ENGELBERG CENTER for Health Care Reform at BROOKINGS

Learning from the Observational Medical Outcomes Partnership (OMOP)

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July 1, 2010

Brookings Roundtable on Active Medical Product Surveillance

Some Initial Housekeeping

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or '*6'. (To unmute, press '*7' as well.)
- **There will be several opportunities for questions and discussion throughout today's session. Please use the Q&A tab at the top of your screen to submit your questions into the queue at any point and we will call upon you to state your question.**
- We will open up the lines for questions from those participating only by phone at the end of each Q&A session.
- Call the Brookings IT Help Desk at 202-797-6193 with technical problems.

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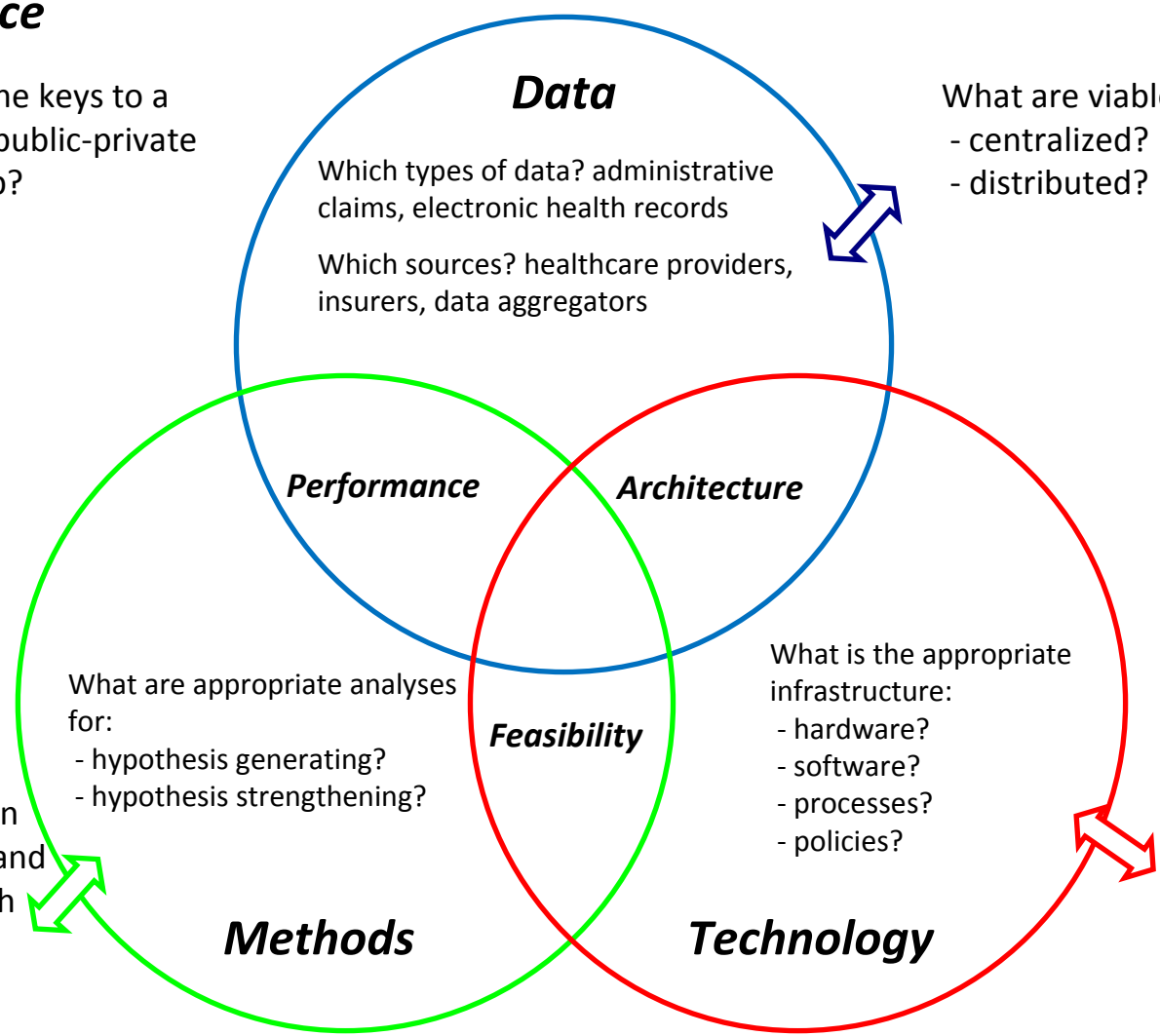
OMOP Overview and Methods Development Progress

Patrick Ryan, David Madigan
on behalf of OMOP Research Team
July 1, 2010

Outstanding questions for active surveillance

Governance

What are the keys to a successful public-private partnership?



What are viable data access models:
- centralized?
- distributed?

