



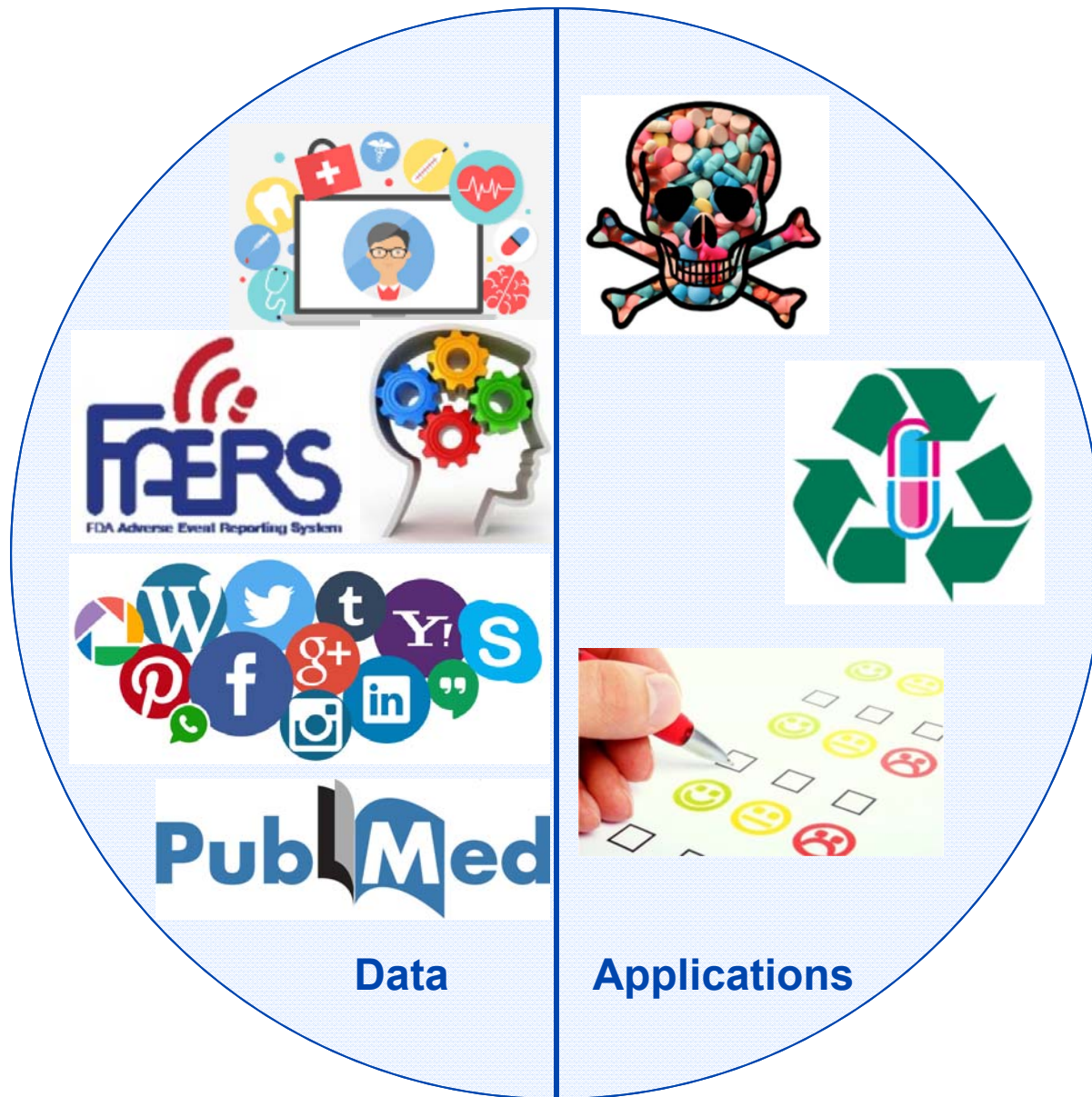
A Mayo Solution for Drug Safety, Repositioning and Other Patient-Reported Medication Outcomes

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Data

Information retrieval
Named entity recognition
Information extraction
Word sense disambiguation
Topic modeling & sentiment analysis
Terminology, ontology & standard
Machine learning
...

Methods



Applications

Detecting Drug Safety Signals

| Data Categories in the Mayo Clinic <i>Unified Data Platform</i> | | | |
|---|----------------------------|--------------------------------------|------------------------------|
| Patient | Provider | Location | Diagnosis (billing) |
| Procedure (billing) | Flowsheet | Lab (Microbiology) | Lab (Pathology) |
| Lab (specimen) | Admit, Discharge, Transfer | Radiology | Diagnosis |
| Surgical Procedures | Orders | Medication Administration | ECG |
| Allergy | Immunization | Clinical Documents | Patient Provided Information |
| Clinical Decision Support | | TERMS (infrastructure & conformance) | |

9.2 million patients at various sites of Mayo Clinic

Query via diagnostic codes or specific i2b2 inclusion & exclusion criteria

Free text and non-discrete field search supported by natural language processing with machine-learning techniques

COUNTIES IN THE REP



Dr. Leonard T. Kurland helped launch **the Rochester Epidemiology Project (REP)** in 1966.

"The REP allows the study of health and disease across the entire community, from birth to death, and from primary to specialty care."

– Barbara Yawn, MD, REP Co-Principal Investigator 2006-2015

FDA Drug Safety Communication: Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer

