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The Role of Statistics and Opportunities for Statisticians in Active Drug Safety Surveillance

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GlaxoSmithKline
Observational Medical Outcomes Partnership (OMOP)

August 01, 2010

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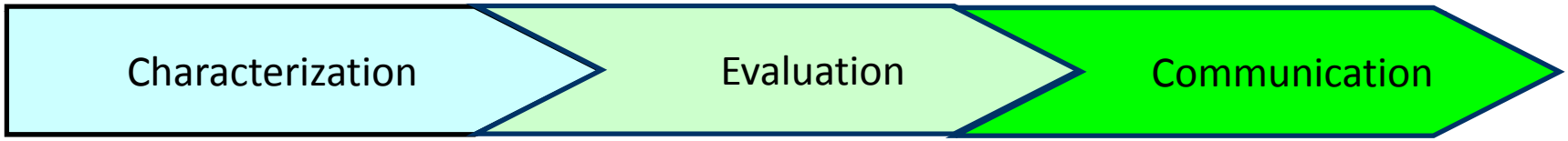
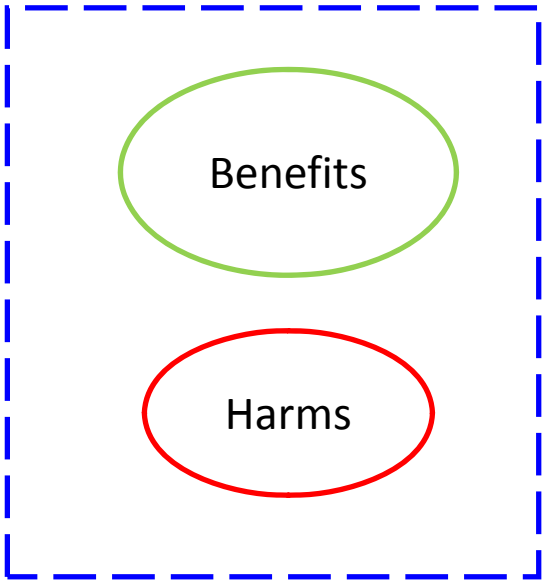
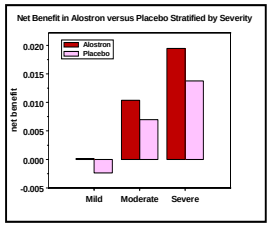
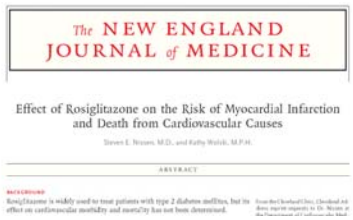
Steps within the process of understanding of medicines









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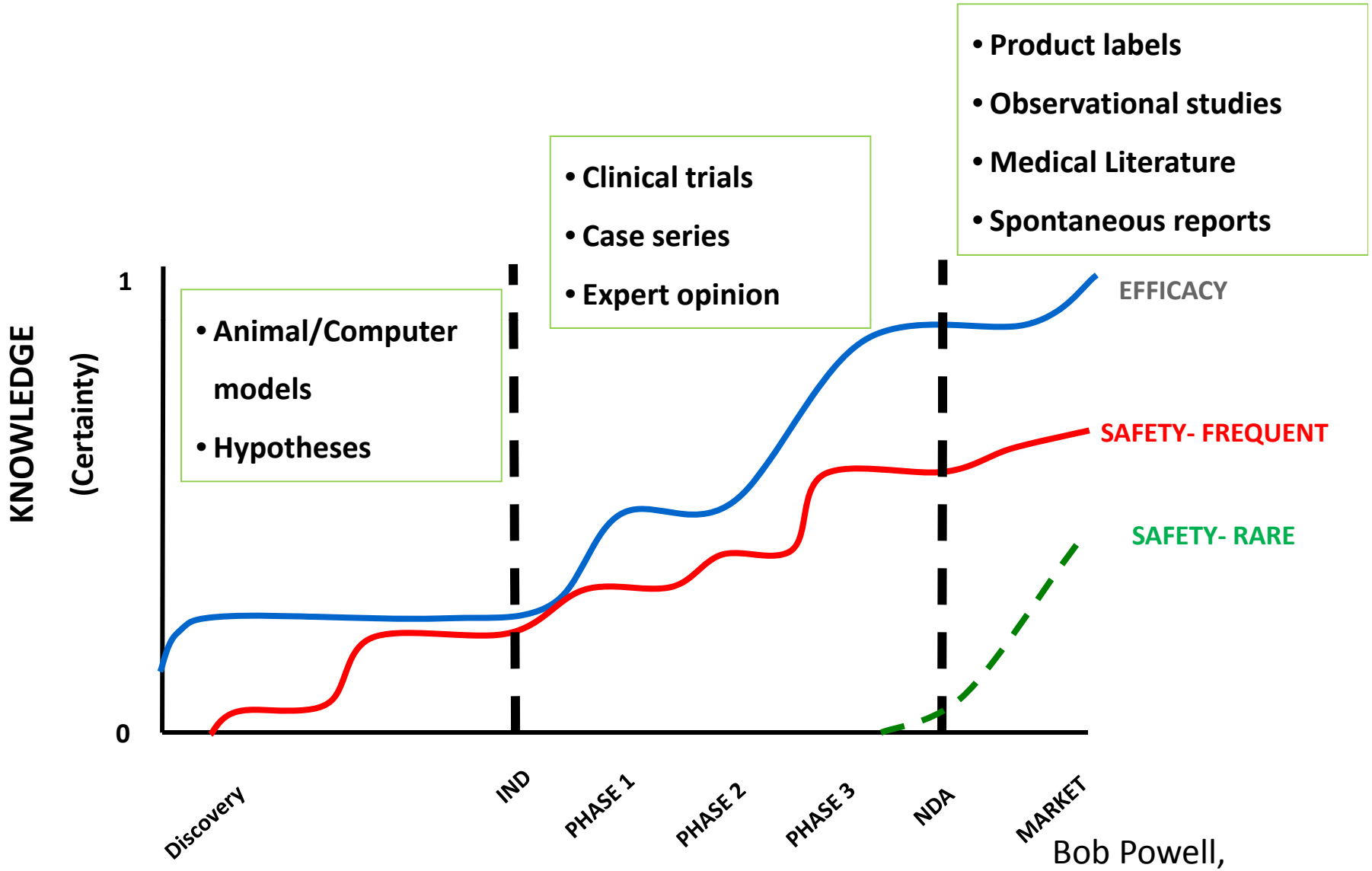
Diversity in data and analyses throughout development



