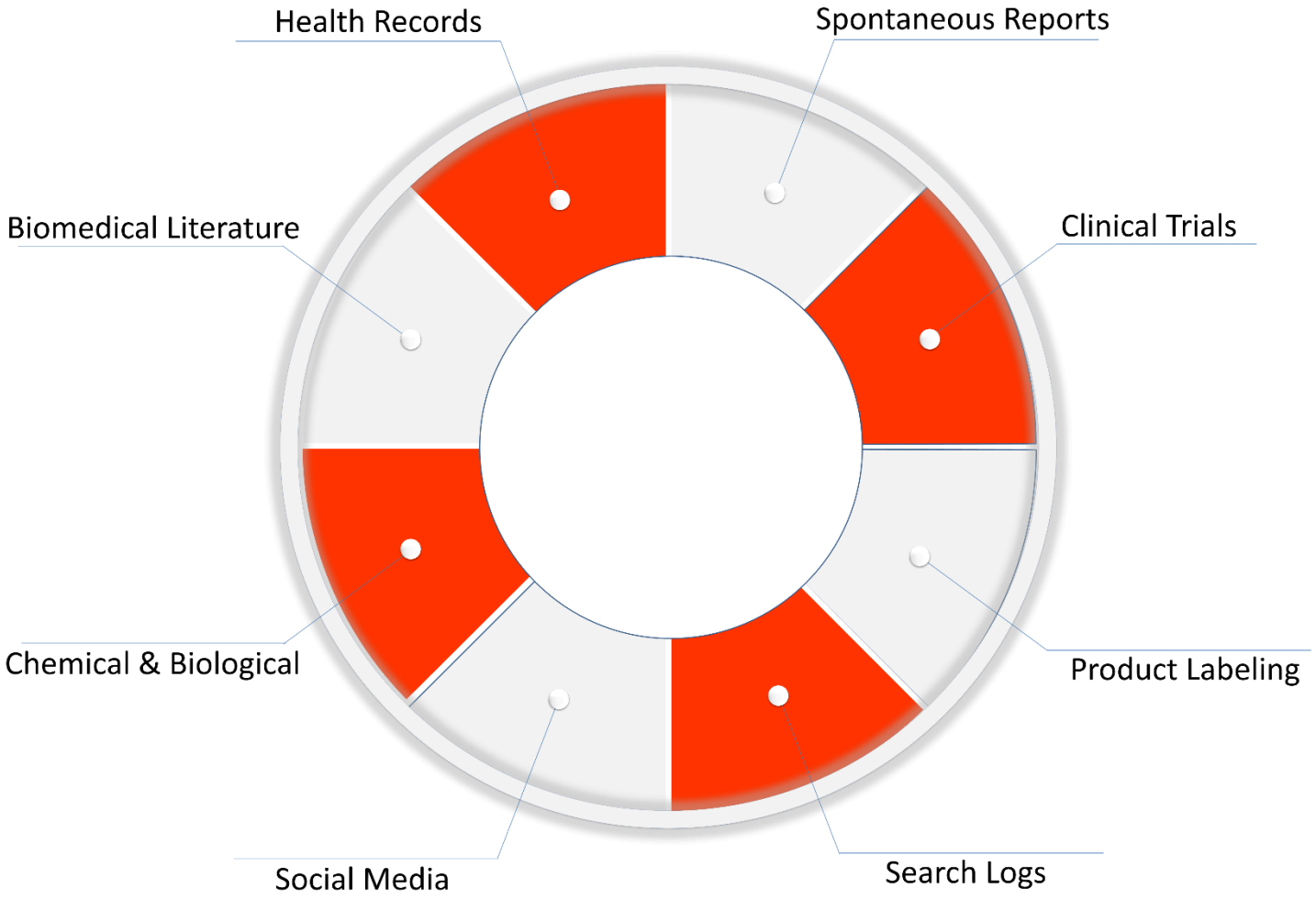
Data Sources for Drug Safety

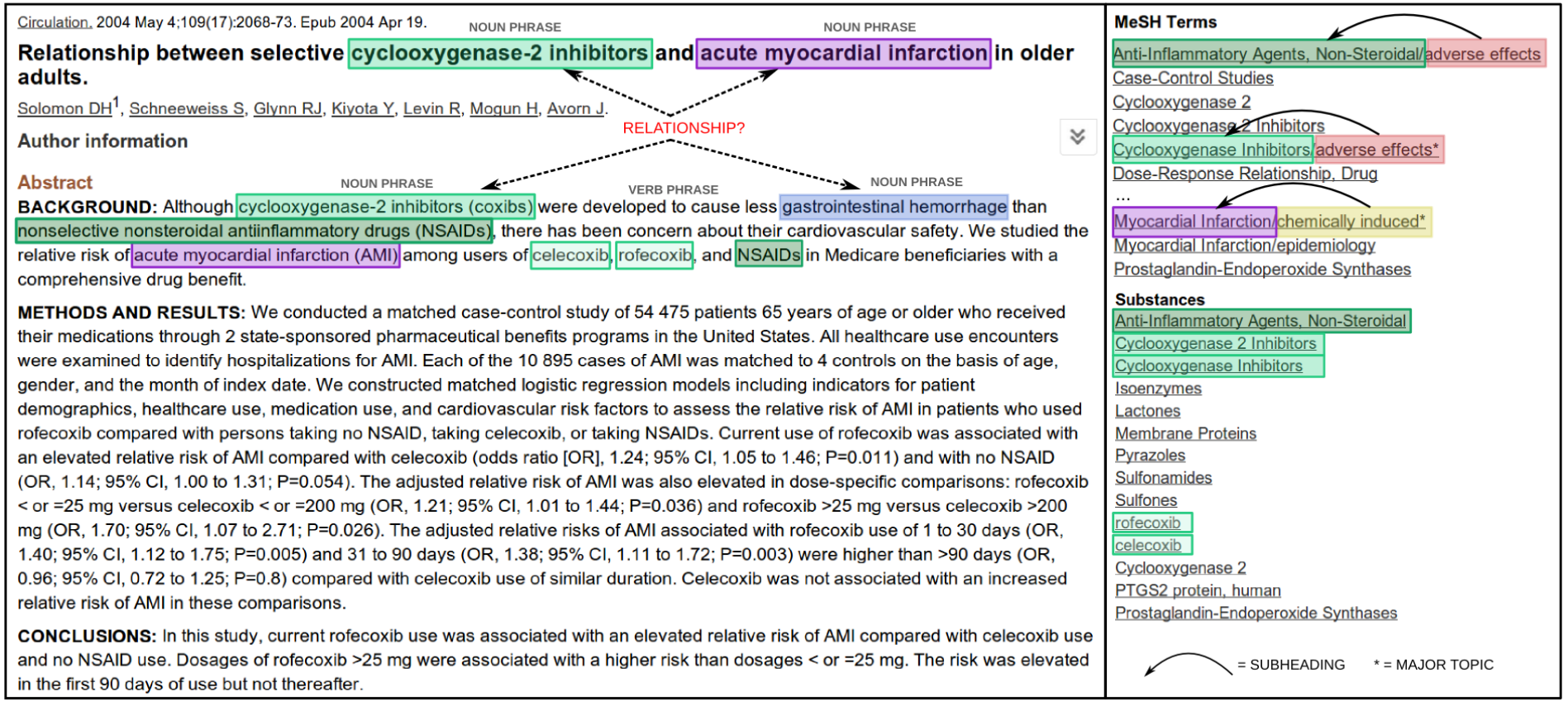


Outline

1. Data sources for drug safety
   - Literature, medical records, product labels, Web search logs
2. Multimodal signal detection
3. Safety 360

Medline – ADR Extraction

http://www.ncbi.nlm.nih.gov/pubmed/15096449



Circulation. 2004 May 4;109(17):2068-73. Epub 2004 Apr 19.

NOUN PHRASE — NOUN PHRASE

Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults.

RELATIONSHIP?

Solomon DH[1], Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J.

Author information

Abstract

NOUN PHRASE — VERB PHRASE — NOUN PHRASE

BACKGROUND: Although cyclooxygenase-2 inhibitors (coxibs) were developed to cause less gastrointestinal hemorrhage than nonselective nonsteroidal antiinflammatory drugs (NSAIDs), there has been concern about their cardiovascular safety. We studied the relative risk of acute myocardial infarction (AMI) among users of celecoxib, rofecoxib, and NSAIDs in Medicare beneficiaries with a comprehensive drug benefit.

