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Patient-centered observational analytics: New directions toward studying the effects of medical products

Patrick Ryan
on behalf of OMOP Research Team
May 22, 2012

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Observational Medical Outcomes Partnership

Public-Private Research Partnership established to inform the appropriate use of observational healthcare databases for studying the effects of medical products:

- Conducting methodological research to empirically evaluate the performance of alternative methods on their ability to identify true associations
- Developing tools and capabilities for transforming, characterizing, and analyzing disparate data sources across the health care delivery spectrum
- Establishing a shared resource so that the broader research community can collaboratively advance the science

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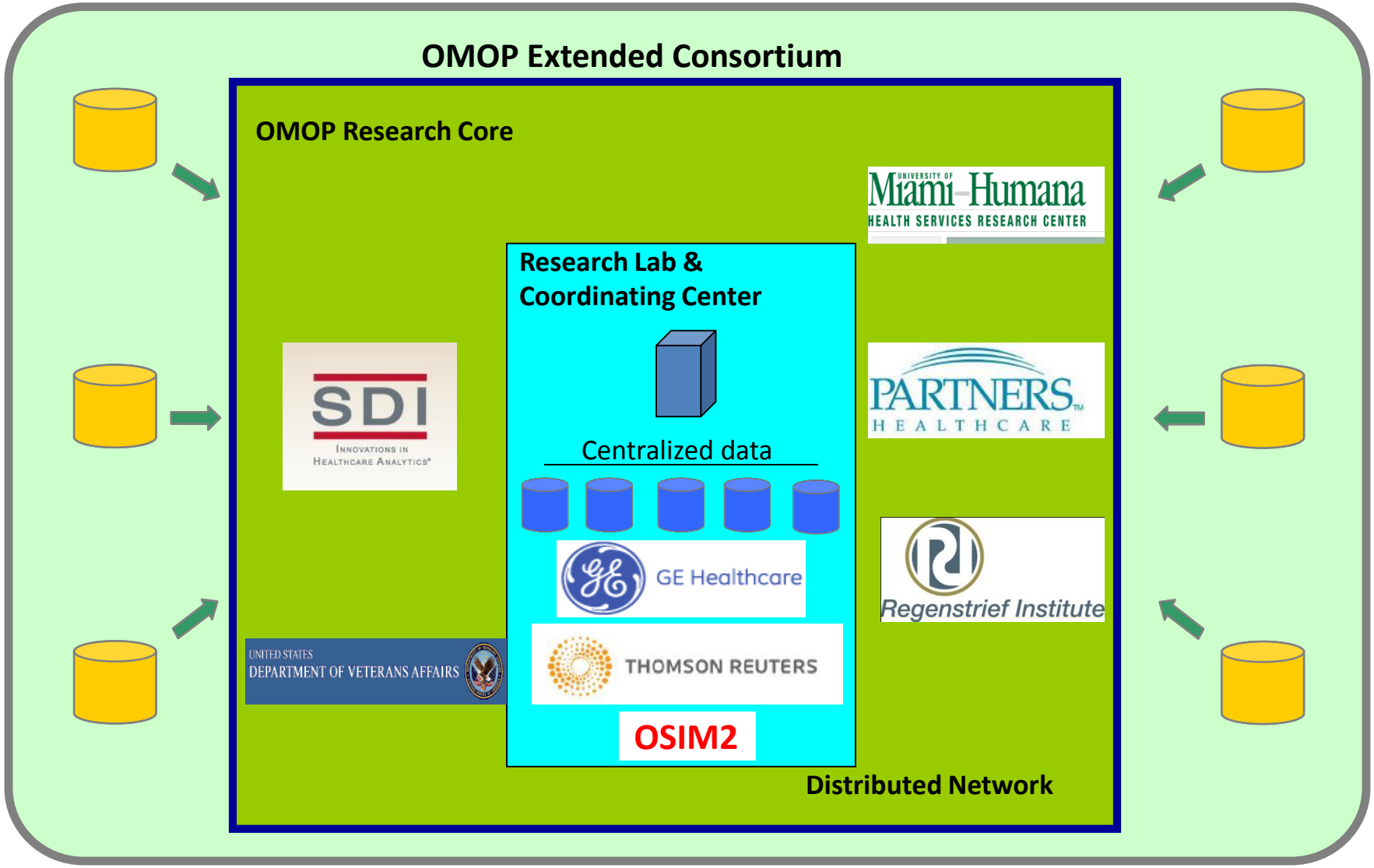
OMOP Data Community – First Two Years



178 million persons with patient-level data

5.4 billion drug exposures, 5.8 billion procedures, 2.3 billion clinical observations

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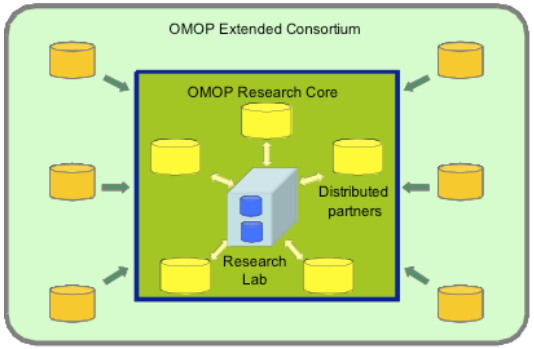
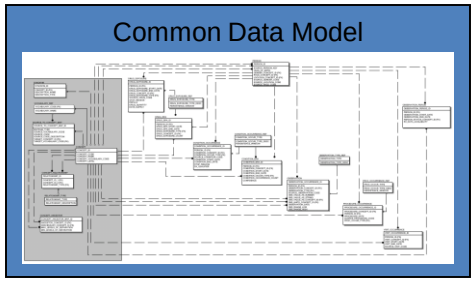
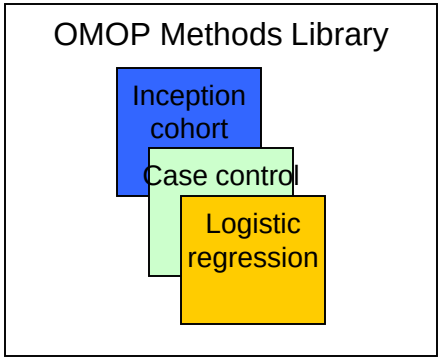
OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 170M+ lives
- Simulated data (OSIM)

- Open-source
- Standards-based
- Systematic data characterization and quality assurance





- 14 methods implemented as standardized procedures
- Full transparency with open-source code and documentation
- Epidemiology, statistical and machine learning designs

Outcome	ACE Inhibitors	Amphotericin B	Antibiotics: erythromycins, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, phenytoin	Benzodiazepines	Beta blockers	Bisphosphonates: alendronate	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema										
Aplastic Anemia										
Acute Liver Injury										
Bleeding										
Hip Fracture										
Hospitalization										
Myocardial Infarction										
Mortality after MI										
Renal Failure										
GI Ulcer Hospitalization										