What are appropriate analyses for:
- hypothesis generating?
- hypothesis strengthening?

What is the appropriate infrastructure:
- hardware?
- software?
- processes?
- policies?

How to maintain collaborations and engage research community?

What are best practices for protecting data?

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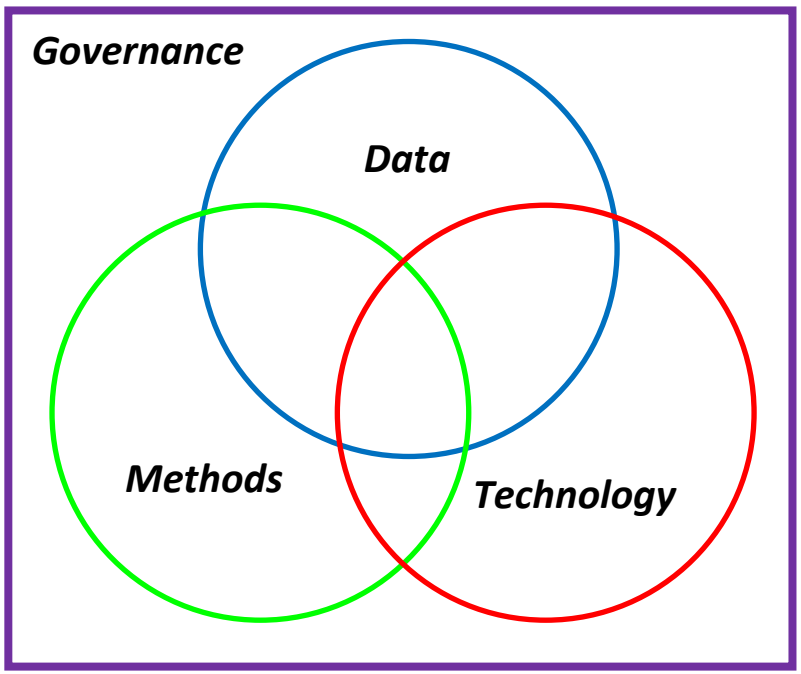
Breadth and diversity of OMOP research community

OMOP's research community requires active participation from all key stakeholders, including government, academia, industry, health care organizations, and patient groups.



Governance

- 10 Executive Board members, chaired by FDA and managed by Foundation for NIH
- 21 Advisory Board members
- Led by 6 research investigators and PMO

Methods

- 17 methods collaborators

Data

- 6 distributed research partners
- 5 central databases included in the OMOP Research Lab

Technology

- 2 data access models, 7 different systems architectures

Over 100 collaborating partners

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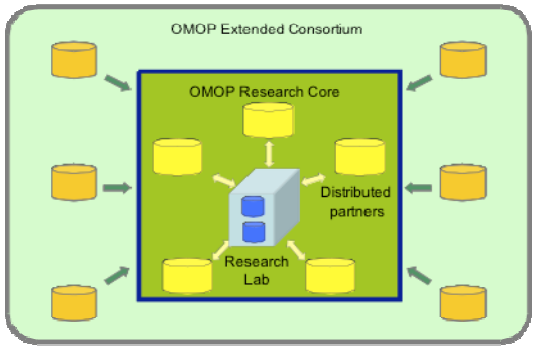
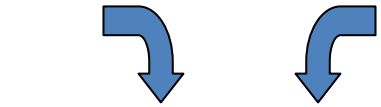
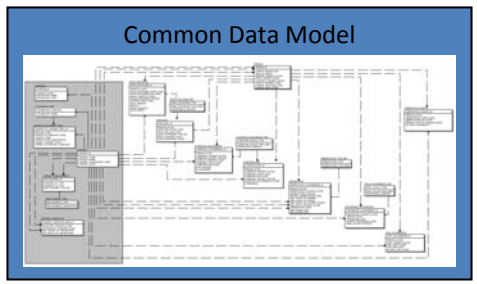
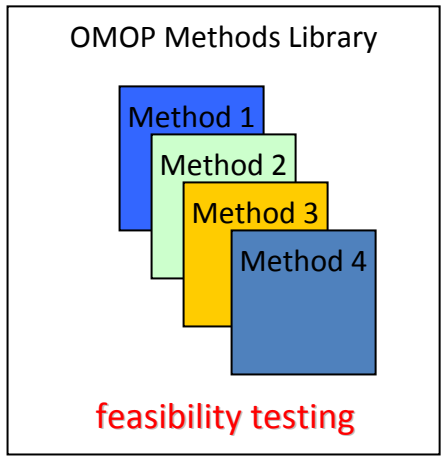
OMOP research experiment workflow









Drugs

- ACE Inhibitors
- Amphotericin B
- Antibiotics
- Antiepileptics
- Benzodiazepines
- Beta blockers
- Bisphosphonates
- Tricyclic antidepressants
- Typical antipsychotics
- Warfarin