METHODS AND RESULTS: We conducted a matched case-control study of 54 475 patients 65 years of age or older who received their medications through 2 state-sponsored pharmaceutical benefits programs in the United States. All healthcare use encounters were examined to identify hospitalizations for AMI. Each of the 10 895 cases of AMI was matched to 4 controls on the basis of age, gender, and the month of index date. We constructed matched logistic regression models including indicators for patient demographics, healthcare use, medication use, and cardiovascular risk factors to assess the relative risk of AMI in patients who used rofecoxib compared with persons taking no NSAID, taking celecoxib, or taking NSAIDs. Current use of rofecoxib was associated with an elevated relative risk of AMI compared with celecoxib (odds ratio [OR], 1.24; 95% CI, 1.05 to 1.46; P=0.011) and with no NSAID (OR, 1.14; 95% CI, 1.00 to 1.31; P=0.054). The adjusted relative risk of AMI was also elevated in dose-specific comparisons: rofecoxib < or =25 mg versus celecoxib < or =200 mg (OR, 1.21; 95% CI, 1.01 to 1.44; P=0.036) and rofecoxib >25 mg versus celecoxib >200 mg (OR, 1.70; 95% CI, 1.07 to 2.71; P=0.026). The adjusted relative risks of AMI associated with rofecoxib use of 1 to 30 days (OR, 1.40; 95% CI, 1.12 to 1.75; P=0.005) and 31 to 90 days (OR, 1.38; 95% CI, 1.11 to 1.72; P=0.003) were higher than >90 days (OR, 0.96; 95% CI, 0.72 to 1.25; P=0.8) compared with celecoxib use of similar duration. Celecoxib was not associated with an increased relative risk of AMI in these comparisons.

CONCLUSIONS: In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use and no NSAID use. Dosages of rofecoxib >25 mg were associated with a higher risk than dosages < or =25 mg. The risk was elevated in the first 90 days of use but not thereafter.

MeSH Terms

- Anti-Inflammatory Agents, Non-Steroidal/adverse effects
- Case-Control Studies
- Cyclooxygenase 2
- Cyclooxygenase 2 Inhibitors
- Cyclooxygenase Inhibitors/adverse effects*
- Dose-Response Relationship, Drug
- ...
- Myocardial Infarction/chemically induced*
- Myocardial Infarction/epidemiology
- Prostaglandin-Endoperoxide Synthases