Bob Powell,
ISPOR 2008

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Post-approval opportunities for statisticians

- Identify and evaluate emerging safety concerns of medical products using observational healthcare databases (***active surveillance***)
- Explore patient subgroups that have differentiated response (***personalized medicine***)
- Study long-term outcomes of alternative treatments in real-world populations (***comparative effectiveness***)
- Integrate disparate data sources to provide composite evaluation that weighs the evidence of the all potential effects of a medicine (***benefit-risk analysis***)

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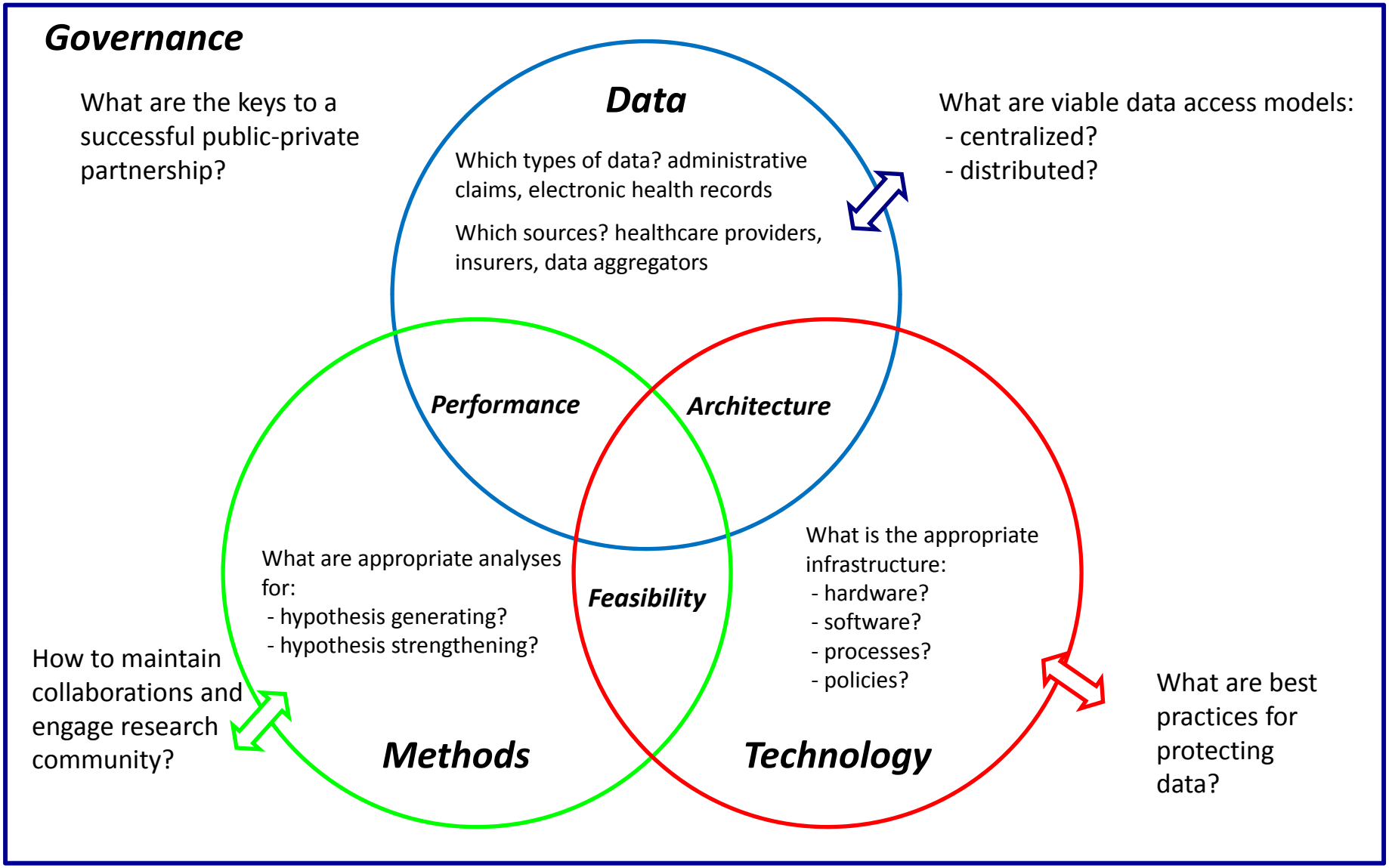
Outstanding questions for active surveillance