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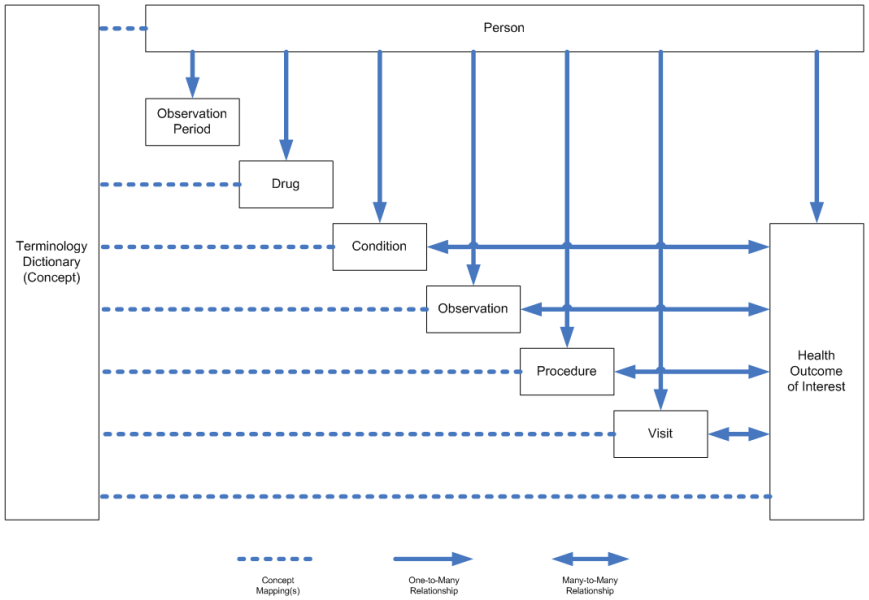
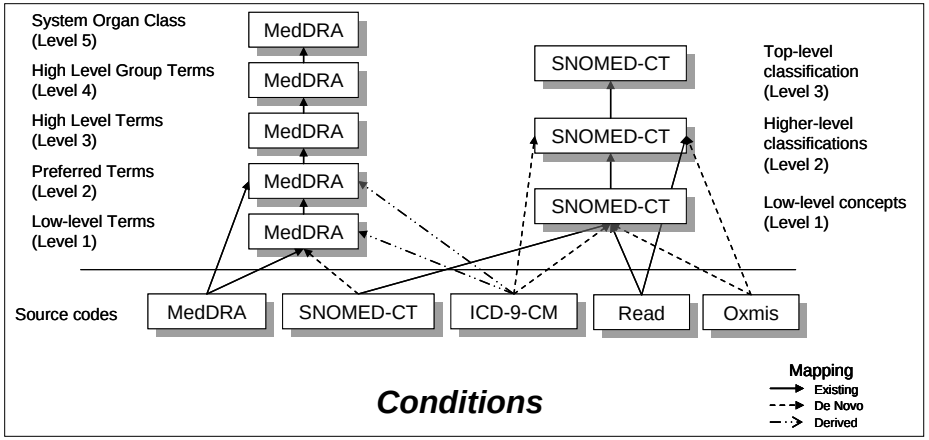
Common Framework

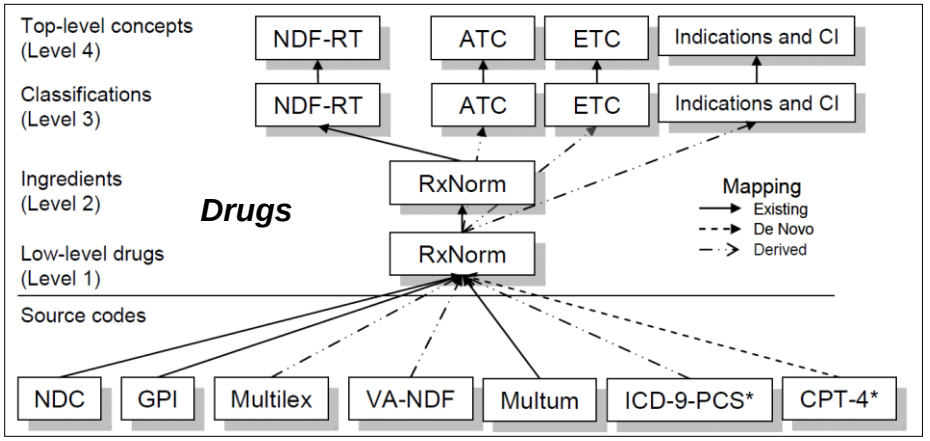
Accommodating Disparate Observational Data Sources

Common Data Model



Standardized Terminologies





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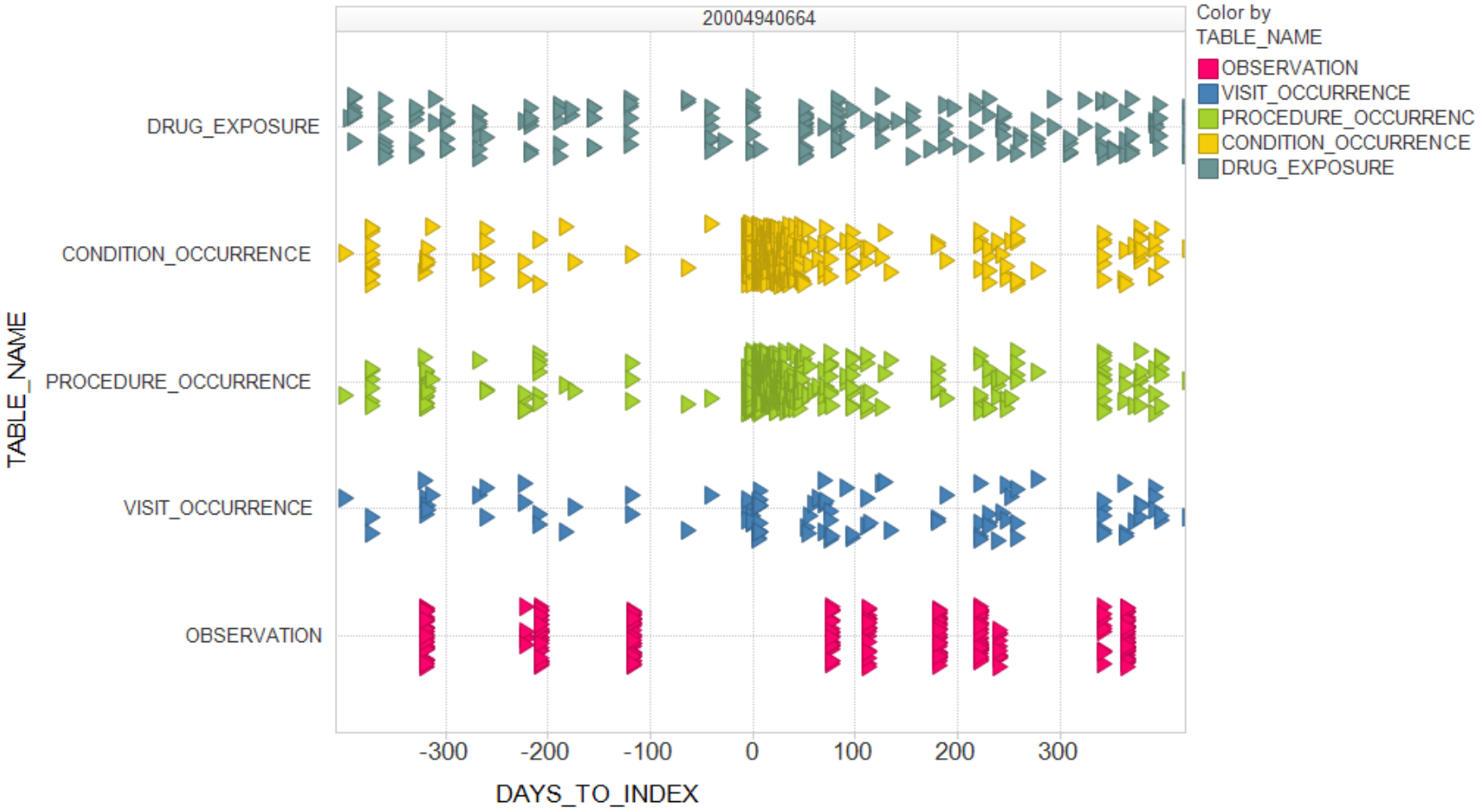
A couple years in the life of a patient in an observational healthcare database