Health Outcomes of Interest

- Angioedema
- Aplastic Anemia
- Acute Liver Injury
- Bleeding
- GI Ulcer Hospitalization
- Hip Fracture
- Hospitalization
- Myocardial Infarction
- Mortality after MI
- Renal Failure

Non-specified conditions

-All outcomes in condition terminology

-'Labeled events' as reference
-Warning
-Precautions
-Adverse Reactions
-Postmarketing Experience

Methods Philosophy

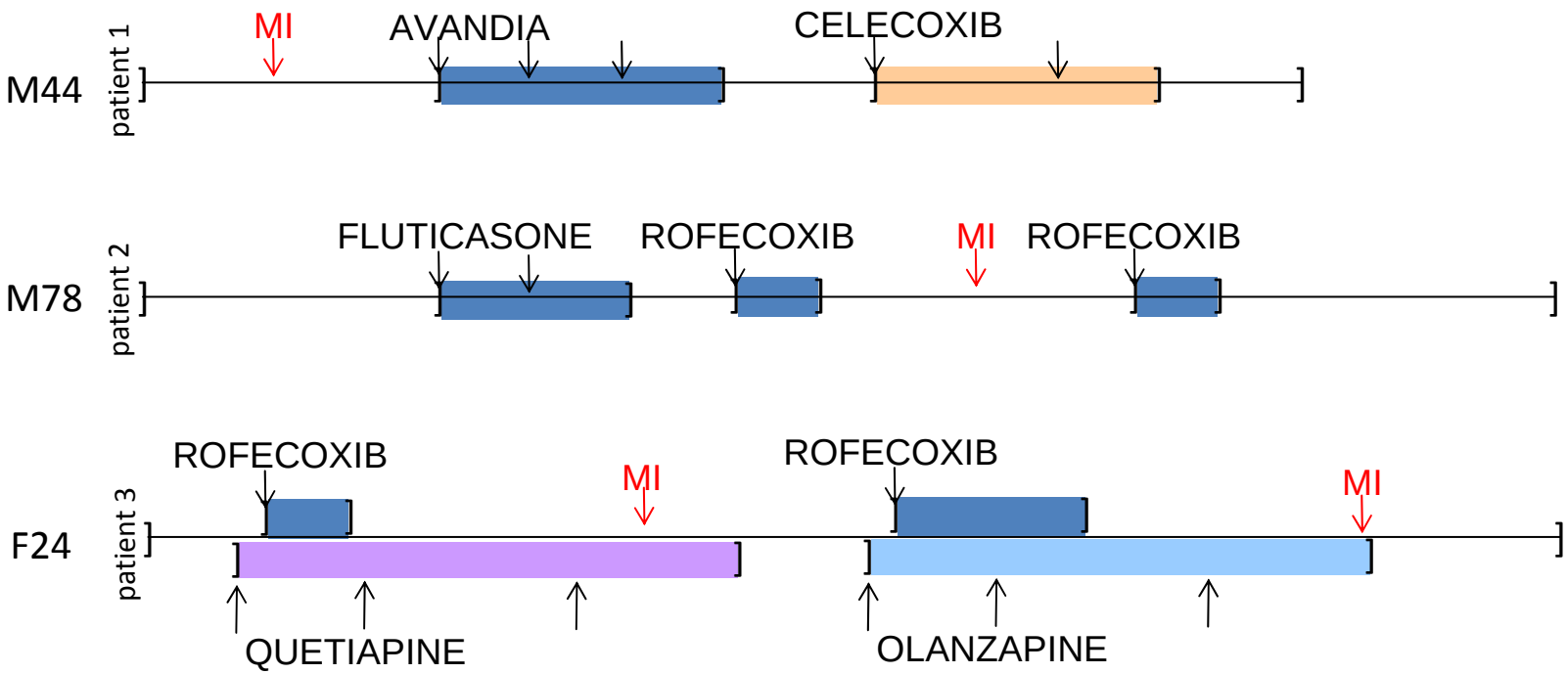
- Many different analysts have considerable experience with different statistical and epidemiological approaches in different observational settings
- Massive claims/EHR databases present challenges where little theory exists to guide methodological choices
- Our approach is empirical
- Implement a broad swathe of methods and evaluate them against "ground truth." Place code in the public domain.
- No magic bullet - but we expect to identify gross differences between different methods in different scenarios

Characterizing drug-outcome associations

- Active surveillance means different things to different people
  - Studying one drug-condition pair at a time
  - Broad-based screening across medical products and outcomes
- OMOP approach is to develop and test methods that may be appropriate anywhere on this continuum

Fundamental task: *Estimate* the strength of the drug-outcome relationship

What do the data look like?