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Observational Medical Outcomes Partnership

A public-private partnership to serve the public health by testing whether multi-source observational data can improve our ability to assess drug safety and benefits.

- Assess the appropriate technology and data infrastructure required for systematic monitoring of observational data
- Develop and test the feasibility and performance of the analysis methods
- Evaluate required governance structures

OMOP: http://omop.fnih.org

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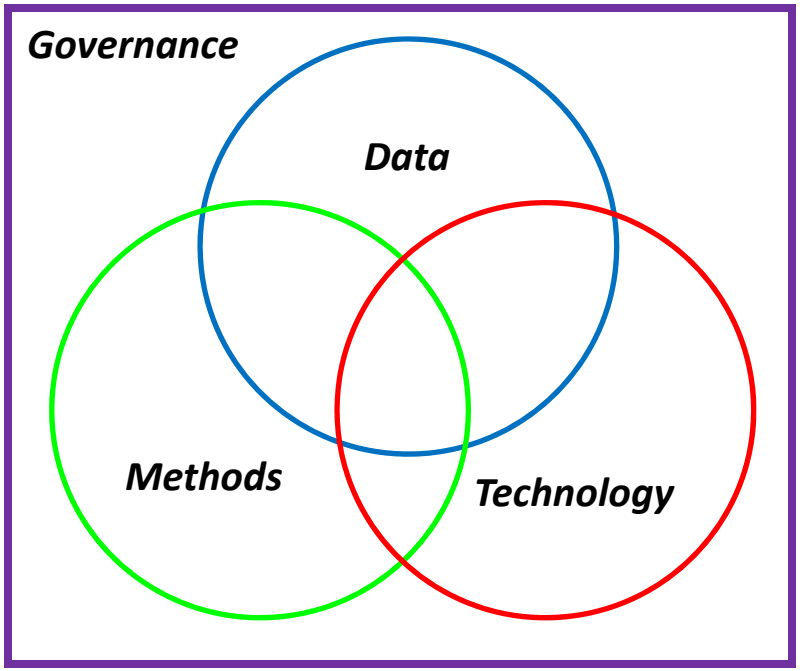
Breadth and diversity of OMOP research community