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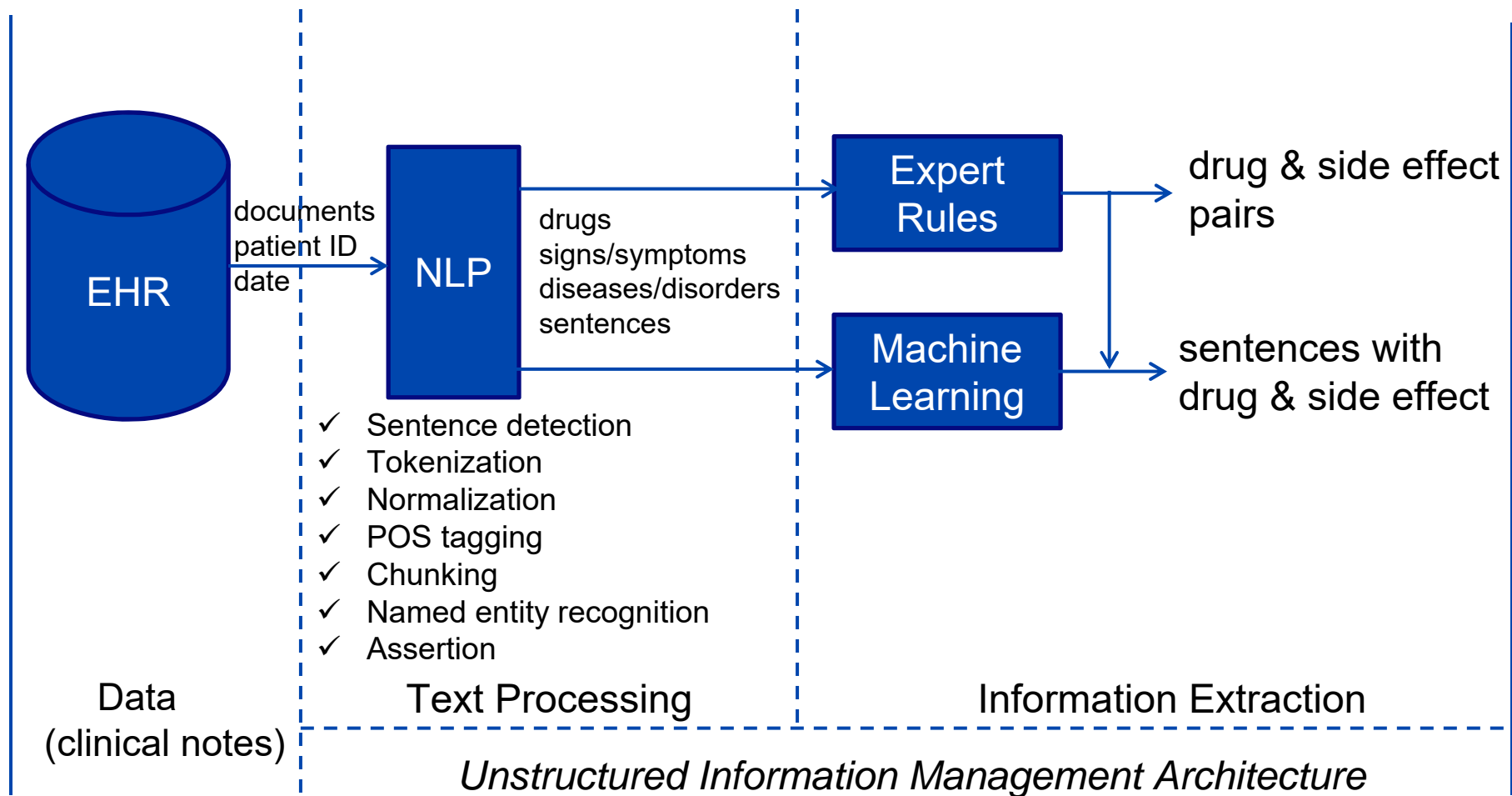
[12-12-2016]

This information is an update to the [FDA Drug Safety Communication: Updated drug labels for pioglitazone-containing medicines](#) issued on August 4, 2011.

A really **quick** query in 10 minutes for 1/1/2010 – 12/31/2016

| | Bladder cancer | No Bladder cancer |
|-----------------|----------------|-------------------|
| Pioglitazone | 54 | 3,860 |
| No Pioglitazone | 4,235 | 1,041,899 |

Odds Ratio = 3.44 (95% CI: 2.60, 4.54), p value < 0.001



A generic NLP process for drug side effect extraction

Side effect extraction on independent test set for psychiatry & psychology drugs

| | Including allergy section | | Excluding allergy section | |
|----------------------|---------------------------|----------------|---------------------------|----------------|
| | Rules | Rules+C4.5 | Rules | Rules+C4.5 |
| Precision | 0.862 | 0.640 | 0.750 | 0.423 |
| Recall | 0.875 | 0.891 | 0.778 | 0.815 |
| F score | 0.868 | 0.745 | 0.764 | 0.557 |
| SE_recall* | 0.867 | 0.893 | 0.806 | 0.861 |
| 90% CI of SE_recall† | 0.788 to 0.920 | 0.820 to 0.940 | 0.675 to 0.893 | 0.738 to 0.934 |