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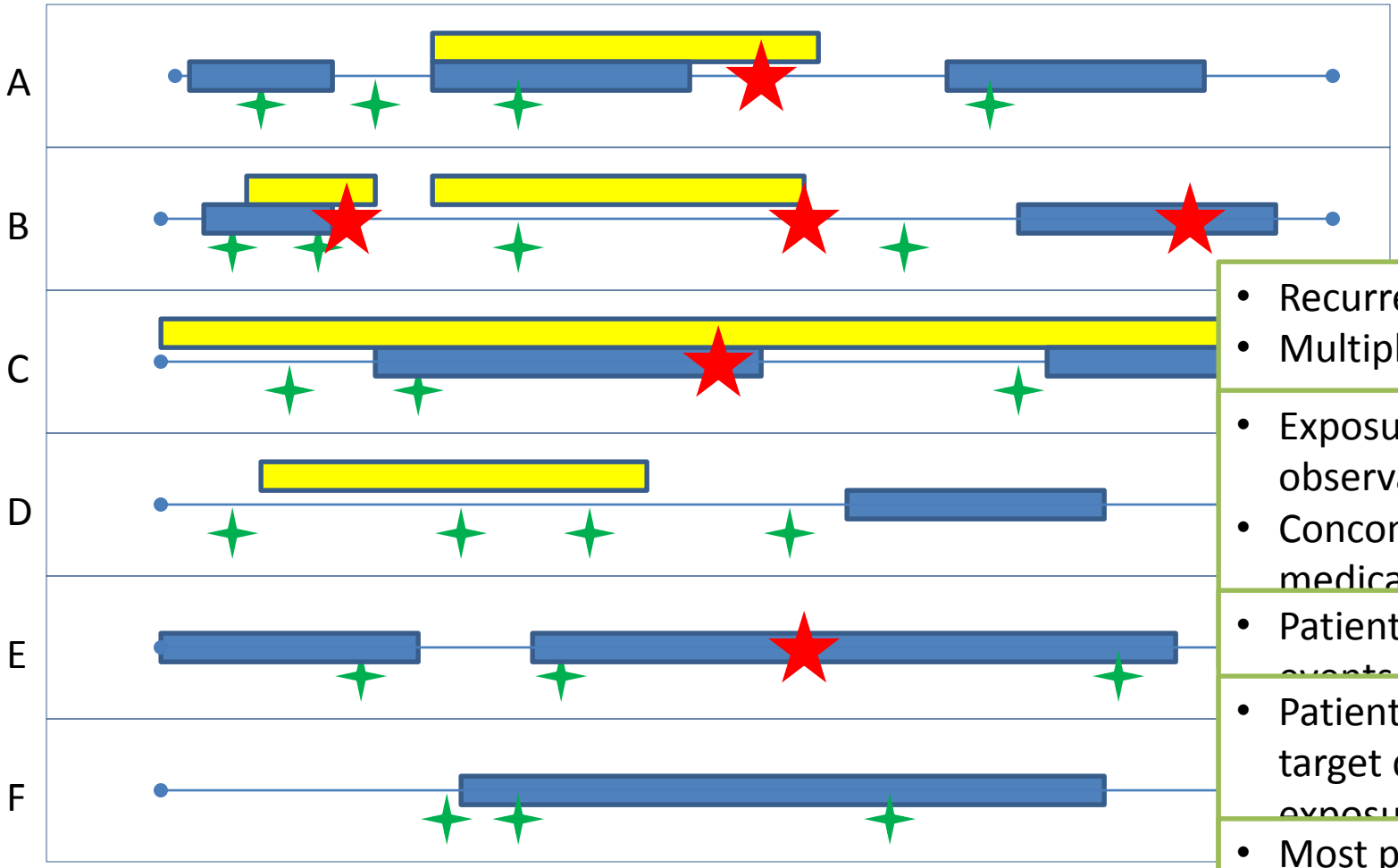
Patient profiles in observational data when studying the effects of medical products



- Recurrent events
- Multiple periods of

- Exposure spanning observation period
- Concomitant medications during

- Patients without events may

- Patients without target drug exposure are

- Most patients in the database have neither the target drug nor the target outcome

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Data used for new user cohort design to estimate average treatment effect

New user design

- Focus on comparing rates of events among patients exposed to target drug, relative to rates of events among patients in some referent comparator group
- Relative risk can be adjusted for baseline covariates through various strategies, including propensity score

- Define cohorts based on index exposure (first use after washout period)
- Observations prior to index may be used as covariates
- Observations on or after index, except for incident outcome, are not considered in analysis

Target drug
Target condition
Other conditions
Other drugs

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Exploring isoniazid and acute liver injury

CMAJ RESEARCH

Adverse events associated with treatment of latent tuberculosis in the general population

Benjamin M. Smith MD, Kevin Schwartzman MD MPH, Gillian Bartlett PhD, Dick Menzies MD MSc

ABSTRACT

Background: Guidelines recommend treatment of latent tuberculosis in patients at increased risk for active tuberculosis. Studies investigating the association of therapy with serious adverse events have not included the entire treated population nor accounted for comorbidities or occurrence of similar events in the untreated general population. Our objective was to estimate the risk of adverse events requiring hospital admission that were associated with therapy for latent tuberculosis infection in the general population.

Methods: Using administrative health data from the province of Quebec, we created a historical cohort of all residents dispensed therapy for latent tuberculosis between 1998 and 2003. Each patient was matched on age, sex and postal region with two untreated residents. The observation period was 18 months (from 6 months before to 12 months after initiation of therapy). The primary outcome was hospital admission for therapy-associated adverse events.

Results: During the period of observation, therapy for latent tuberculosis was dispensed to 9145 residents, of whom 95% started isoniazid and 5% started rifampin. Pretreatment comorbid illness was significantly more common among patients receiving such therapy compared with the matched untreated cohort. Of all patients dispensed therapy, 45 (0.5%) were admitted to hospital for a hepatic event compared with 15 (0.1%) of the untreated patients. For people over age 65 years, the odds of hospital admission for a hepatic event among patients treated for latent tuberculosis infection was significantly greater than among matched untreated people after adjustment for comorbidities (odds ratio [OR] 6.4, 95% CI 2.2–18.3). Excluding patients with comorbid illness, there were two excess admissions to hospital for hepatic events per 100 patients initiating therapy compared with the rate among untreated people over 65 years (95% CI 0.1–3.87).

Interpretation: The risk of adverse events requiring hospital admission increased significantly among patients over 65 years receiving treatment for latent tuberculosis infection. The decision to treat latent tuberculosis infection in elderly patients should be made after careful consideration of risks and benefits.

Competing interests:
None declared.

This article has been peer reviewed.