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



Over 100 collaborating partners

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

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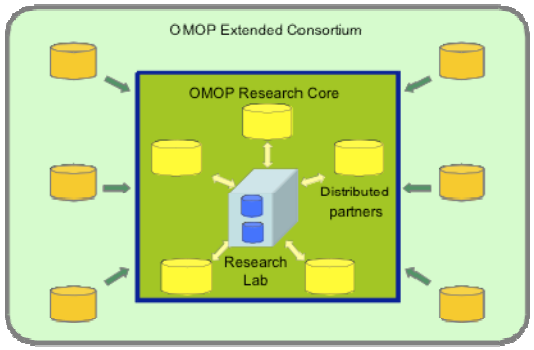
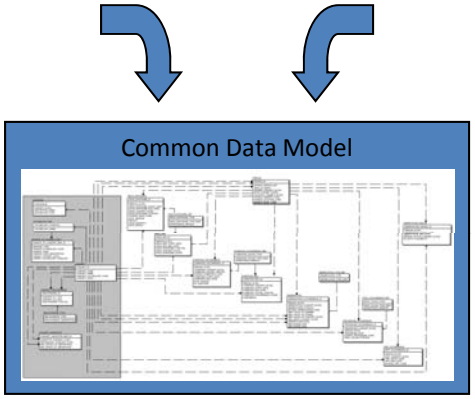
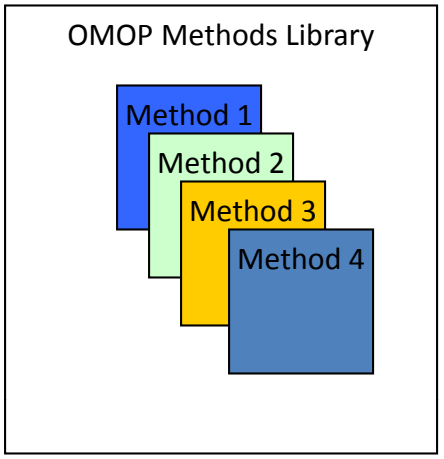
OMOP research experiment workflow







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

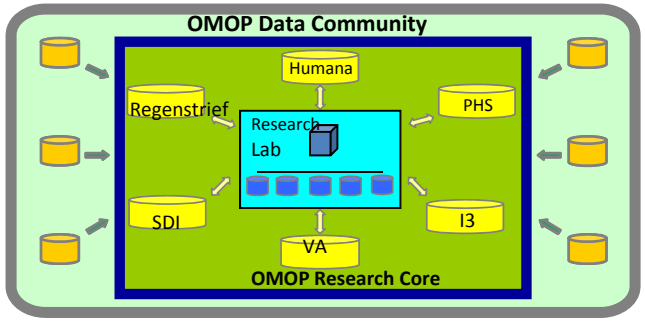
Health Outcomes of Interest
- Angioedema
- Aplastic Anemia
- Acute Liver Injury
- Bleeding
- GI Ulcer Hospitalization
- Hip Fracture
- Hospitalization
- Myocardial Infarction
- Mortality after MI
- Renal Failure