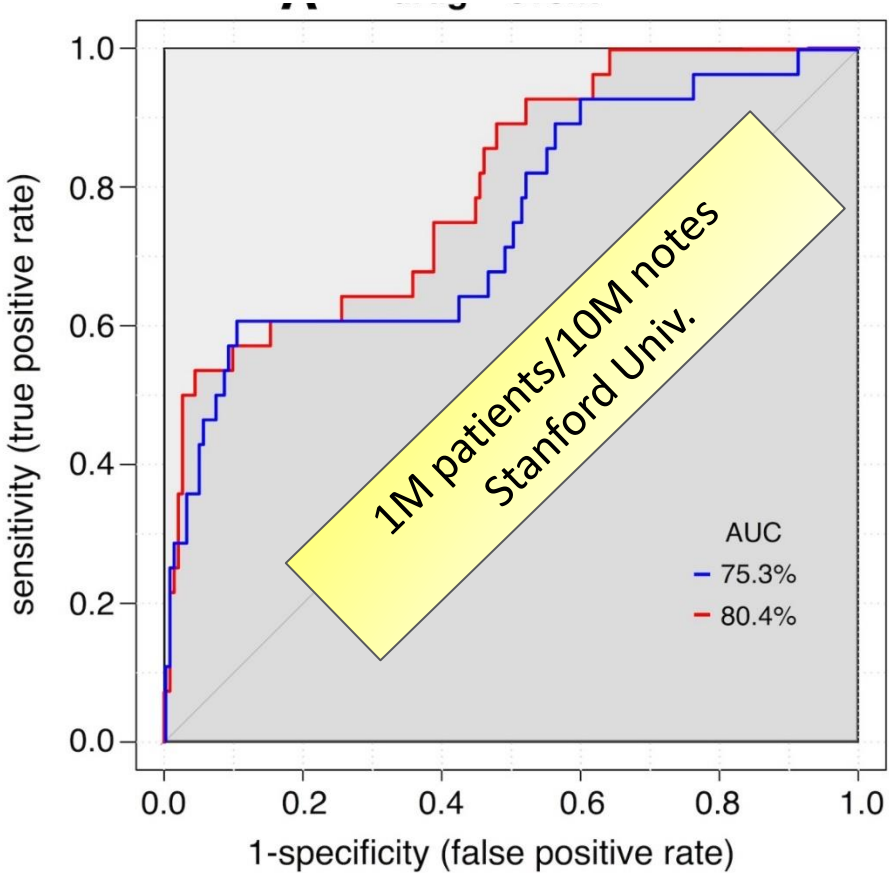
Substances

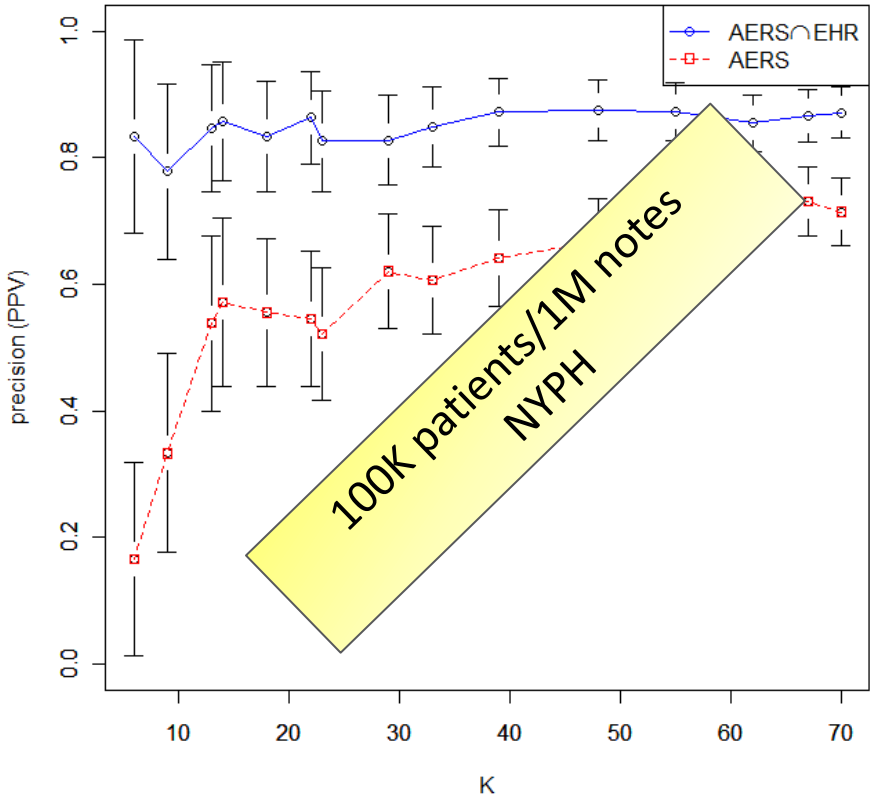
- Anti-Inflammatory Agents, Non-Steroidal
- Cyclooxygenase 2 Inhibitors
- Cyclooxygenase Inhibitors
- Isoenzymes
- Lactones
- Membrane Proteins
- Pyrazoles
- Sulfonamides
- Sulfones
- rofecoxib
- celecoxib
- Cyclooxygenase 2
- PTGS2 protein, human
- Prostaglandin-Endoperoxide Synthases

= SUBHEADING * = MAJOR TOPIC

Leveraging MEDLINE indexing for pharmacovigilance – inherent limitations and mitigation strategies; Winnenburg R, Sorbello R, Ripple A, Harpaz R, Tonning J, Szarfman R, Francis H, Bodenreider O., JBI 2015

Signal Detection based on Clinical Narratives





Combing signals from spontaneous reports and electronic health records for detection of adverse drug reactions.
Harpaz R, Vilar S, Dumouchel W, Salmasian H, Haerian K, Shah NH, Chase HS, Friedman C. JAMIA 2013