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CMAJ 2011. DOI:10.1503/cmaj.091824

Average treatment effect, patients > 65 years of age:
OR = 6.4 (2.2 – 18.3)

CMAJ, February 22, 2011, 183(3)

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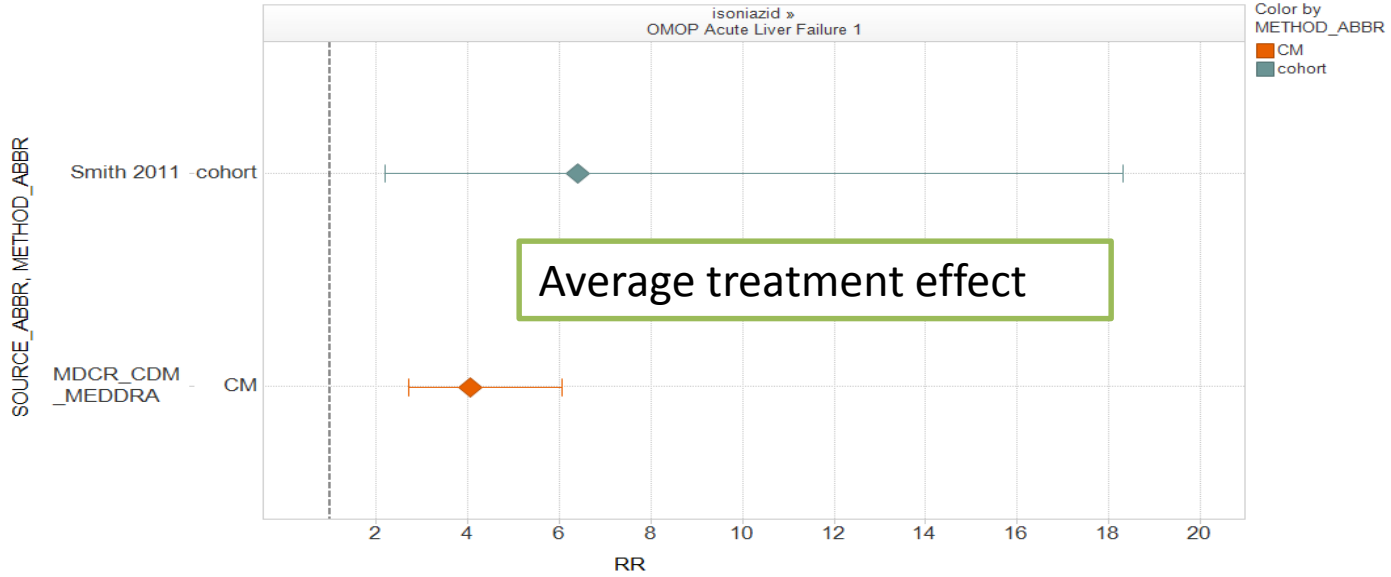
OMOP replication: isoniazid – acute liver injury

- Data source: MarketScan Medicare Beneficiaries (MDCR)
- Study design: Cohort
- Exposure: all patients dispensed new use of isoniazid, 180d washout
- Unexposed cohort: Patient with indicated diagnosis (e.g. pulmonary tuberculosis) but no exposure to isoniazid; negative control drug referents
- Time-at-risk: Length of exposure + 30 days, censored at incident events
- Covariates: age, sex, index year, Charlson score, number of prior visits, all prior medications, all comorbidities, all priority procedures
- "Odds ratio" estimated through propensity score stratification (20 strata)



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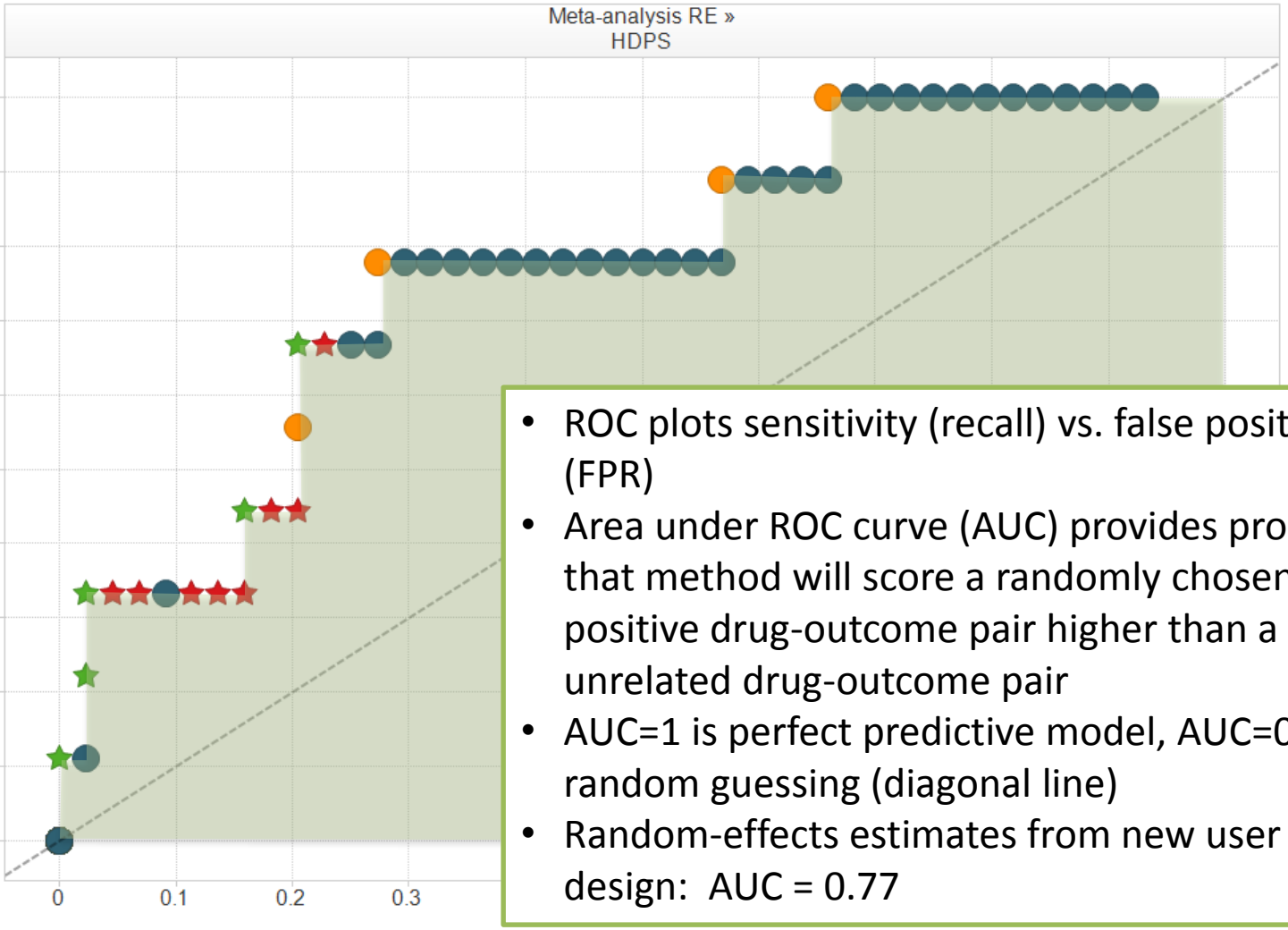
Receiver Operating Characteristic (ROC) curve



- ROC plots sensitivity (recall) vs. false positive rate (FPR)
- Area under ROC curve (AUC) provides probability that method will score a randomly chosen true positive drug-outcome pair higher than a random unrelated drug-outcome pair
- AUC=1 is perfect predictive model, AUC=0.50 is random guessing (diagonal line)
- Random-effects estimates from new user cohort design: AUC = 0.77