Computational considerations require few passes through the data

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OMOP's Methods Landscape

Disproportionality Analysis

	AE j = Yes	*AE j = No*
Drug *i* = Yes	*a*=20	*b*=100
Drug *i* = No	*c*=100	*d*=1080

- Distinct Patients
- SRS
- Modified SRS

X

MGPS
BCPNN
PRR
Chi
etc.

X

Stratified

- Temporal Pattern Discovery (WHO)

Sequential Methods

	AE j = Yes	*AE j = No*
Drug *i* = Yes	*a*=20	
Drug *i* = No		

Compare to baseline Poisson

- Maximized Sequential Probability Ratio Teat (MaxSPRT)
- Conditional Sequential Sampling Procedure (CSSP)

Exposure Based Methods

Exposed → Case?

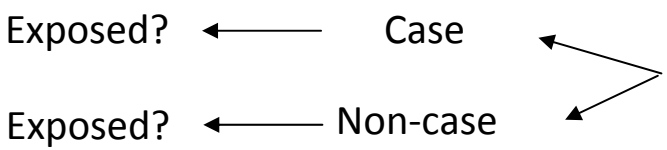
Non-exposed → Case?

- Observational screening
- HSIU
- Incident User Designs
- High-Dimensional Propensity Scoring
- Local control

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

OMOP's Methods Landscape

Case Based Methods



- Case control surveillance
- Multiset case control
- Self-controlled case series
- Case crossover

Other Methods

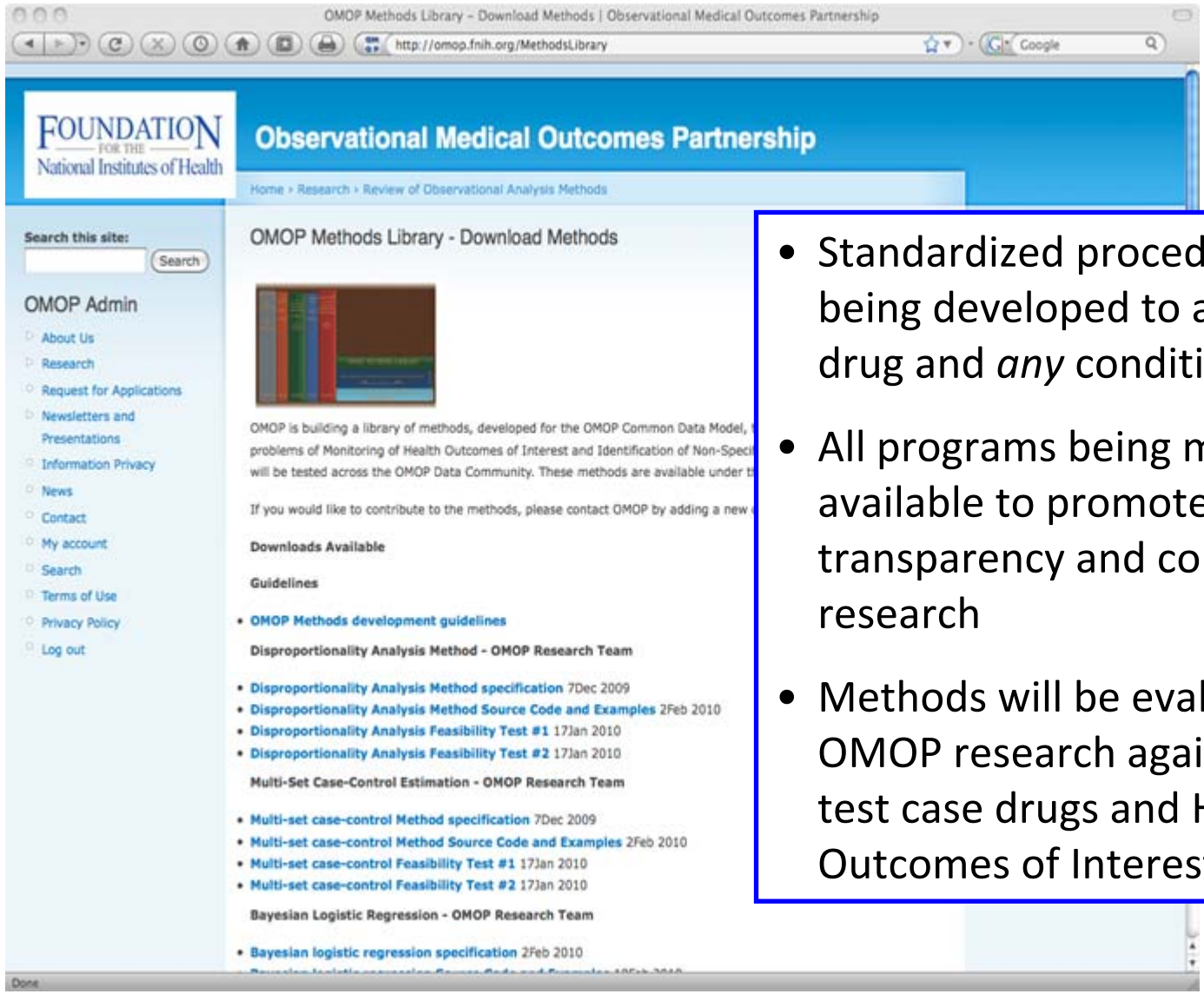
- Hi-Dimensional logistic regression
- Statistical relational learning