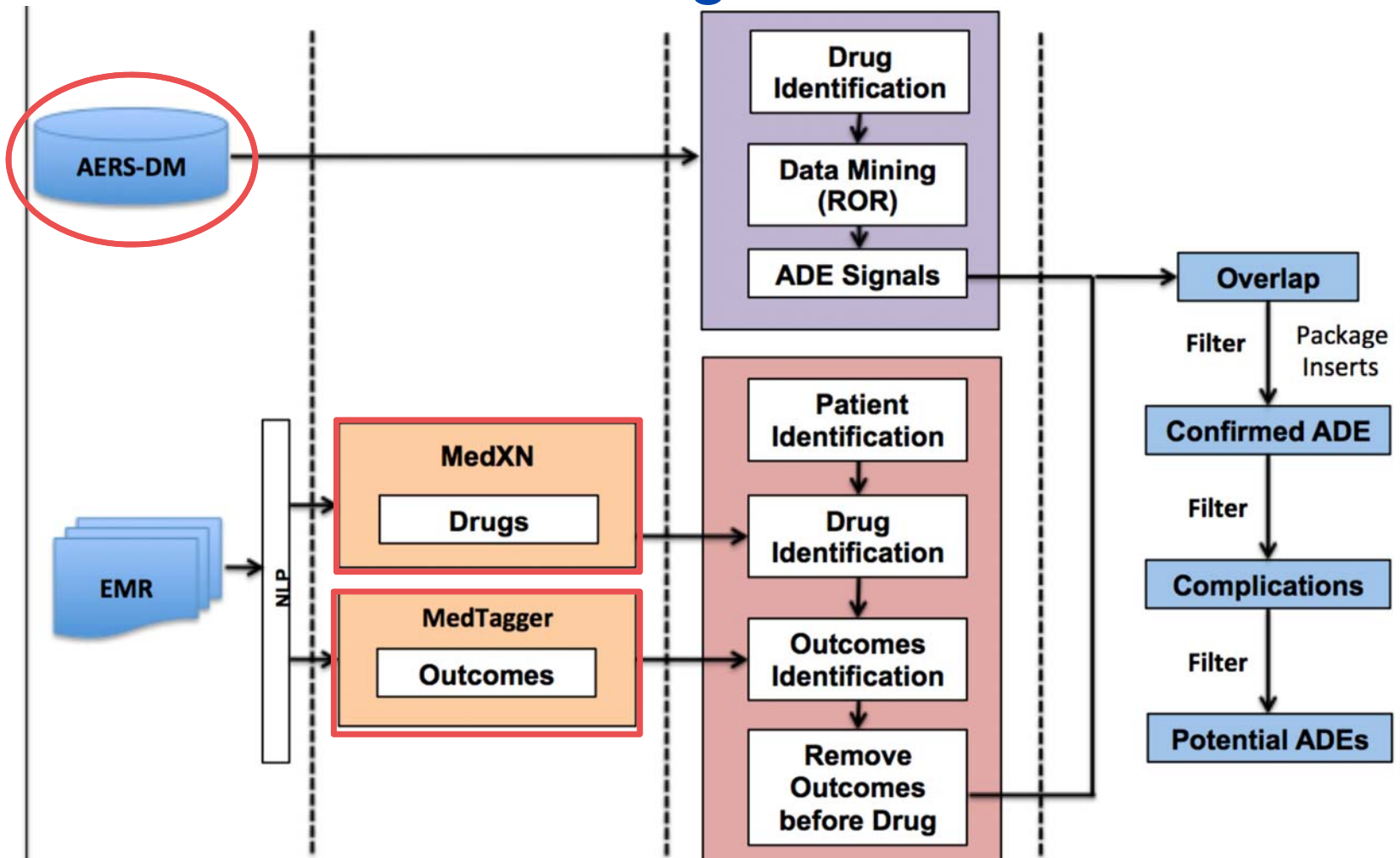
*Number of side effect and drug pairs in retrieved side effect sentences/total number of side effect and drug pairs.

†CI was obtained by using a modified Wald method



Sohn, Sunghwan, et al. "Drug side effect extraction from clinical narratives of psychiatry and psychology patients." *Journal of the American Medical Informatics Association* 18.Supplement 1 (2011): i144-i149.

Combining FDA spontaneous reports with EMR for adverse drug event detection



Adverse Events for Disease-Modifying Antirheumatic Drugs (DMARDs)

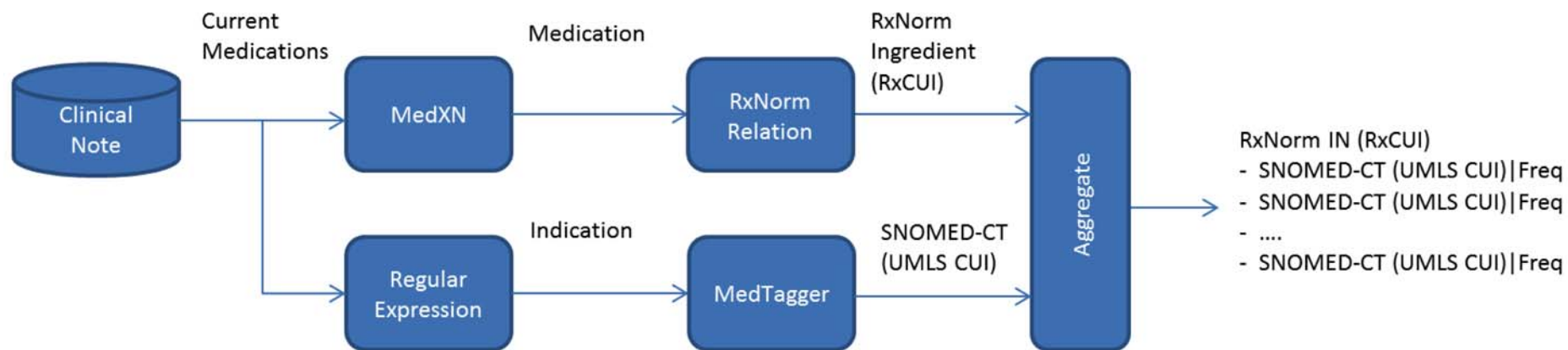
| Adverse Event | Number and Percentage of Cases in EMR | Report number from AERS-DM | ROR | Number and Percentage of Control in EMR |
|-------------------------------------|---------------------------------------|----------------------------|------|---|
| Endometrial cancer | 128 (25.8%) | 30 | 2.87 | 124 (12.8%) |
| Rhinorrhea | 111 (22.3%) | 355 | 2.81 | 119 (12.3%) |
| Productive cough | 100 (20.1%) | 346 | 2.83 | 102 (10.5%) |
| Bladder neoplasm | 71 (14.3%) | 17 | 2.60 | 0 |
| Gastroduodenal ulcer | 54 (10.9%) | 7 | 3.07 | 0 |
| Amyotrophic lateral sclerosis (ALS) | 44 (8.9%) | 26 | 2.71 | 107 (11.0%) |
| Sinus congestion | 40 (8.0%) | 237 | 4.87 | 34 (3.5%) |
| Sjogren's syndrome | 36 (7.2%) | 72 | 5.54 | 0 |
| Respiratory tract congestion | 36 (7.2%) | 230 | 6.59 | 0 |
| Bunion | 34 (6.8%) | 79 | 6.41 | 10 (9.7%) |