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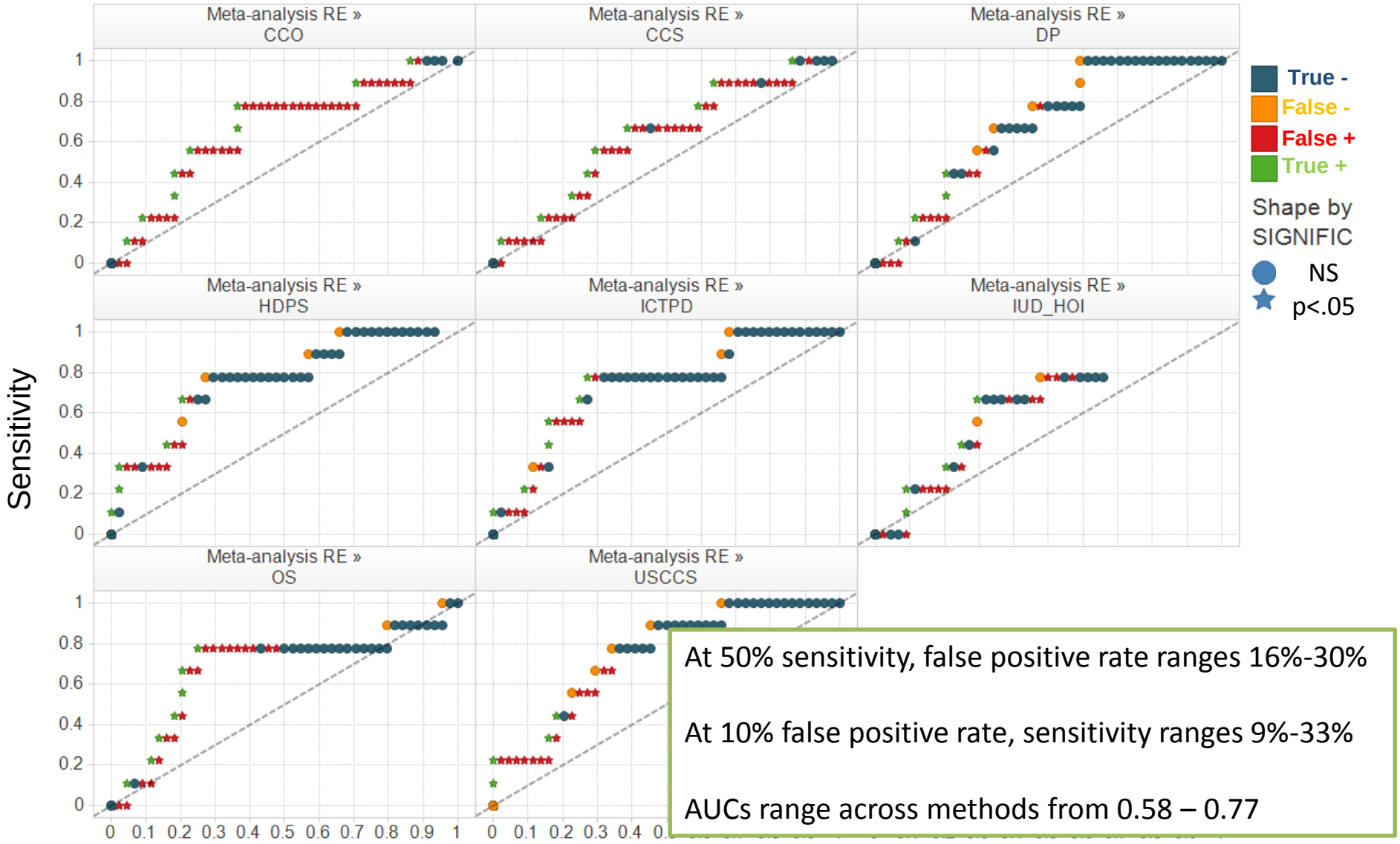
ROC curves of random-effects meta-analysis estimations for all methods



At 50% sensitivity, false positive rate ranges 16%-30%

At 10% false positive rate, sensitivity ranges 9%-33%

AUCs range across methods from 0.58 – 0.77

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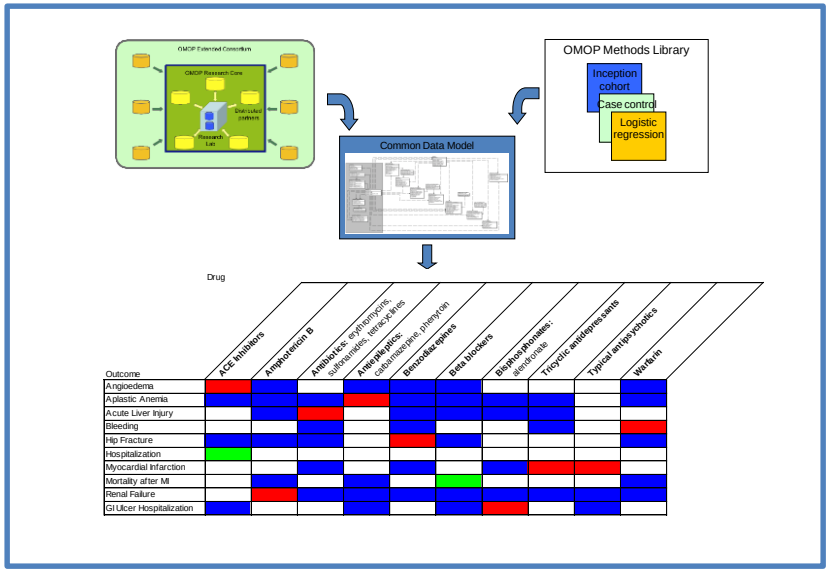
Where do we go from here?



Further exploration of average treatment effects

- Increased methods development
- Expansion of test cases
- Evaluate predictive accuracy

New direction:
Patient-centered predictions

- Estimate probability of future outcome, based on past clinical observations
- Evaluate predictive accuracy