Extracting ADRs from Product Labels

TAC 2017

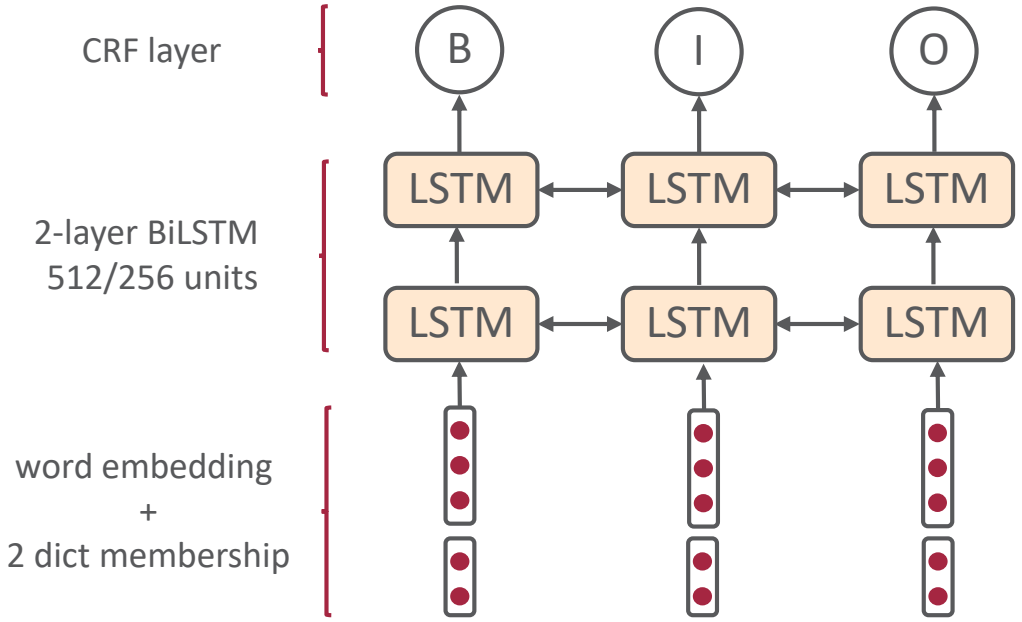
Adverse Drug Reaction Extraction from Drug Labels

Drug labels (prescribing information or package inserts) describe what a particular medicine is supposed to do, who should or should not take it, how to use it, and specific safety concerns. The US Food and Drug Administration (FDA) publishes regulations governing the content and format of this information to provide recommendations for applicants developing labeling for new drugs and revising labeling for already approved drugs. One of the major aspects of drug information are safety concerns in the form of Adverse Drug Reactions (ADRs). In this evaluation, we are focusing on extraction of ADRs from the prescription drug labels.

Oracle:

- Used Machine learning (CRFs & Deep Learning) to identify adverse reactions
- Used a rule-based approach for negation detection of adverse reactions
- Ranked second out of 13 teams