Future Methods

- Multivariate self-controlled case series
- Case-time control
- Lasso propensity scoring
- Online algorithms
- OMOP Cup (50+ submissions)

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

OMOP Methods Library



- Standardized procedures are being developed to analyze *any* drug and *any* condition
- All programs being made publicly available to promote transparency and consistency in research
- Methods will be evaluated in OMOP research against specific test case drugs and Health Outcomes of Interest

http://omop.fnih.org/MethodsLibrary

Methodological considerations common across multiple approaches

- Exposure definition
  - Incident vs. prevalent exposure
  - Source of data capture
- Outcome definition
  - Incident vs. prevalent events
  - Diagnosis codes vs. HOI
- Defining temporal relationship
  - Time from exposure start
  - Time after exposure end
- Comparator selection
- Inclusion/exclusion criteria
  - Baseline history
  - Follow-up time
- Covariate selection and adjustment
  - Matching
  - Stratification
  - Multivariate modeling
- Output metric/statistic
  - Estimation vs. testing
  - Relative vs. attributable risk
  - Measure of uncertainty

Each method has user input parameters that encode these choices

Need for establishing 'ground truth' in methodological research

- Methodological research: goal is to measure performance of methods in their ability to identify 'true' relationships and discern from false positive findings
- Research requires 'ground truth', classification of test cases to evaluate methods against
- Challenge with real data: 'truth' is unknown or ill-defined
- Challenge with simulated data: data may not reflect complexities of real-world data

Analysis problems under study by OMOP

- **Monitoring of Health Outcomes of Interest (HOIs):**
  - Estimate the strength of the association between drug exposure and specific events (e.g. acute liver failure, bleeding, MI)
  - Modest in number so can customize analytic approach
  - Expert assessment of drug-HOI causal associations based on literature search
- **Identification of non-specified associations:**
  - More exploratory in nature
  - Same goal: estimate the strength of the association between drug exposure and conditions
  - Necessarily more generic analyses (e.g., adjust for age and sex)
  - Causality assessment relies on the product labels
- **Performance against simulated data**
  - Complement 'real world' experiments
  - Ground truth explicitly defined

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Reference set for Monitoring Health Outcomes of Interest

Test cases to be used for evaluating method performance for 'Monitoring of Health Outcomes of Interest'

	Outcome									
Drug	Angioedema	Aplastic Anemia	Acute Liver Injury	Bleeding	GI Ulcer Hospital-ization	Hip Fracture	Hospital-ization	Myocardial Infarction	Mortality after MI	Renal Failure
ACE Inhibitors	R	N			N	N	B			
Amphotericin B	N	N	N			N			N	R
Antibiotics		N	R	N		N		N		N
Antiepileptics	N	R			N				N	N
Benzodiazepines	N	N	N	N		R		N		N
Beta blockers	N	N	N		N	N			B	N
Bisphosphonates		N	N		R			N		N
Tricyclic antidepressants		N	N	N				R		N
Typical antipsychotics					N			R		N
Warfarin	N	N		R		N			N	N

Legend	Total
B- 'True positive' benefit	2
R- 'True positive' risk	9
N- 'Negative control'	44
Avoid selection due to labeling	
Not selected due to correlation with HOI	

Measuring method performance

Drug-condition status
Y – 'true association',
N – 'negative control'

Method prediction: Drug-condition pair met a defined threshold

	Y	N
Y	True positives	False positives
N	False negatives	True negatives

Positive predictive value = precision = TP/ (TP+FP)

Negative predictive value = TN / (FN+TN)

Sensitivity = Recall = TP/ (TP+FN)

Specificity = TN/ (FP+TN)