OMOP Symposium: 28 June 2012

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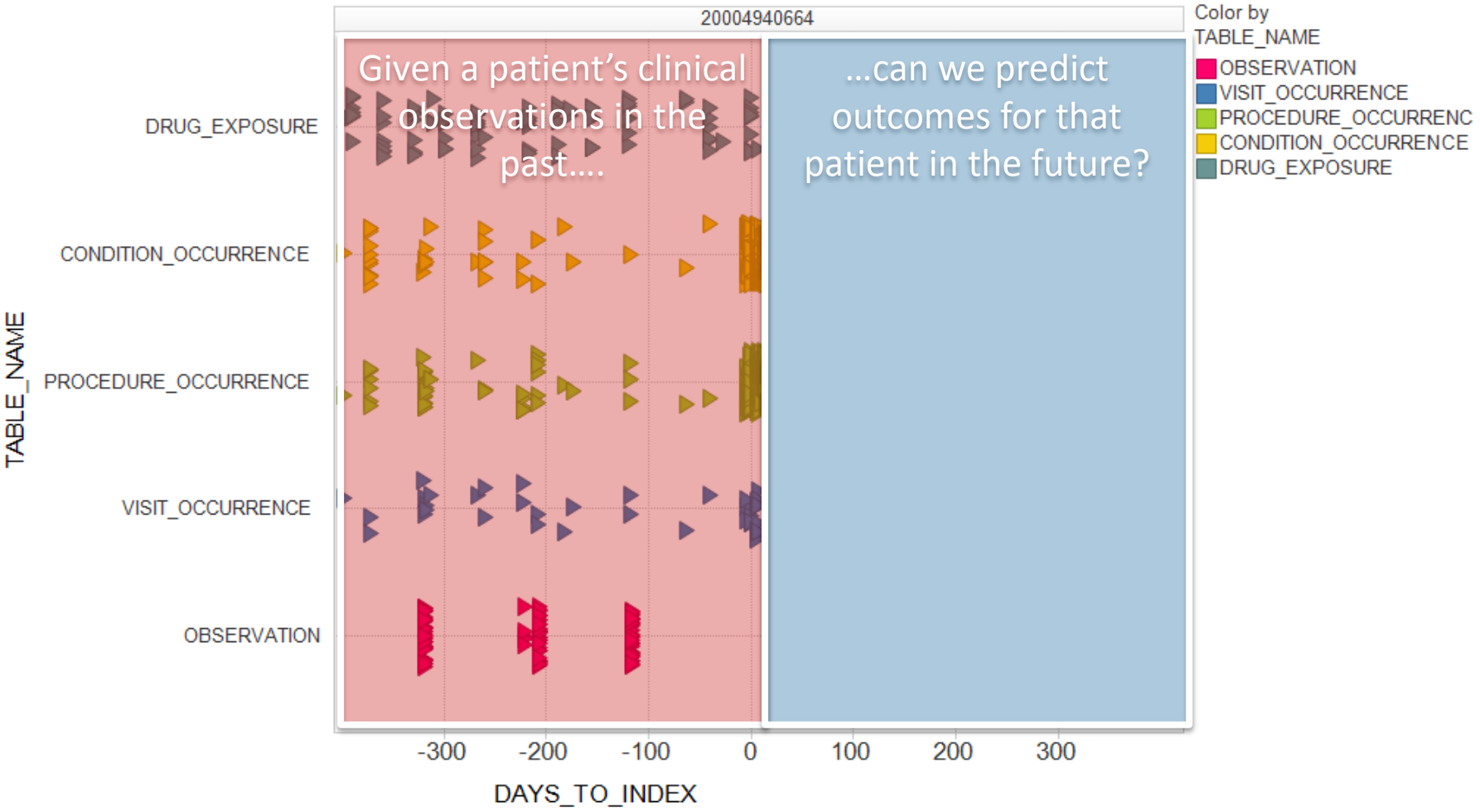
A couple years in the life of a patient in an observational healthcare database



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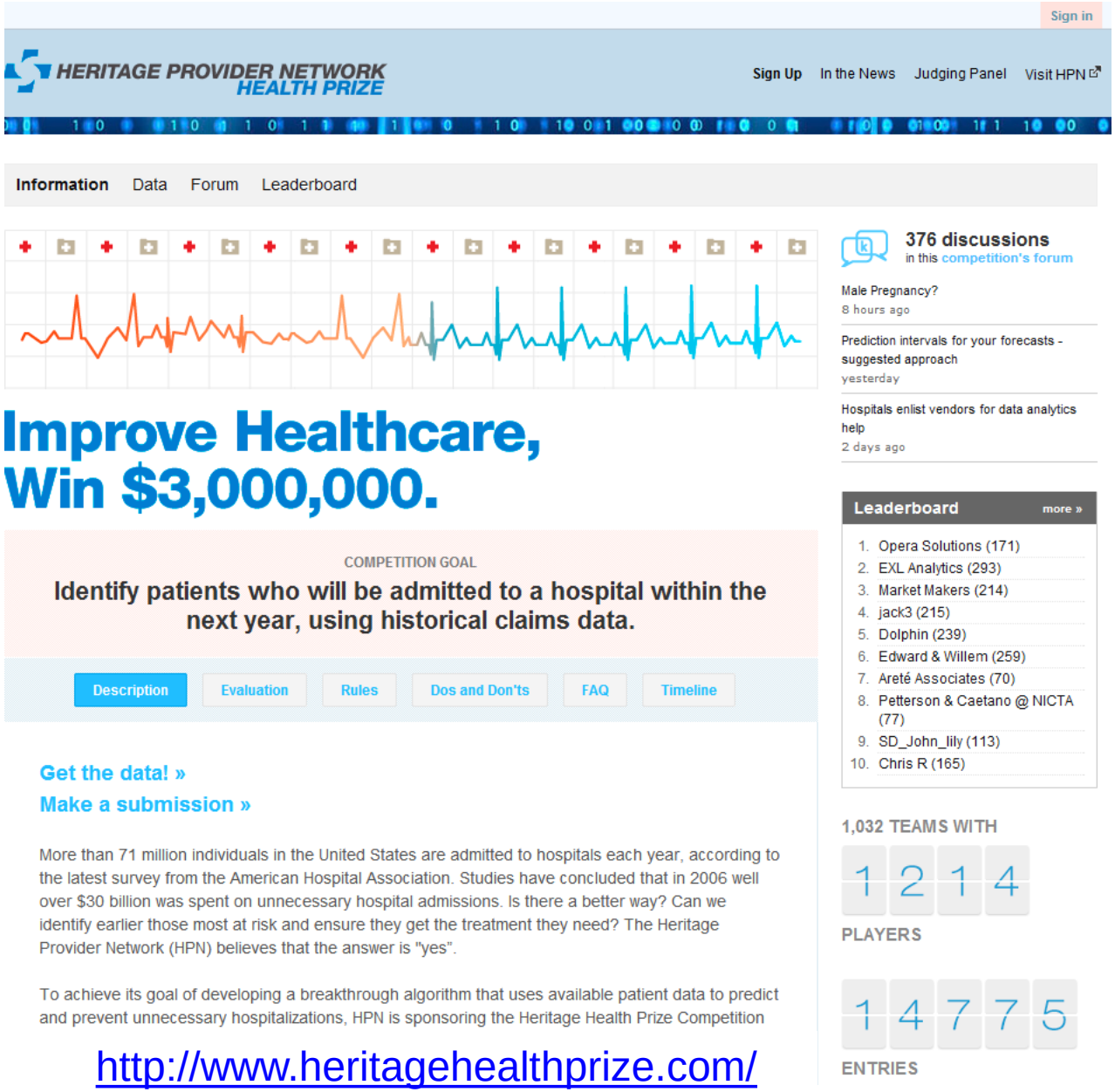
Patient-centered predictive modeling on big data has big value and big interest



http://www.heritagehealthprize.com/

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Patient-centered predictive models are already in clinical practice

Validation of Clinical Classification Schemes for Predicting Stroke

Results From the National Registry of Atrial Fibrillation

Brian F. Gage, MD, MSc
Amy D. Waterman, PhD
William Shannon, PhD
Michael Boechler, PhD
Michael W. Rich, MD
Martha J. Radford, MD

Context Patients who have atrial fibrillation (AF) have an increased risk of stroke, but their absolute rate of stroke depends on age and comorbid conditions.

Objective To assess the predictive value of classification schemes that estimate stroke risk in patients with AF.

Design, Setting, and Patients Two existing classification schemes were combined into a new stroke-risk scheme, the $CHADS_2$ index, and all 3 classification schemes were validated. The $CHADS_2$ was formed by assigning 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack. Data from peer review organizations representing 7 states were used to assemble a National Registry of AF (NRAF) consisting of 1733 Medicare beneficiaries aged 65 to 95 years who had nonrheumatic AF and were not prescribed warfarin at hospital discharge.

Main Outcome Measure Hospitalization for ischemic stroke, determined by Medicare claims data.