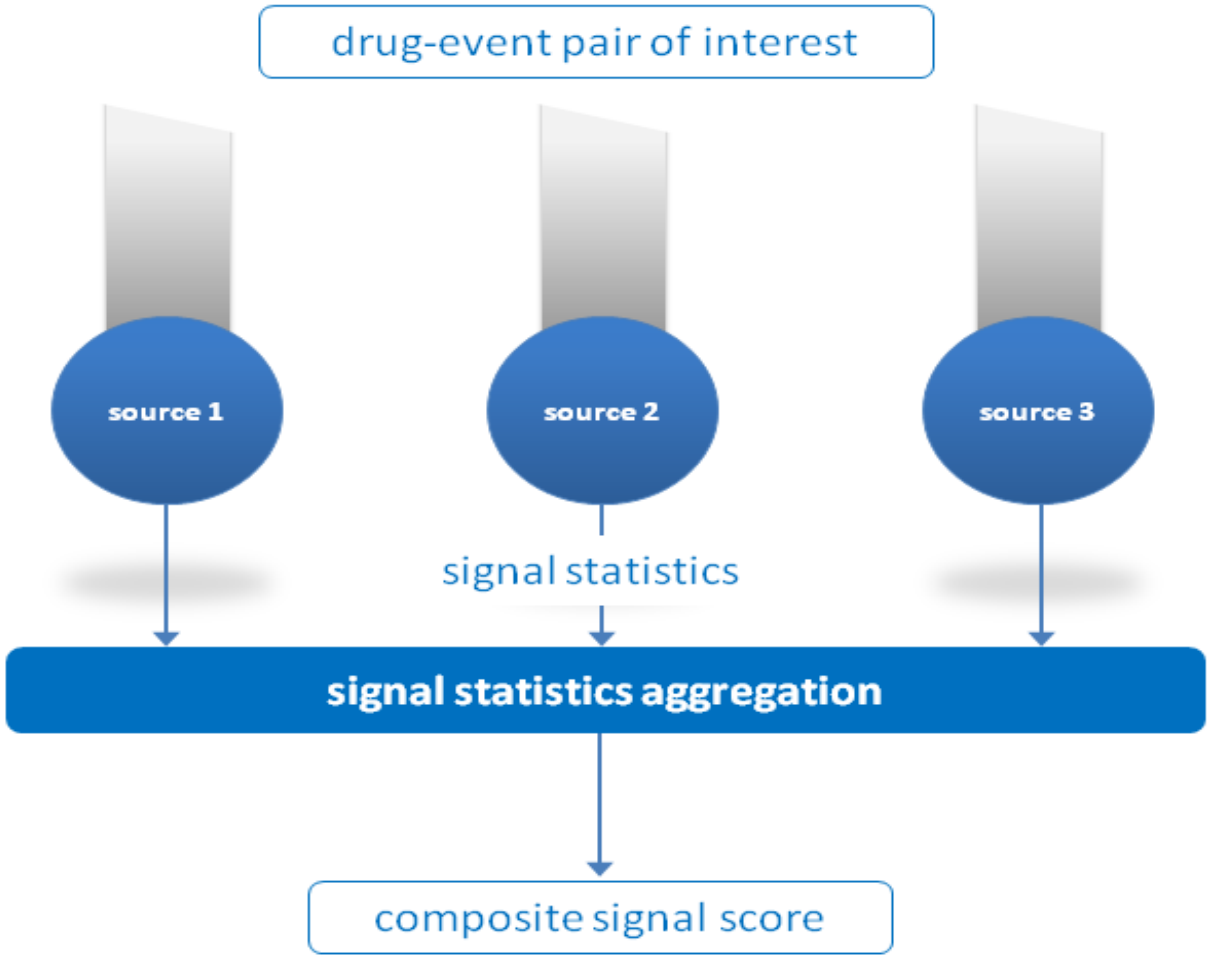
Conditional Random Fields & Deep Learning



accuracy

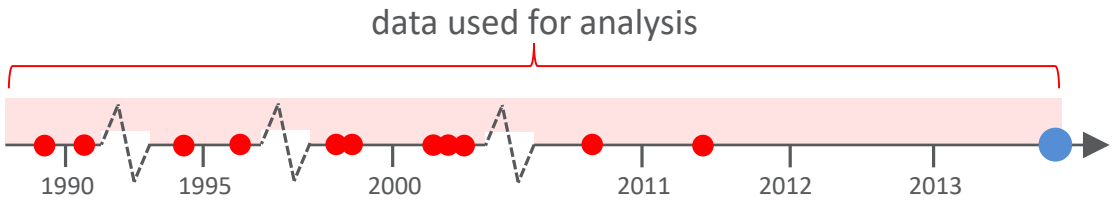
	test		
	precision	recall	F1
CRF ensemble - R	81.2%	79.7%	80.43%
BiLSTM-CRF	84.7%	78.5%	81.47%

Signal Fusion

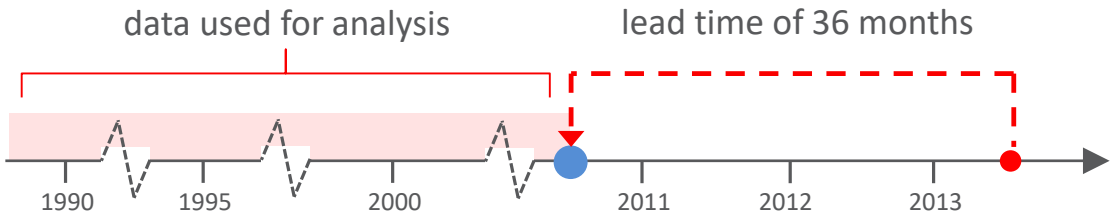


Toward Multimodal Signal Detection of Adverse Drug Reactions
Harpaz R, DuMouchel W, et al., J Biomed Inform 2017