Accuracy measures from different perspectives

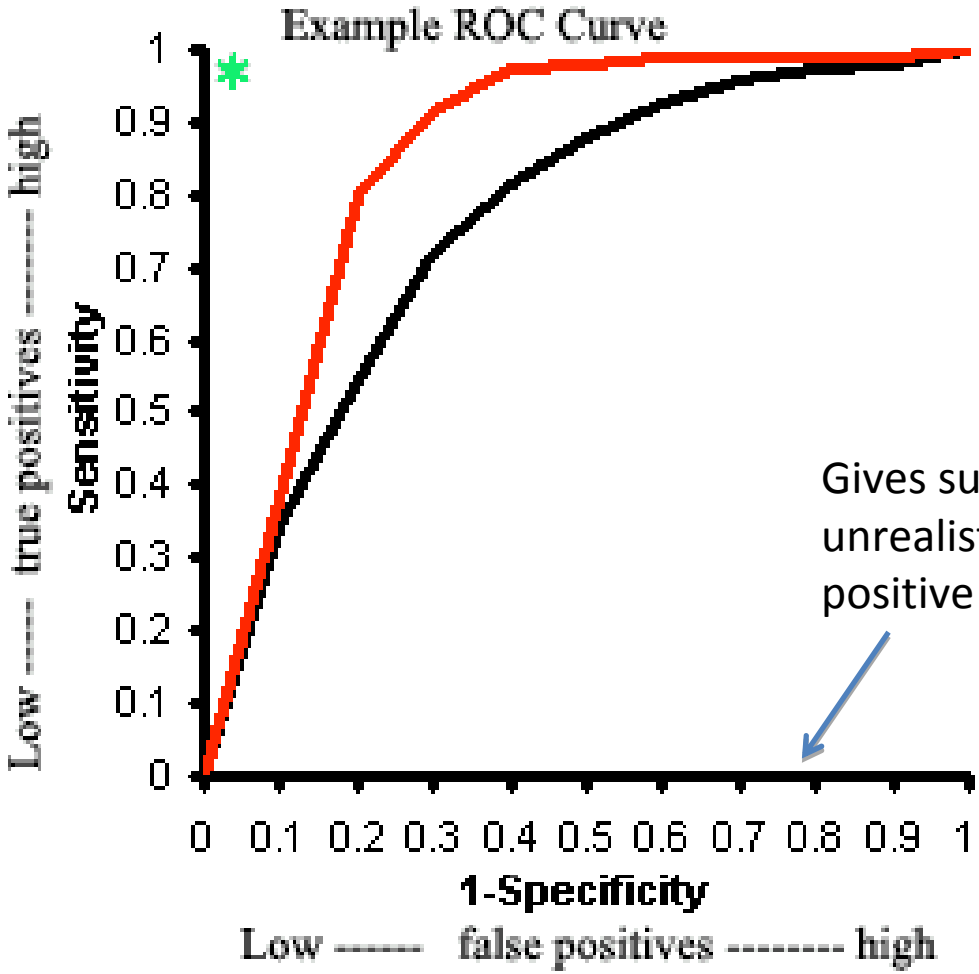
- **Mean average precision (MAP)** – on average, what proportion of predictions are true at different thresholds?
- **Area under ROC curve (AUC)** – what is the composite tradeoff between sensitivity and specificity at all possible threshold values?
- **p@k** - among the top k (e.g. 100) scores, what percentage are true?
- **recall@FPR** - if we can tolerate a particular false positive rate (e.g. 5%), what fraction of the true positives will we identify?
- **Average false positive rate** – what is the average false positive rate observed for each of the true positives?

Mean Average Precision

		Original Values			Sorted Values		
Drug	**Condition**	z_i	y_i		$z_{(i)}$	$y_{(i)}$	$P^{(K)}$
D1	C1	5	1		8	1	1/1=1
	C2	0	1		8	1	2/2=1
	C3	8	1		5	0	
D2	C1	8	1		5	1	3/4=0.75
	C2	4	1		4	1	4/5=0.8
	C3	0	0		0	0	
D3	C1	0	0		0	0	
	C2	0	0		0	0	
	C3	5	0		0	1	5/9=0.55
						Total Score	(1+1+0.75+0 .8+0.55)/5 =0.82

e.g. also consider, for example, $P^{(100)}$, "Precision at 100"