Drug repositioning

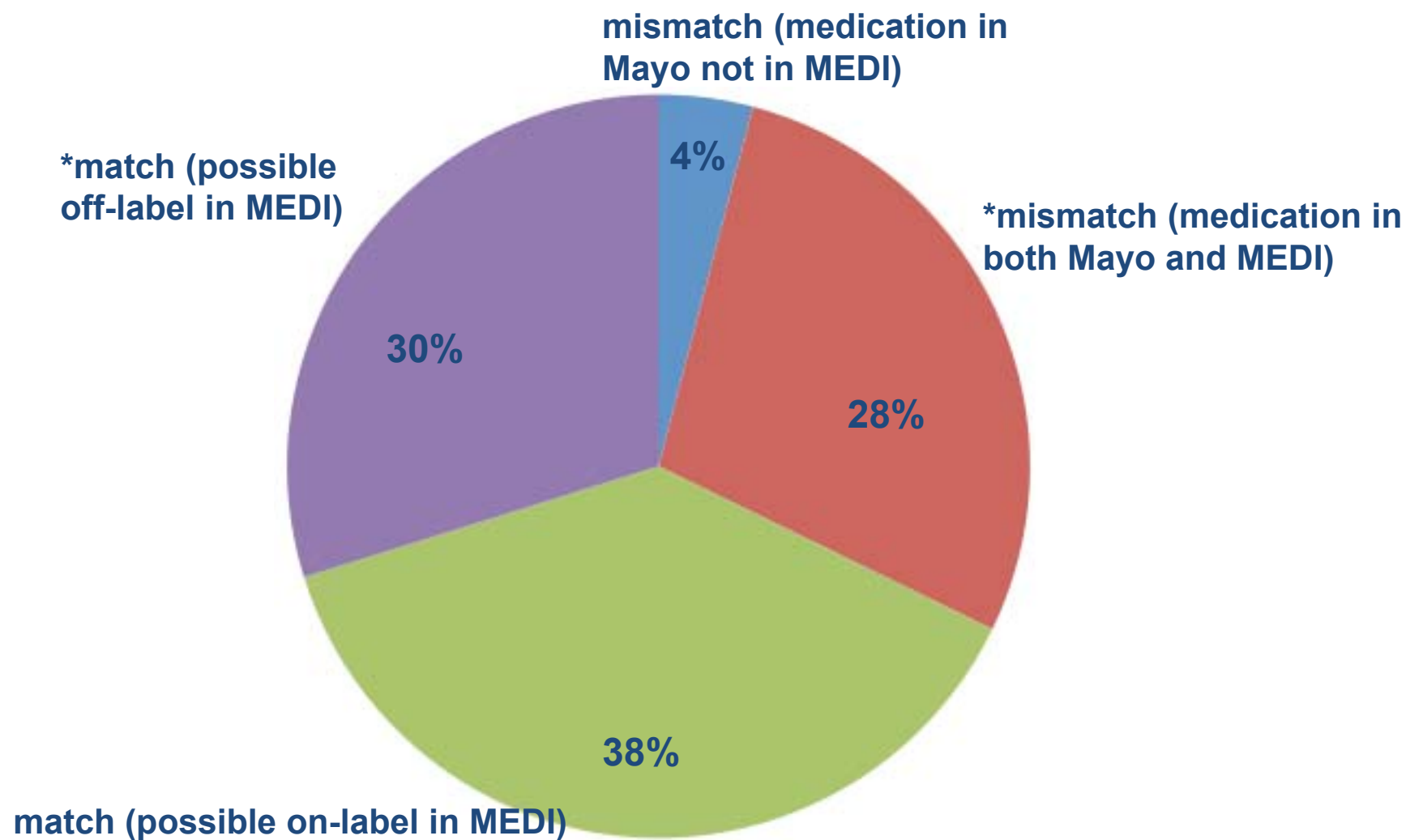


- Drug usage in reality is messy
No consensus on clinically meaningful drug-indication relationships
- Literature Mining
- Social media Mining
- Electronic Health Record Validation

- Aspirin 325-mg tablet enteric-coated 1 tablet by mouth one-time daily. Indication: stroke prevention.
- Bactrim-DS 160-800 mg tablet 1 tablet by mouth one-time daily.
- Ativan 1-mg tablet 1 tablet by mouth once-a-month.
- Indication, Site, Instruction: anxiety. take 1-mg one-hour every month.
- Azopt 1% drop suspension 1 drop ophthalmic two times a day. Site: Both eyes. Indication: glaucoma.