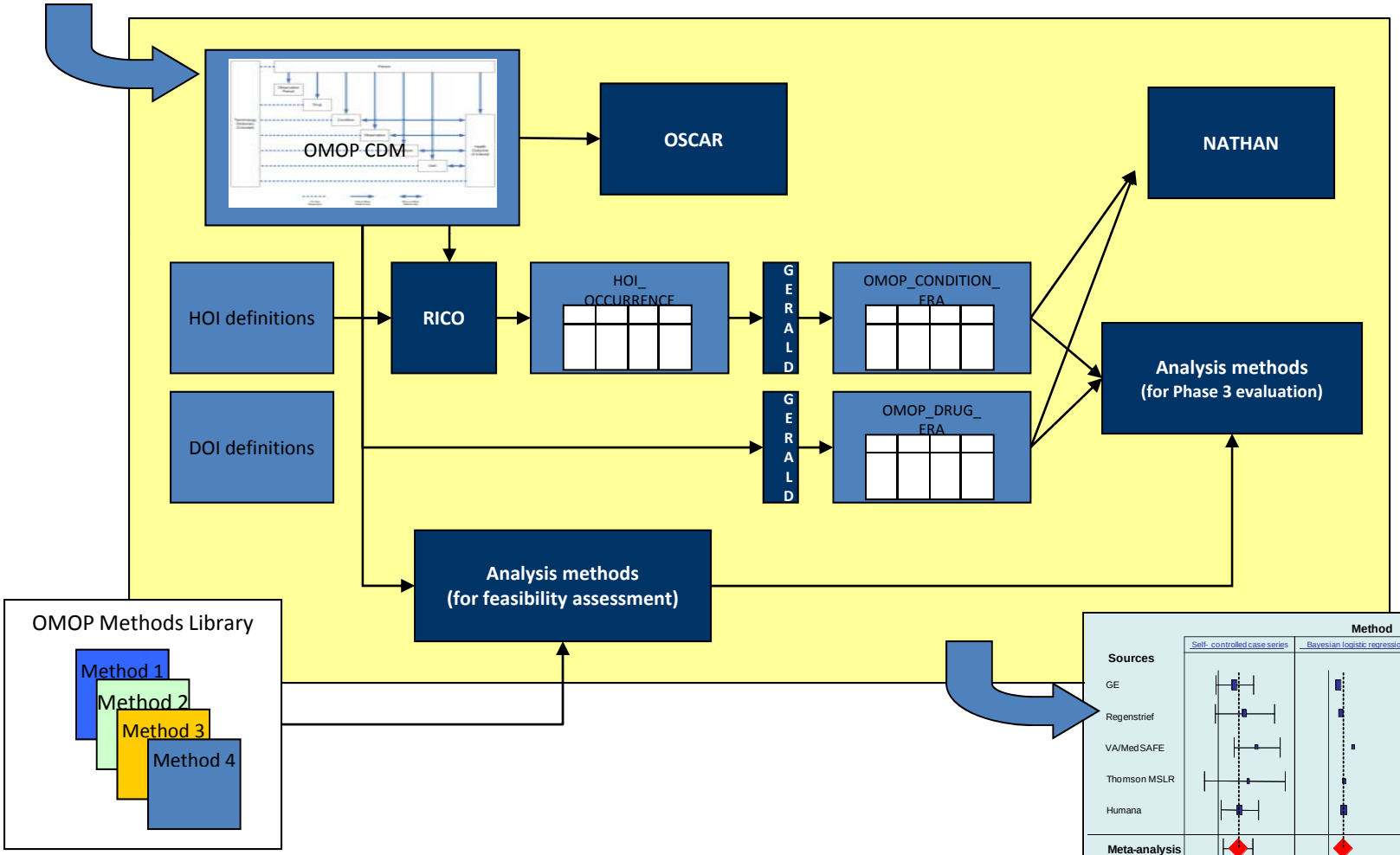
Non-specified conditions

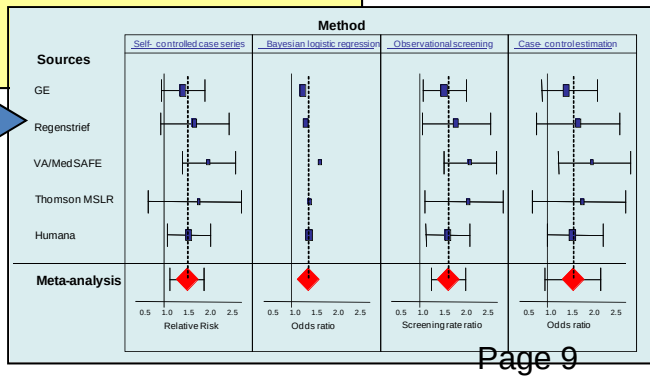
-All outcomes in condition terminology

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

OMOP Progression