Evaluation Strategies

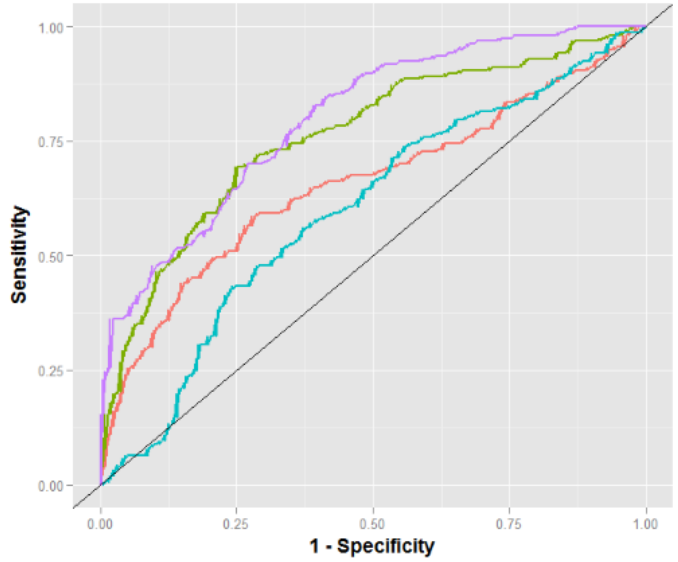


retrospective



prospective

- time of analysis
- time ADR recognized



Methods

Unimodal

Bayesian observed-to-expected ratio

$$\frac{N + \alpha}{c \cdot E + \alpha}$$

(from each data source)

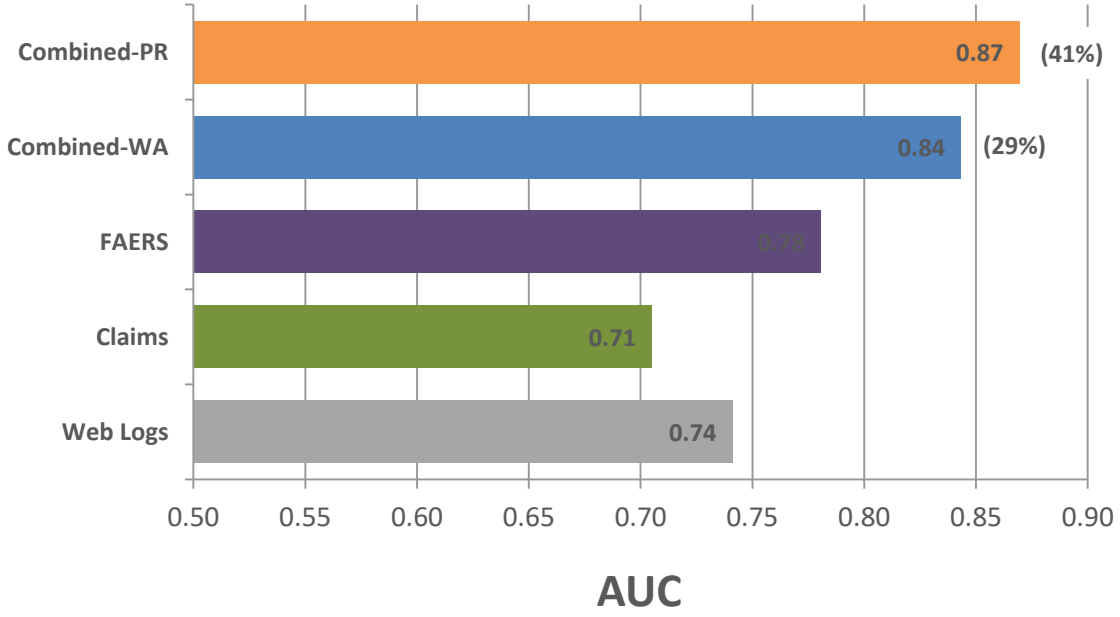
Multimodal

predictive
- Logistic Regression
- Random Forests
- Support Vector Machines
- Naive Bayes Smoothing

weighted averaging
- Arithmetic Average
- Geometric Average
- Fixed Effects MA
- Random Effects MA
- Empirical Bayes FAMA