Threshold-free Methods



Gives substantial weight to unrealistically high false positive rates

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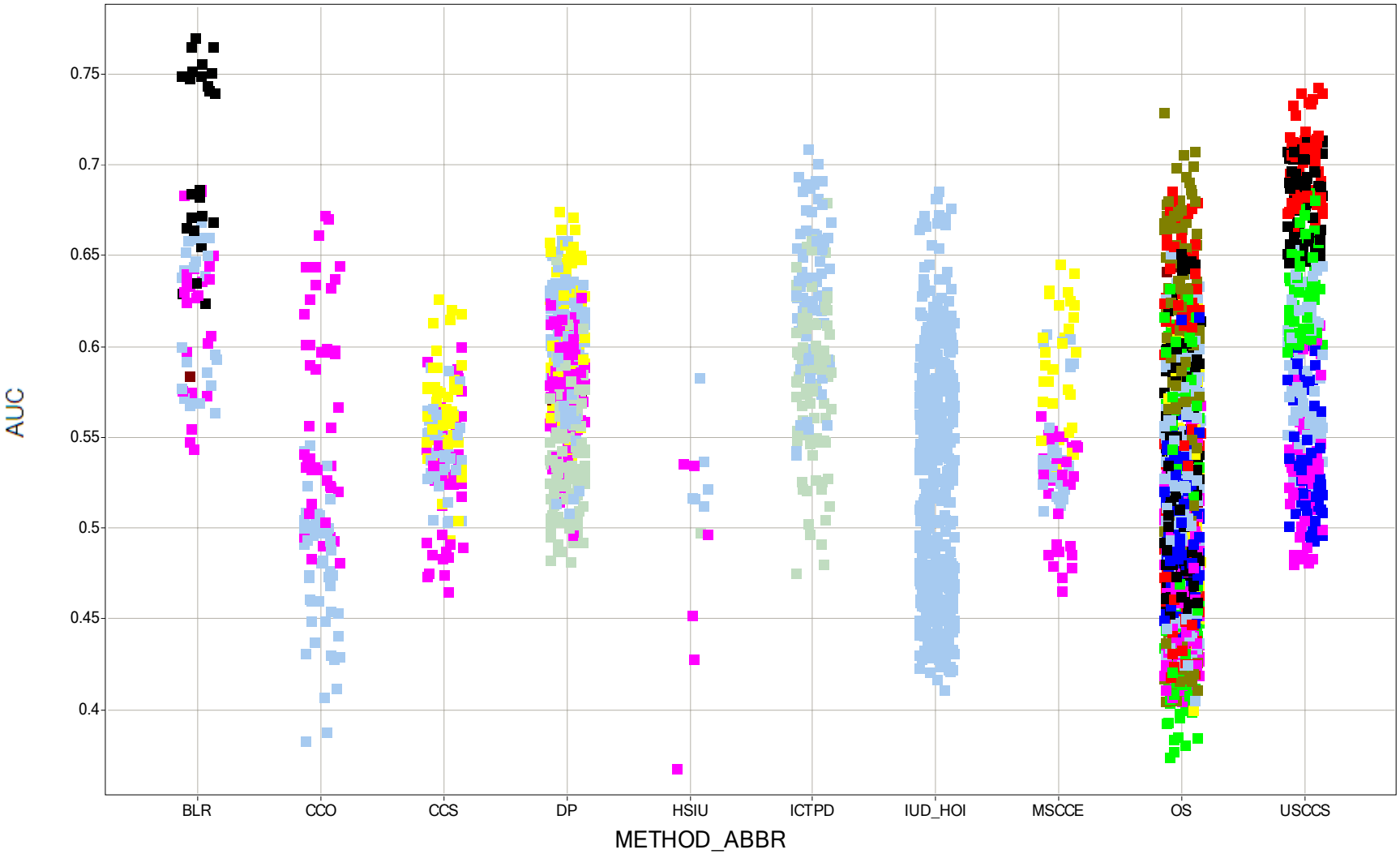
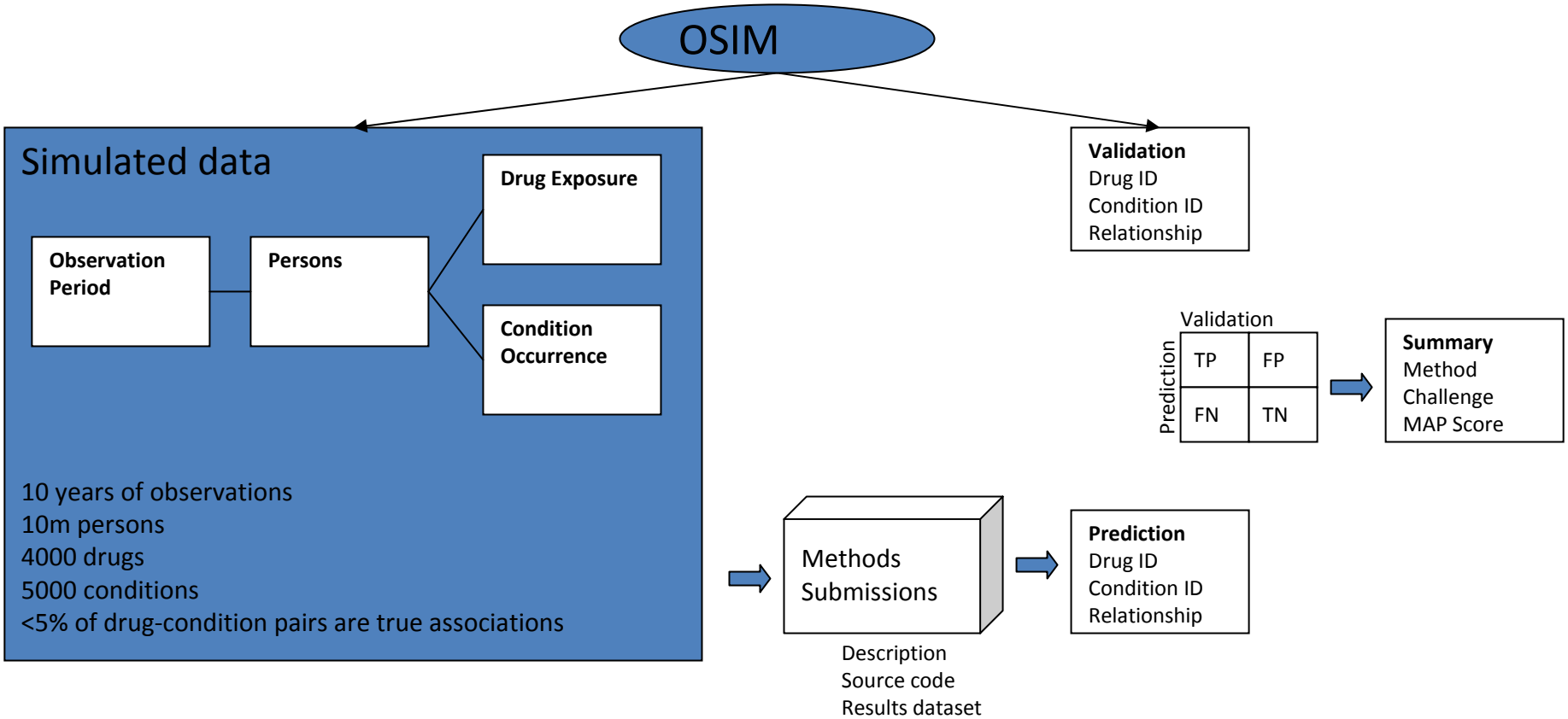
Visualizing performance of alternative methods across a network of databases