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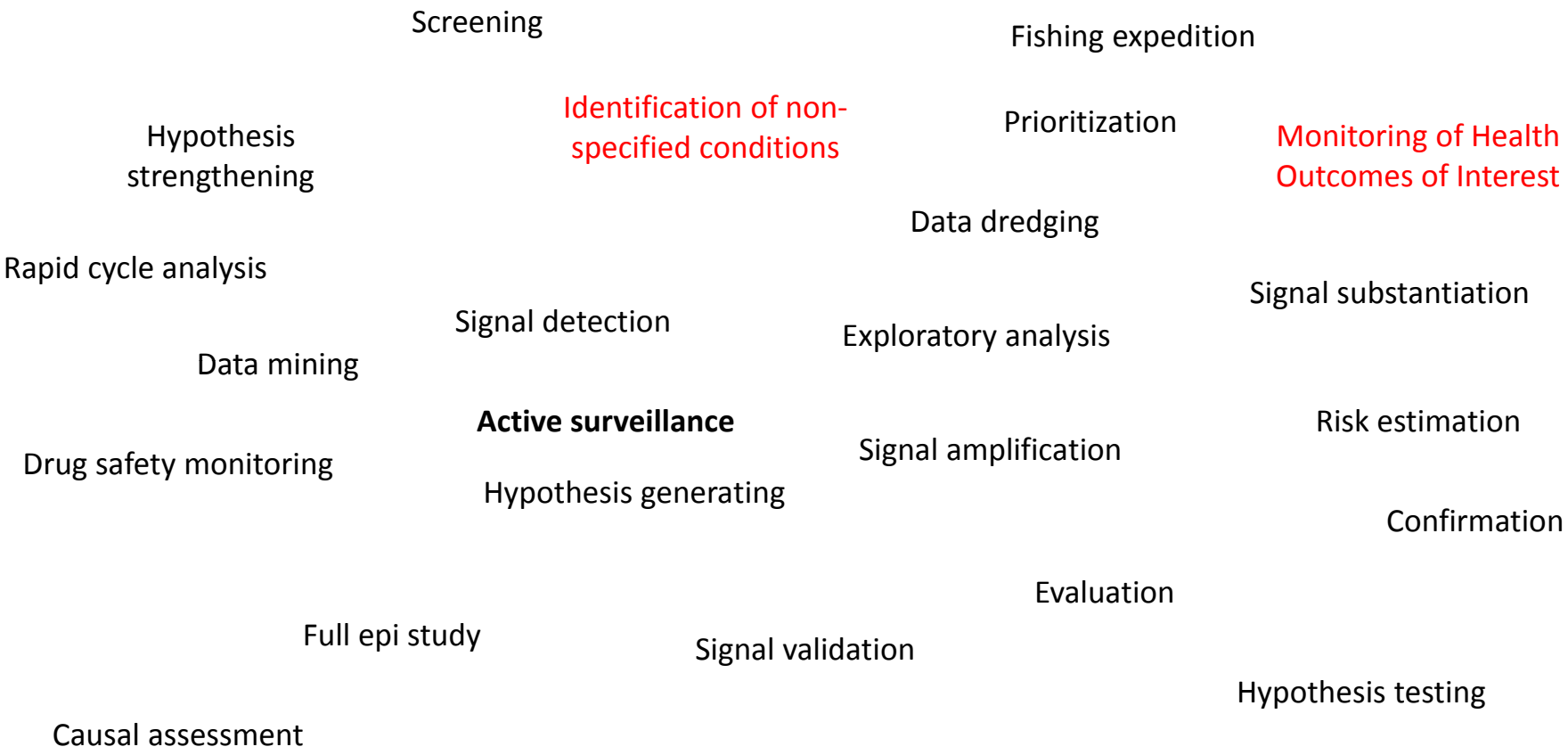
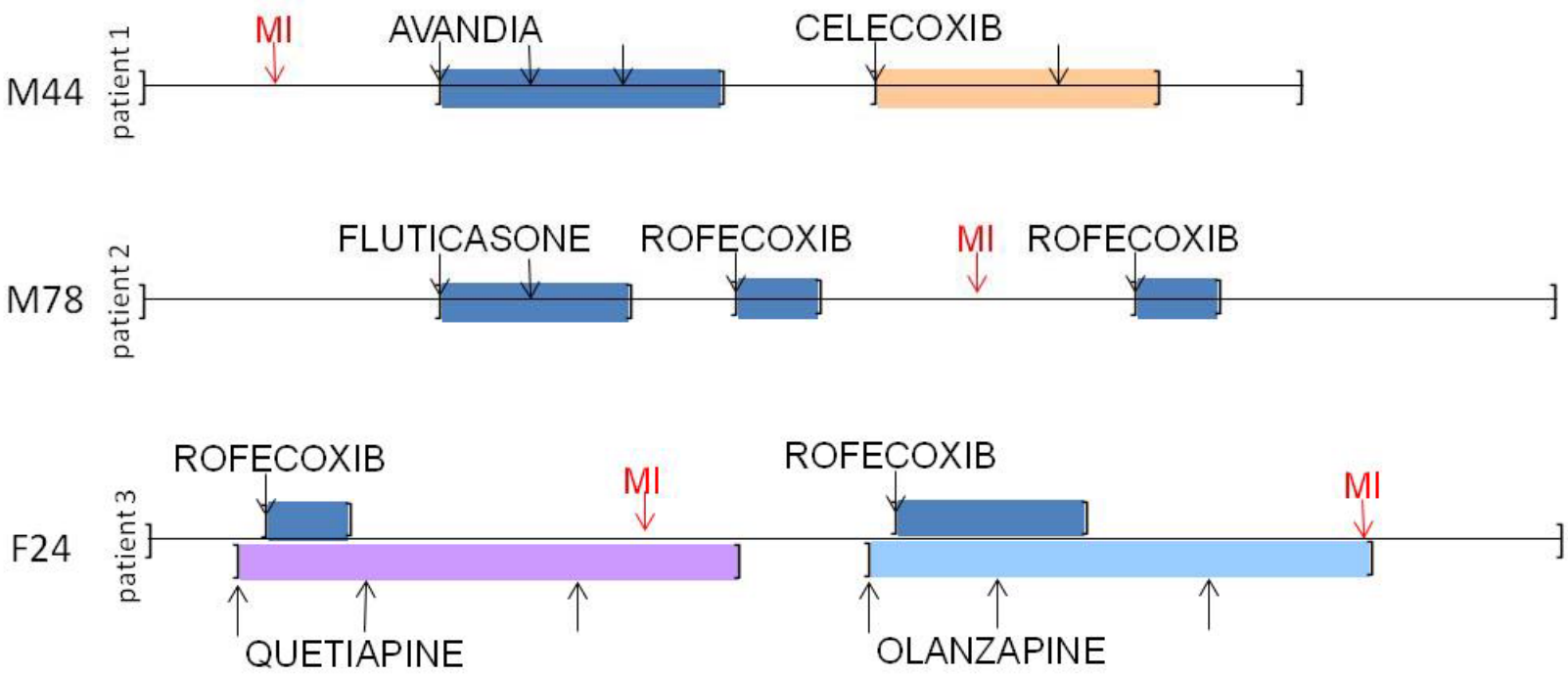
Characterizing Drug-Outcome Associations



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

What do the data look like?