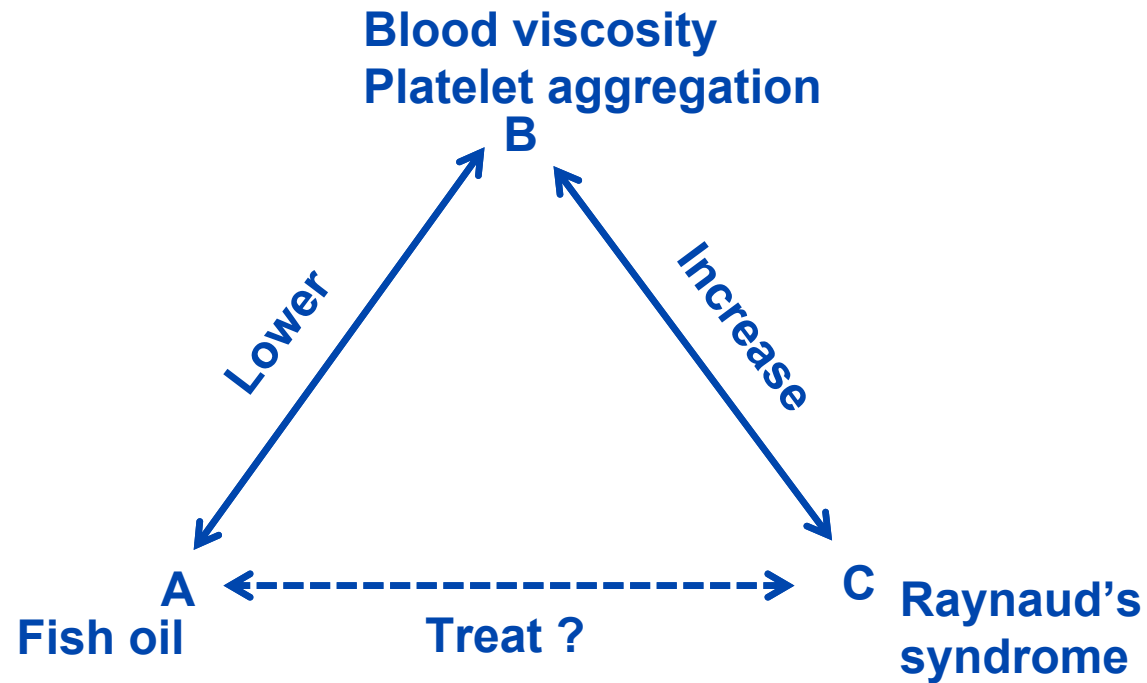


A workflow to extract medication and indication pairs from clinical notes



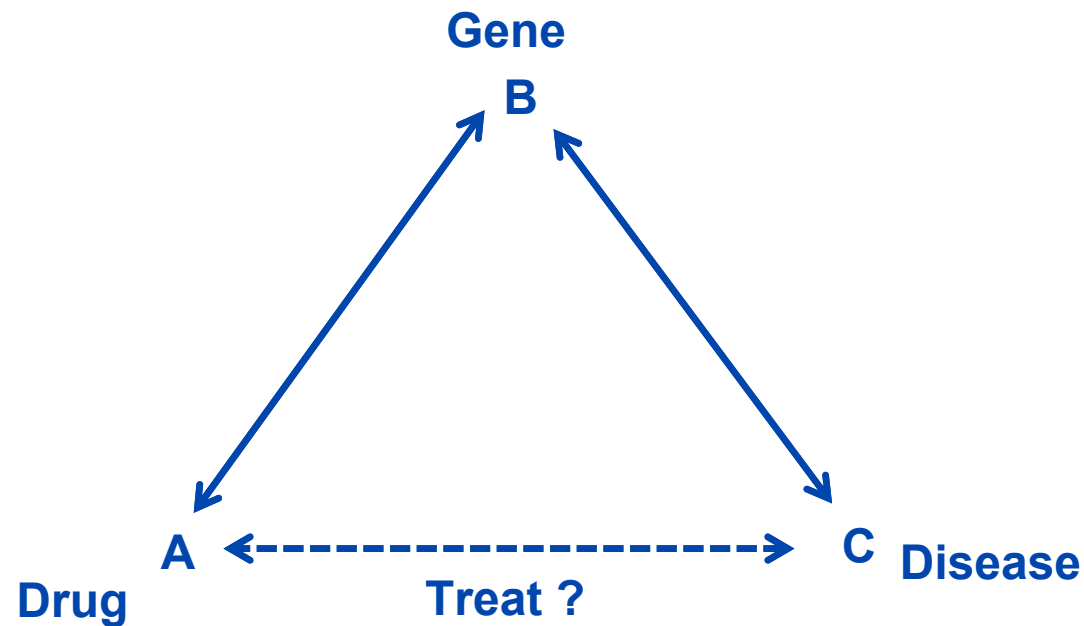
** Possible off-label uses ($\log_2(\# \text{ of patients}) \geq 5$, Flexible match)*

Mining literature for drug repositioning



Swanson ABC Model

Mining literature for drug repositioning

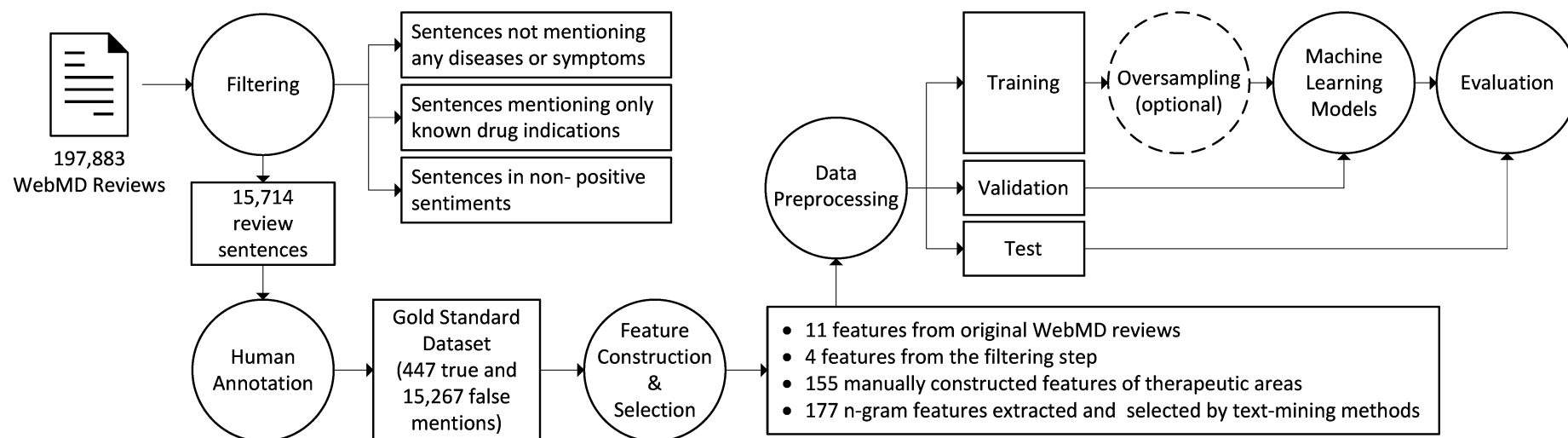


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Li, Jiao, et al. "A survey of current trends in computational drug repositioning." *Briefings in bioinformatics* 17.1 (2016): 2-12.

Rastegar-Mojarad, Majid, et al. "A new method for prioritizing drug repositioning candidates extracted by literature-based discovery." *Bioinformatics and Biomedicine (BIBM)*, 2015 IEEE International Conference on. IEEE, 2015.

Mining social media for drug repositioning



Model Performance

| Model | Test dataset | | | 10-fold cross validation | | |
|---------------------------------|--------------|-----------|--------|--------------------------|-----------|--------|
| | AUC | Precision | Recall | AUC | Precision | Recall |
| SVM | 0.900 | 0.758 | 0.397 | 0.926 | 0.817 | 0.539 |
| SVM - Oversampling | 0.893 | 0.474 | 0.429 | 0.932 | 0.470 | 0.620 |
| Random Forest | 0.926 | 0.857 | 0.381 | 0.935 | 0.840 | 0.506 |
| Random Forest - Oversampling | 0.915 | 0.781 | 0.397 | 0.944 | 0.866 | 0.530 |
| AdaBoost.M1 | 0.937 | 0.811 | 0.476 | 0.949 | 0.791 | 0.575 |
| AdaBoost.M1 - Oversampling | 0.934 | 0.800 | 0.444 | 0.950 | 0.769 | 0.559 |