Data is for illustrative purposes only

OMOP Cup: Methods Competition



- Two competitions: http://omopcup.orwik.com
  - Challenge 1: Identifying drug-condition associations within an entire observational dataset
  - Challenge 2: Identifying drug-condition associations as data accumulates over time
- Evaluation criteria: Weighted Mean Average Precision
- Winning entries were given cash prize and methods and invited to be further tested against OMOP data community

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OMOP Cup: Interactive Website

OMOP Cup: Leader Board

Challenge 1 Leaderboard

User	Best Score
Martijn J Schuemie	0.2662359
David S Vogel	0.2570616
Hawkeye DORP	0.2569417
Mohammad Khoshneshin	0.2569404
Nick Street	0.2568678
Craig G Carmichael	0.2483813
Harris T Lin	0.2483137
girishkumar ramesh sabhnani	0.2358521
Liang Xiong	0.2317307
Christophe G Giraud-Carrier	0.2310854
Vladimir N Nikulin	0.2309664
Bin Liu	0.2303903
Andrew J Zitzelberger	0.2301842
Derrall Heath	0.2301842
Nathaniel Gustafson	0.2298511
Sam Ogden	0.2298361
David L Wilcox	0.2293719
Rob Smith	0.2292806
Michael T Roscheck	0.2263714
Yisong Guo	0.2262477
Robin Sabhnani	0.2256460
Benchmark (BLR)	0.2244814
Benchmark (BCPNN-M)	0.2241564

Challenge 2 : Identifying associations over time

Challenge 2 Leaderboard

User	Best Score
Vladimir N Nikulin	0.2376259
Martijn J Schuemie	0.2132523
Hawkeye DORP	0.2032173
David S Vogel	0.2000853
Harris T Lin	0.1949657
Peng Liu	0.1859670
Ed Ramsden	0.1719514
Robin Sabhnani	0.1037598
Lisa D Friedland	0.1032716
Benchmark (Random)	0.0156415

OMOP Cup: Top Four Performers

- Binary prediction model
- Drug-condition pair is unit of analysis
- Construct a feature vector per pair
- Random forest

- Two stage disproportionality (IC)
- Stage 1: find signals
- Stage 2: remove signals confounded by indication

- Ensemble of two disproportionality methods plus Poisson method using exposure times

- Disproportionality
- Ensembling
- Matrix factorization
- Calibration

OMOP Cup: Summary

- Two-fold purpose: Build community and generate new ideas
- 60+ competitors with over 600 submissions
- Community-building requires continuity so we need to plan for OMOP Cup 2
- Some methods did beat benchmarks, but no method dramatically outperformed current approaches
- Improving simulation capability may provide opportunities for further methods innovation

OMOP Current Status

- OMOP data community established to conduct methodological research
- Open-source methods implementation largely complete
- Methods evaluation underway
- OMOP Cup provides another avenue to stimulate methods innovation...watch out for OMOP Cup 2!

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OMOP website: http://omop.fnih.org
OMOP Cup website: http://omopcup.orwik.com

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Roundtable Discussion and Questions

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