Database contain millions of persons with years of (incomplete) longitudinal data

Computational considerations require efficient use of data in analyses

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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)

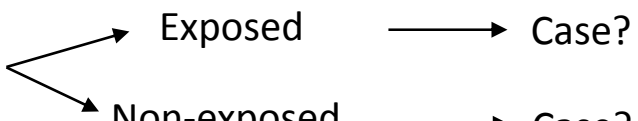
Sequential Methods

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

Compare to baseline Poisson

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

Exposure Based Methods



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

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

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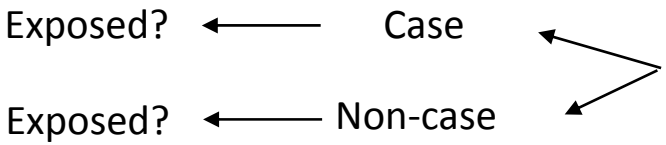
OMOP's Methods Landscape

Case Based Methods



- Case control surveillance
- Multiset case control estimation
- 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 (60+ submissions)

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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 input parameters that encode these choices

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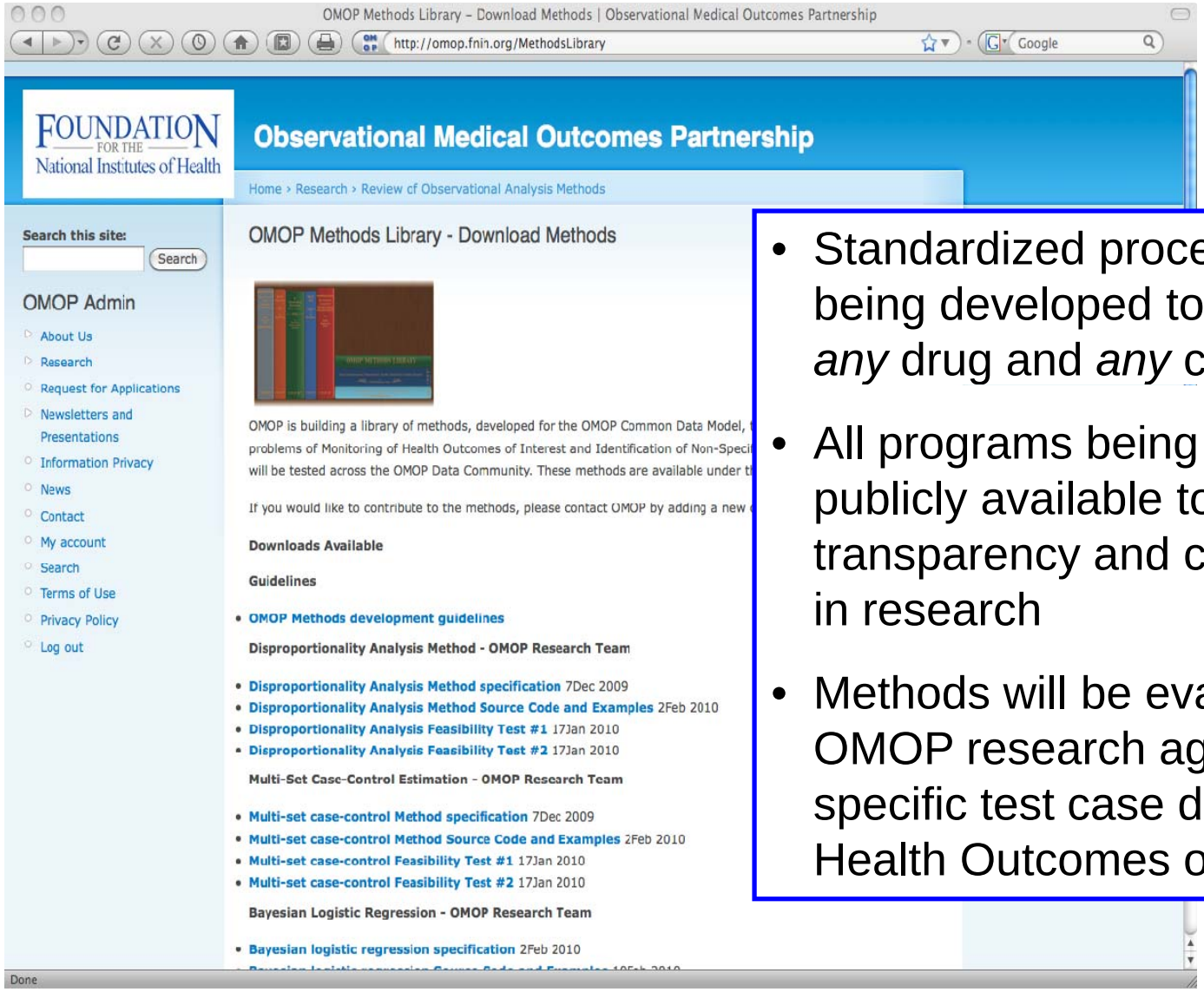
OMOP Methods Library