True Positive Predictions

| Drug | Known indications | Serendipitous usage | Example | # of references |
|---------------------------|---|--|--|-----------------|
| Metformin | Type 2 Diabetes Mellitus, Polycystic Ovary Syndrome, etc. | Obesity | I feel AWFUL most of the day, but the weight loss is great. | >10 |
| Tramadol | Pain | Depression , anxiety | It also has helped with my depression and anxiety. | 1 |
| Acetaminophen & oxycodone | Pain | Depression | While taking for pain I have also found it relieves my major depression and actually gives me the energy and a clear mind to do things. | 1 |
| Bupropion | Depression, attention deficit & hyperactivity disorder | Obesity | I had energy and experienced needed weight loss and was very pleased, as I did not do well on SSRI or SNRIs. | 4 |
| Ondansetron | Vomiting | Irritable bowel syndrome with diarrhea | A lot of people have trouble with the constipation that comes with it, but since I have IBS-D (irritable bowel syndrome with diarrhea), it has actually regulated me . | 1 |
| Desvenlafaxine | Depression | Lack of energy | I have had a very positive mood and energy change, while also experiencing much less anxiety. | |

Validating drug repositioning signal using EHR

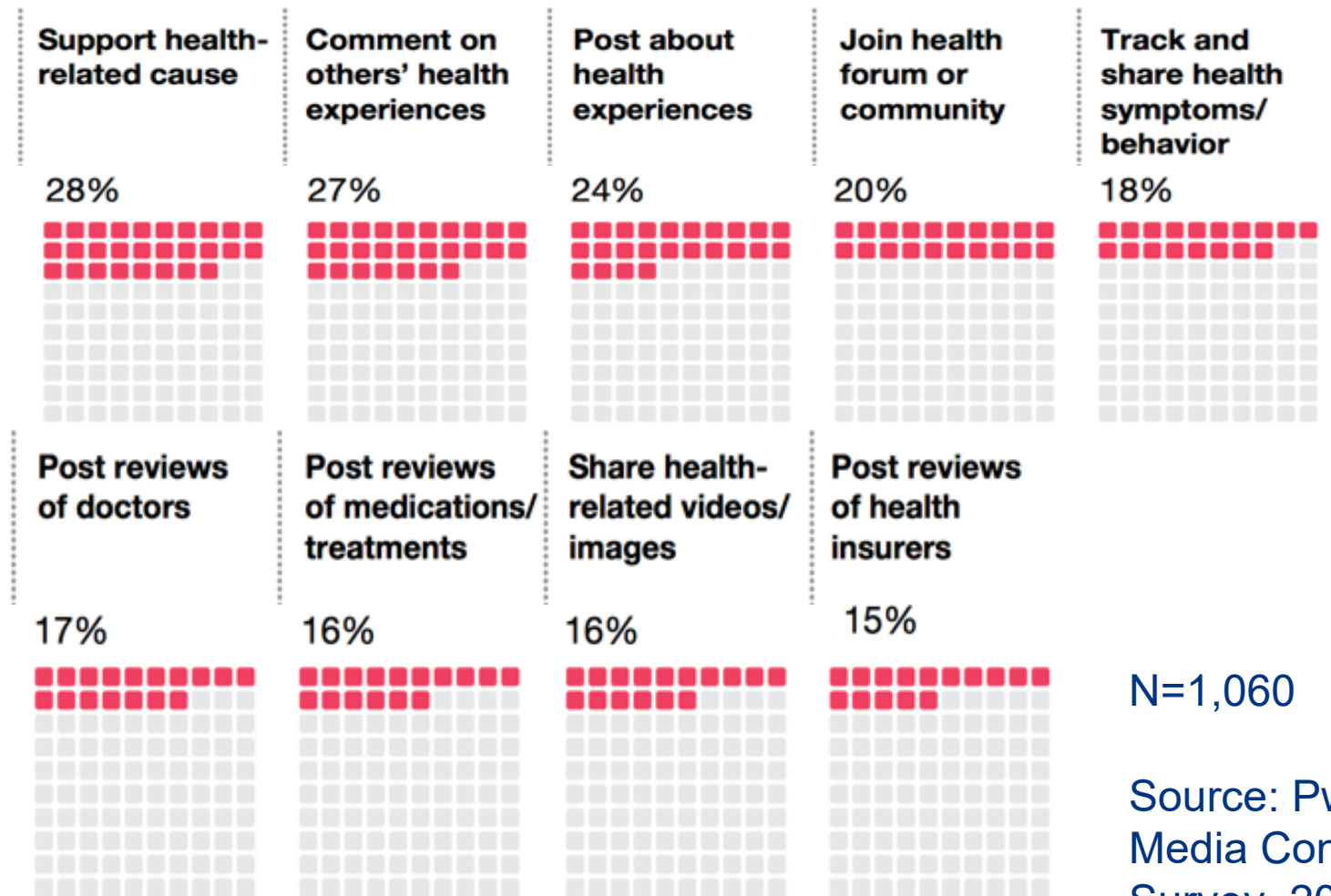
| Data Summary | Vanderbuilt | Mayo Clinic |
|---|-------------|-------------|
| Unique patient count (May 2013) | 2.2 M | 7.4 M |
| Cancer patients (excluding skin cancer and age <18) diagnosed between 1995 and 2010, based on Tumor Registry | 44,257 | 102,546 |
| Cancer patients from above, but excluding congestive heart failure and chronic kidney disease before tumor diagnosis date | 42,165 | 96,169 |
| With Type 2 Diabetes | 5,796 | 8,939 |
| Taking Metformin | 2,218 | 3,029 |
| Taking other oral diabetes drug | 903 | 1,629 |
| Taking insulin monotherapy | 377 | 1,462 |
| Ineligible & Excluded | 2,298 | 2,819 |
| Without Type 2 Diabetes | 28,917 | 73,138 |



Xu, Hua, et al. "Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality." *Journal of the American Medical Informatics Association* 22, no. 1 (2015): 179-191.

Using stratified Cox proportional hazard models, we found that cancer patients using metformin was associated with decreased mortality, compared to cancer patients (diabetic and non-diabetic) not on metformin.