Prospective Evaluation - Mean Lead Time to Detection

Retrospective Evaluation – OMOP Reference Set



Safety 360

prototype

Publications

- **Toward Multimodal Signal Detection of Adverse Drug Reactions.** *Harpaz R, DuMouchel W, et al., J Biomed Inform* 2017
- **Reverse translation of adverse event reports paves the way for de-risking preclinical off-targets.** *Maciejewski M*, *DuMouchel W, et al.,* ***eLife 2017***
- ***Big Data and Adverse Drug Reaction Detection.*** *Harpaz R, DuMouchel W, Shah N, Clinical Pharmacology & Therapeutics 2016*
- ***Leveraging MEDLINE indexing for pharmacovigilance – inherent limitations and mitigation strategies;*** *Winnenburg R, Sorbello R, Ripple A, Harpaz R, Tonning J, Szarfman R, Francis H, Bodenreider O., Journal of Biomedical Informatics 2015*
- ***A time-indexed reference standard of adverse drug reactions.*** *Harpaz R, Odgers D, Gaskin G, DuMouchel W, Winnenburg R, Bodenreider O, Ripple A, Szarfman A, Sorbello A, Horvitz E, White R, Shah N., Scientific Data, 2014*
- ***Text Mining for Adverse Drug Events: the Promise, Challenges, and State of the Art.*** *Harpaz et al. Drug Safety 2014*
- ***Toward Enhanced Pharmacovigilance using Patient-Generated Data on the Internet;*** *White R, Harpaz R, Shah NH, DuMouchel W, Horvitz E, Nature - Clinical Pharmacology & Therapeutics 2014*
- ***Performance of pharmacovigilance signal-detection algorithms for the FDA Adverse Event Reporting System.*** Harpaz R, DuMouchel W, LePendu P, et al *Clinical Pharmacology & Therapeutics, 2013*
- ***Empirical Bayes Model to Combine Signals of Adverse Drug Reactions;*** *R Harpaz, W DuMouchel, P LePendu and NH Shah, KDD 2013*
- ***Pharmacovigilance Using Clinical Notes.*** *LePendu P, Iyer SV, Bauer-Mehren A, Harpaz R, Mortensen JM, Podchiyska T, Ferris TA, Shah NH. Nature - Clinical Pharmacology & Therapeutics 2013*

Publications

- ***Combing signals from spontaneous reports and electronic health records for detection of adverse drug reactions***. *Harpaz R, Vilar S, DuMouchel W, Salmasian H, Haerian K, Shah NH, Chase HS, Friedman C. JAMIA 2013*
- ***Evaluating the impact of database heterogeneity on observational study results.*** *Madigan D, Ryan PB, Schuemie M, Stang PE, Overhage JM, Hartzema AG, Suchard MA, DuMouchel W, Berlin JA , Am J Epidemiol. 2013*
- ***A Comparison of the Empirical Performance of Methods for a Risk Identification System.*** *Ryan PB, Stang PE, Overhage JM, Suchard MA, Hartzema AG, DuMouchel W, Reich C, Schuemie MJ, Madigan D. Drug Safety 2013*
- ***Interpreting observational studies: why empirical calibration is needed to correct p-values.*** *Schuemie MJ, Ryan PB, DuMouchel W, Suchard MA, Madigan D. Statistics in Medicine 2013*
- ***Evaluation of disproportionality safety signaling applied to healthcare databases.*** *DuMouchel W, Ryan PB, Schuemie MJ, Madigan D , Drug Safety 2013*
- ***Multivariate Bayesian Logistic Regression for analysis of clinical study safety issues*** (with Discussion and Rejoinder). DuMouchel W, *Statistical Science*, *2012*
- ***Novel Data-Mining Methodologies for Adverse Drug Event Discovery and Analysis.*** Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, Friedman C, *Clinical Pharmacology & Therapeutics*, 2012