- 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

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‘Ground truth’ for Monitoring Health Outcomes of Interest

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

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

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Measuring method performance

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

Method prediction: Drug-condition pair met a specific 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

- **Area under ROC curve (AUC)** – what is the composite tradeoff between sensitivity and specificity at all possible threshold values?
- **Mean average precision (MAP)** – on average, what proportion of predictions are true at different thresholds?
- **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?

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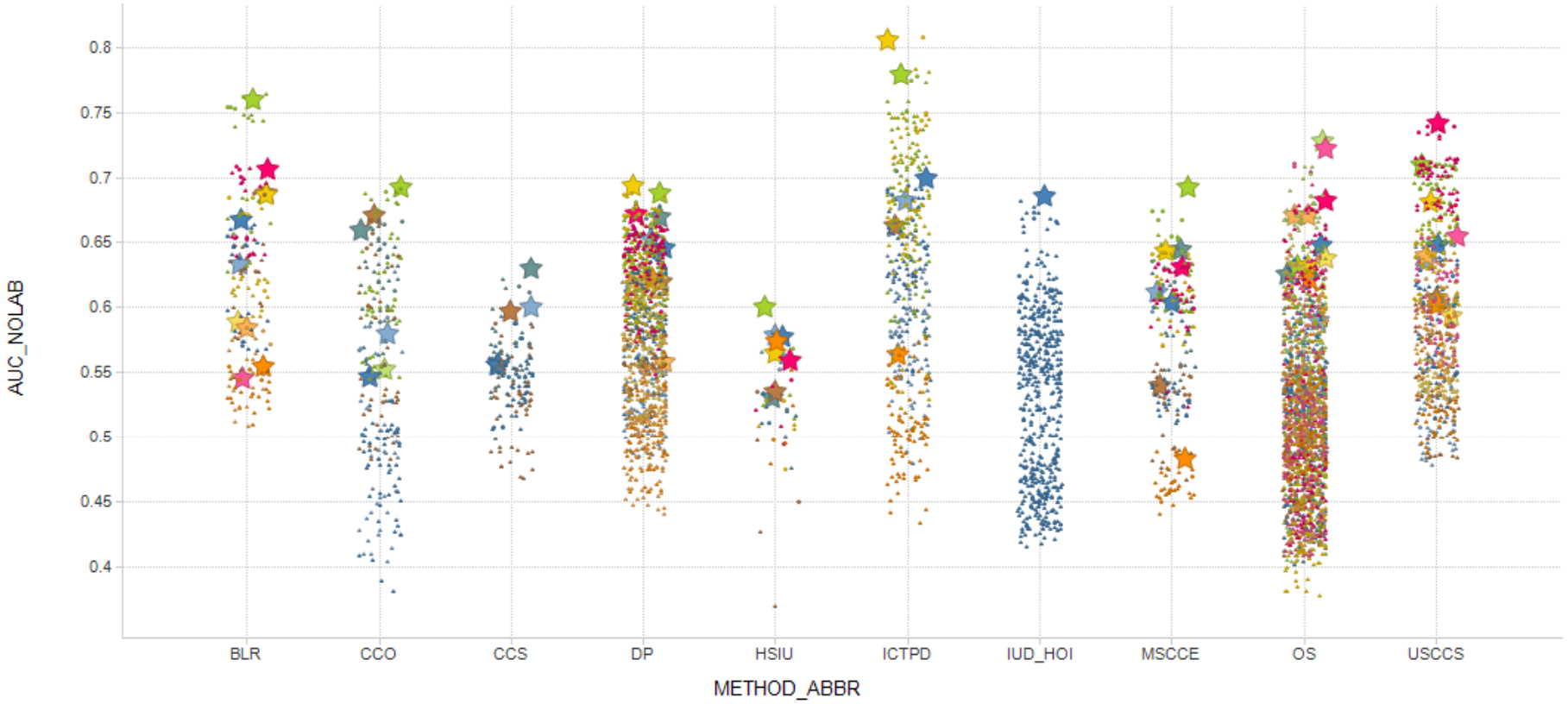
Visualizing performance of alternative methods across a network of databases



Data is for illustrative purposes only

Summary

- Increased focus on post-approval analyses presents significant opportunities for statisticians
- Post-approval analyses can meaningfully inform health care policy, but appropriate use of data and methods needs to be established
- Further research and application require statisticians to play a more active role in the design, conduct, and evaluation of analyses

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