Mining patient-reported medication outcomes



N=1,060

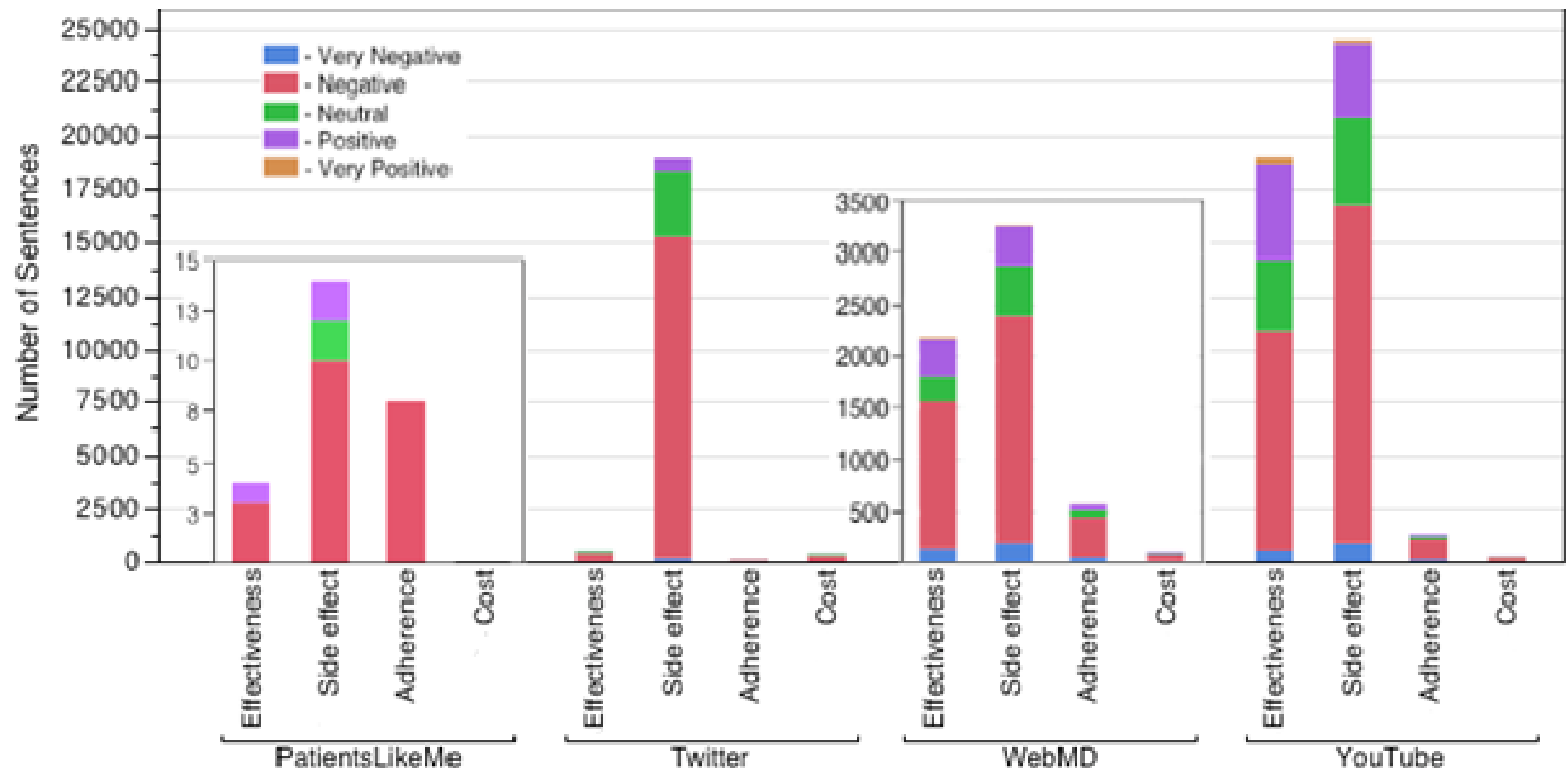
Source: PwC Social Media Consumer Survey, 2012

| <div> <div>Social Media and Metrics</div> <div>Diseases and Drugs</div> </div> | | WebMD | | | | PatientsLikeMe | | | | | YouTube | Twitter |
|--|---------------|---------------|-------------|--------------|----------------|-------------------------|--------------|------------|-------------------|----------------|--------------|--------------|
| | | Effectiveness | Ease of Use | Satisfaction | No. of Reviews | Perceived Effectiveness | Side effects | Adherence* | Financial Burden* | No. of Reviews | No. of Posts | No. of Posts |
| Asthma | Albuterol | 3.87 | 4.39 | 3.55 | 112 | 4.06 | 2.08 | 4.01 | 4.29 | 137 | 2859 | 11381 |
| | Ipratropium | 4.17 | 4.17 | 3.75 | 12 | 4.13 | 1.33 | 4 | 3.95 | 8 | 140 | 271 |
| | Prednisone | 4.00 | 3.92 | 3.32 | 367 | 4.19 | 2.89 | 4.68 | 4.17 | 48 | 8569 | 971 |
| Cystic Fibrosis | Azithromycin | - | - | - | - | 2.91 | 1.73 | 4.55 | 4.65 | 11 | 31 | 90 |
| | Ivacaftor | - | - | - | - | - | - | - | - | - | 818 | 5060 |
| Rheumatoid Arthritis | Meloxicam | 3.39 | 4.18 | 3.11 | 202 | 3.20 | 1.89 | 4.47 | 4.6 | 15 | 558 | 67 |
| | Prednisone | 4.11 | 4.31 | 3.61 | 229 | 4.03 | 3.20 | 4.68 | 4.17 | 63 | 10064 | 670 |
| | Sulfasalazine | 3.19 | 3.28 | 3.17 | 65 | 2.44 | 3.03 | 4.45 | 3.98 | 77 | 581 | 53 |
| Type 2 Diabetes | Bromocriptine | 2.23 | 3.08 | 2.15 | 13 | - | - | - | - | - | 29 | 214 |
| | Insulin | 3.50 | 4.22 | 3.35 | 265 | 4.21 | 1.60 | 4.73 | 4.2 | 106 | 11401 | 16308 |
| | Metformin | 3.29 | 3.91 | 2.93 | 1302 | 3.69 | 2.30 | 4.41 | 4.17 | 331 | 7504 | 4042 |
| Weighted Average: | | 3.52 | 4.00 | 3.14 | - | 3.74 | 2.32 | 4.42 | 4.18 | - | - | - |