Results During 2121 patient-years of follow-up, 94 patients were readmitte
hospital for ischemic stroke (stroke rate, 4.4 per 100 patient-years). As indicat
c statistic greater than 0.5, the 2 existing classification schemes predicted stro
ter than chance: *c* of 0.68 (95% confidence interval [CI], 0.65-0.71) for the
developed by the Atrial Fibrillation Investigators (AFI) and *c* of 0.74 (95% C
0.76) for the Stroke Prevention in Atrial Fibrillation (SPAF) III scheme. Howev
a *c* statistic of 0.82 (95% CI, 0.80-0.84), the $CHADS_2$ index was the most a
predictor of stroke. The stroke rate per 100 patient-years without antithrombotic
increased by a factor of 1.5 (95% CI, 1.3-1.7) for each 1-point increase in the C
score: 1.9 (95% CI, 1.2-3.0) for a score of 0; 2.8 (95% CI, 2.0-3.8) for 1; 4.
CI, 3.1-5.1) for 2; 5.9 (95% CI, 4.6-7.3) for 3; 8.5 (95% CI, 6.3-11.1) for
(95% CI, 8.2-17.5) for 5; and 18.2 (95% CI, 10.5-27.4) for 6.

Conclusion The 2 existing classification schemes and especially a new str
index, $CHADS_2$, can quantify risk of stroke for patients who have AF and ma
selection of antithrombotic therapy.

JAMA. 2001;285:2864-2870

THE ATRIAL FIBRILLATION (AF) population is heterogeneous in terms of ischemic stroke risk. Subpopulations have annual stroke rates that range from less than 2% to more than 10%.[1-5] Because the relative risk reductions from warfarin sodium (62%) and aspirin (22%) therapy are consistent across these subpopulations,[2,6-8] the absolute benefit of antithrombotic therapy depends on the underlying risk of stroke. Although there has been agreement that warfarin therapy is favored when the risk of stroke is high and that aspirin is favored when the risk of stroke is low,[9,10] there has been little agreement about how to predict the risk of stroke.[11-13] Thus, an accurate, objective scheme to estimate the risk of stroke in the AF population would allow physicians and

CHADS2 for patients with atrial fibrillation:

+1 Congestive heart failure
+1 Hypertension
+1 Age >= 75
+1 Diabetes mellitus
+2 History of transient ischemic attack

JAMA, 2001; 285: 2864-2870

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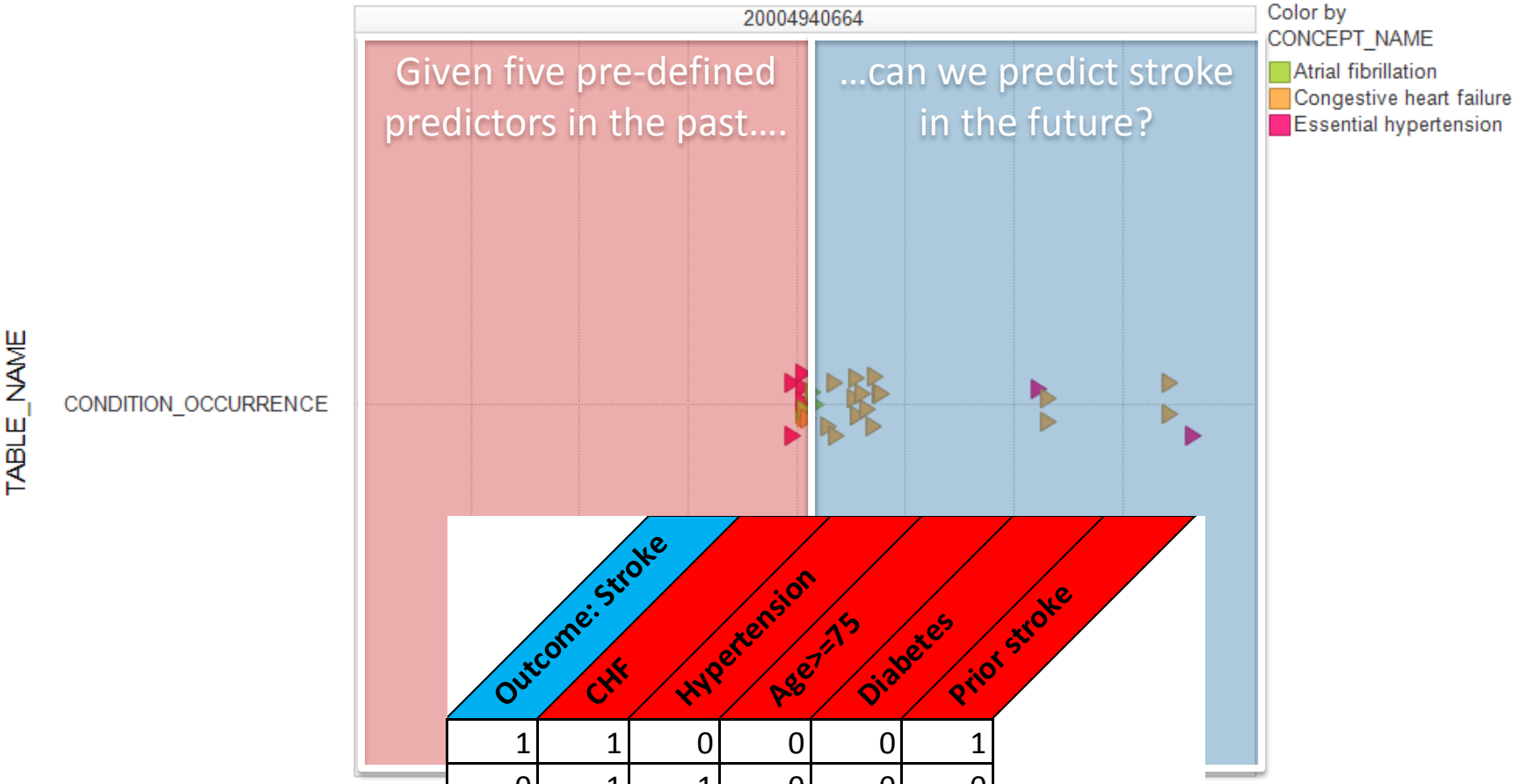
Applying CHADS2 to a patient



Outcome: Stroke	CHF	Hypertension	Age>=75	Diabetes	Prior stroke
1	1	0	0	0	1
0	1	1	0	0	0
0	1	1	1	0	1
1	1	1	0	1	0
0	0	1	0	0	0
1	1	1	1	0	0
0	0	0	1	1	0

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Evaluating the predictive accuracy of CHADS2

Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

AUC = 0.82 (0.80 – 0.84)

JAMA, 2001; 285: 2864-2870

Validation of the $CHADS_2$ clinical prediction rule to predict ischaemic stroke

A systematic review and meta-analysis

Claire Keogh; Emma Wallace; Ciara Dillon; Borislav D. Dimitrov; Tom Fahey
Royal College of Surgeons, Dublin, Ireland

Thromb Haemost 2011; 106: 528–538

Summary

The $CHADS_2$ predicts annual risk of ischaemic stroke in non-valvular atrial fibrillation. This systematic review and meta-analysis aims to determine the predictive value of $CHADS_2$. The literature was systematically searched from 2001 to October 2010. Data was pooled and analysed using discrimination and calibration statistical measures, using a random effects model. Eight data sets (n=2815) were included. The diagnostic accuracy suggested a cut-point of ≥1 has higher sensitivity (92%) than specificity (12%) and a cut-point of ≥4 has higher specificity (96%) than sensitivity (33%). Lower summary estimates were observed for cut-points ≥2 (sensitivity 79%, specificity 42%) and ≥3 (specificity 77%, sensitivity 50%). There was insufficient data to analyse cut-points ≥5 or ≥6. Moderate pooled c statistic values were identified for the classic (0.63, 95% CI 0.52–0.75) and revised (0.60, 95% CI 0.43–0.72) view of stratification of the $CHADS_2$. Calibration analysis indicated no significant difference between the predicted and observed strokes across the three risk strata for the classic or revised view. All results were associated with high heterogeneity, and conclusions should be made cautiously. In conclusion, the pooled c statistic and calibration analysis suggests minimal clinical utility of both the classic and revised view of the $CHADS_2$ in predicting ischaemic stroke across all risk strata. Due to high heterogeneity across studies and low event rates across all risk strata, the results should be interpreted cautiously. Further validation of $CHADS_2$ should perhaps be undertaken, given the methodological differences between many of the available validation studies and the original $CHADS_2$ derivation study.