* The average drug adherence and burden (cost) ratings on PatientsLikeMe may not be disease specific. In case that a drug has multiple indications, the adherence and burden ratings are consolidated across all indications.

| Content Type | Example | Source |
|-------------------------------------|---|---------|
| Effectiveness | day 001 - <i>not so bad so far, but really only 18 hours in.</i> Asthma acting up a little. Taking Advair. Need to refill Albuterol script. | Twitter |
| | Only been on it for 8 days but I noticed <i>relief from pain</i> right away. However, yesterday I was more short of breath than usual and my <i>blood pressure was high</i> , tightness in my chest so I will stop taking it to see if that stops. | WebMD |
| Side effects | make sure it is plain claritin. not claritin D or anything else. <i>Plain claritin has loratadine.</i> that is fine but anything else can kill it. <i>the regular claritin has no side effects.</i> | YouTube |
| | Bubble gut to me is extreme gas... <i>Very extreme gas, be careful for the first few weeks of use.</i> Don't put yourself in situations like elevators or long car rides before your body adjust to the med. | |
| Adherence | It is so very <i>easy to use</i> and the needle is tiny and does not hurt at all. | WebMD |
| | They divide pills down to <i>easier to take</i> portions or fine tune the dose to better fit the patient. Have you ever tried to use a breakfast drink with the pills? Sometimes it helps pills slide down MOBETTA! | YouTube |
| Cost | Private <i>insurance pays</i> for young Shan 's `miracle drug'; Kelsa can't <i>afford</i> it. | Twitter |
| | Being so close to Mexico allowed me to get my inhalers <i>cheaper</i> and quicker. | WebMD |
| Disease comorbidity & repositioning | Doctor prescribed this after I stopped taking Plaquenel due to stomach upset. In addition to RA I have a history of IBS, sensitive stomach and I have tolerated this medication well. <i>It has greatly improved my IBS while moderately improving my RA pain.</i> Ony side effect is feeling full, thirsty and ocassional gut pain. | WebMD |
| | Personal side effect: Very sensitive to sun. <i>This clears up my bronchial spasms so quickly and as a bonus, it clears up my eczema!</i> I have asked my doctor to prescribe it regularly for my skin condition and he says there are too many side effects. too bad. It is a wonder drug. I was able to breathe very well. | |

Sentiment Analysis



Learned lessons

- Individual data source has inherent bias
 - Findings can be inconsistent and hard to get buy-in from multiple stakeholders
- Domain experts needed to be engaged for clinical meaningfulness
- A need to move from counting co-occurrence to capturing the context and synthesizing the information
 - What + Who, When, Where, Why, How

Acknowledgment



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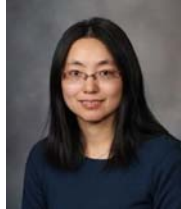
Che Ngufor



Paul Kingsbury



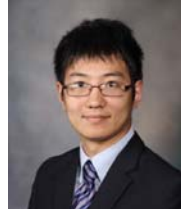
Majid Mojarad



Liwei Wang



Yanshan Wang



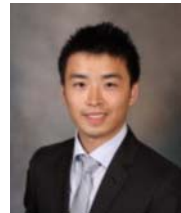
Sijia Liu



Naveed Afzal



Riea Moon



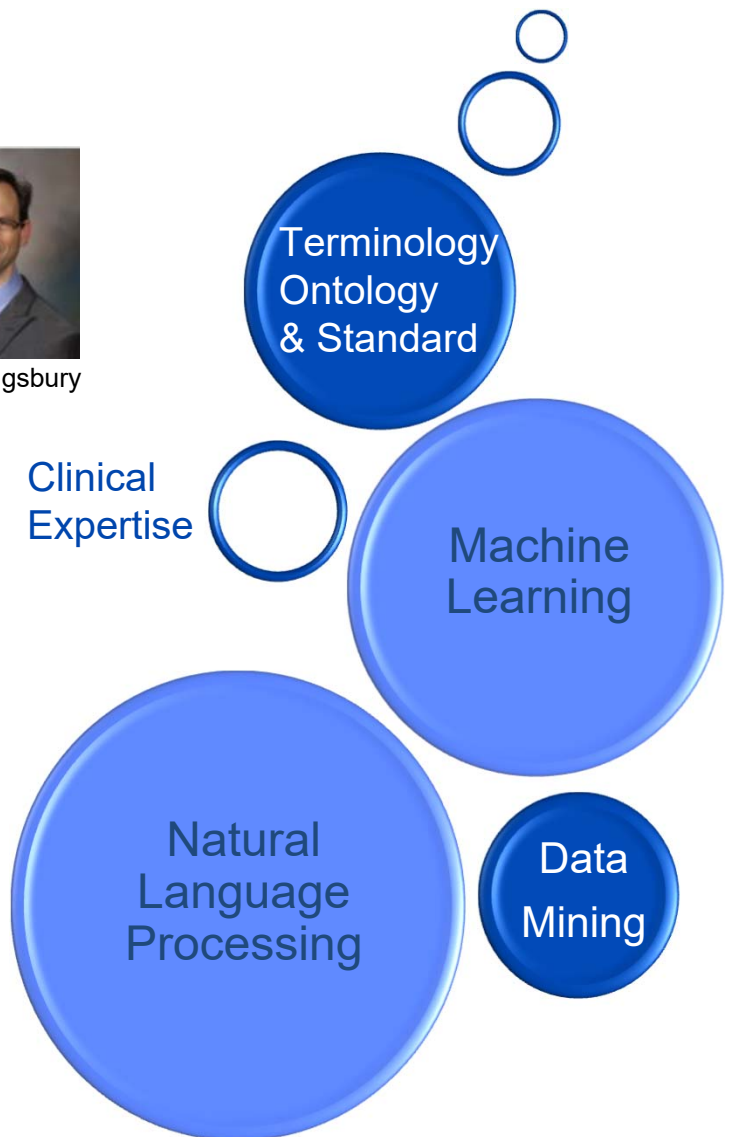
Feichen Shen



David Chen



Na Hong



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Questions?

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