AUC = 0.63 (0.52 – 0.75)

Is CHADS2 as good as we can do?

- What about other measures of CHADS2 predictors?
  - Disease severity and progression
  - Medication adherence
  - Health service utilization
- What about other known risk factors?
  - Hypercholesterolemia
  - Atherosclerosis
  - Anticoagulant exposure
  - Tobacco use
  - Alcohol use
  - Obesity
  - Family history of stroke
- What about other unknown risk factors?

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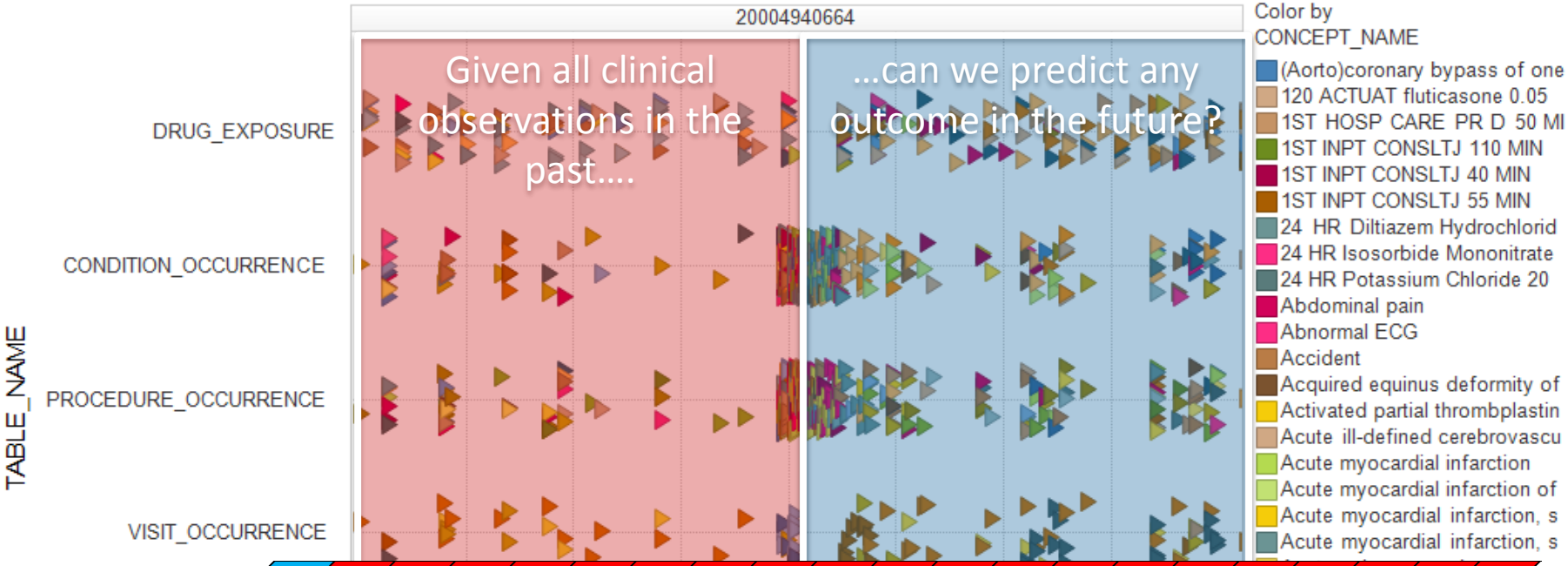
High-dimensional analytics can help reframe the prediction problem



Outcome: Stroke	Age	Gender	Race	Location	Drug 1	Drug 2	…	Drug n	Condition 1	Condition 2	…	Condition n	Procedure 1	Procedure 2	…	Procedure n	Lab 1	Lab 2	…	Lab n
0	76	M	B	441	0	0	1	1	1	1										
1	77	F	W	521	1	0	0	1	0	0										
1	96	F	B	215	1	1	1	0	1	0										
1	76	F	B	646	0	1	0	0	1	0										
0	64	M	B	379	0	0	1	1	1	1										
1	74	M	W	627	0	1	1	1	0	0										
1	68	M	B	348	0	0	0	1	0	0										
	Demographics				All drugs				All conditions				All procedures				All lab values			

Modern predictive modeling techniques, such as Bayesian logistic regression, can handle millions of covariates. The challenge is creating covariates that might be meaningful for the outcome of interest

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Why patient-centered analytics holds promise

Average treatment effects:

- Hundreds of drug-outcome pairs
- Unsatisfactory ground truth:
  - how confident are we that drug is associated with outcome?
  - What is 'true' effect size?
- Questionable generalizability: who does the average treatment effect apply to?
- Final answer often insufficient:
  - Need to drilldown to explore treatment heterogeneity
  - Truth about 'causality' is largely unobtainable

Patient-centered predictions:

- Millions of patients
- Explicit ground truth
  - Each patient did or did not have the outcome within the defined time interval
- Direct applicability: model computes probability for each individual
- Final model can address broader questions:
  - Which patients are most at risk?
  - What factors are most predictive of outcome?
  - How much would change in health behaviors impact risk?
  - What is the average treatment effect?

Concluding thoughts

- Not all patients are created equally…
  - Average treatment effects are commonly estimated from observational databases, but the validity and utility of these estimates remains undetermined
  - Patient-centered predictive modeling offers a complementary perspective for evaluating treatments and understanding disease
- …but all patients can equally benefit from the potential of predictive modeling in observational data
  - Clinical judgment may be useful, but selecting of a handful of predictors is unlikely to maximize the use of the data
  - High-dimensional analytics can enable exploration of high-dimensional data, but further research and evaluation is needed
  - Empirical question still to be answered: Which outcomes can be reliably predicted using which models from which data?

Observational Medical Outcomes Partnership
Third Annual Symposium

A Public Private Partnership of
THE FOUNDATION
FOR THE NATIONAL
INSTITUTES OF HEALTH

June 28, 2012 | Bethesda North Marriott Hotel and Conference Center | Bethesda, Maryland

ABOUT THE SYMPOSIUM

OMOP is a public-private partnership informing on the appropriate use of observational data for studying the real-world effects of medical products. A multi-year methodological research initiative, OMOP has developed a network of administrative claims and electronic health records databases and established a community of methodologists to test the feasibility and utility of large-scale observational analyses. OMOP holds an annual symposium to publicly share insights from the partnership's ongoing research with all stakeholders.

DATE & TIME: Thursday, June 28, 2012 | 8:00 a.m. - 5:00 p.m. Eastern Time

LOCATION: Bethesda North Marriott & Conference Center | 5701 Marinelli Road
North Bethesda, MD 20852, USA

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