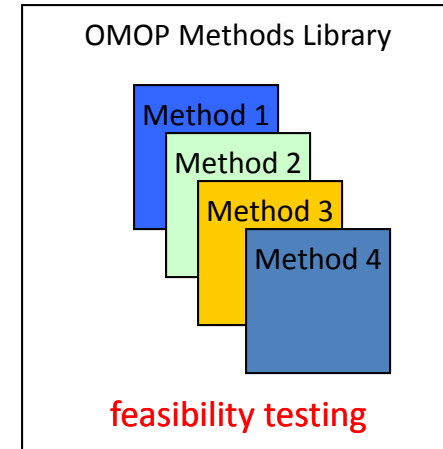
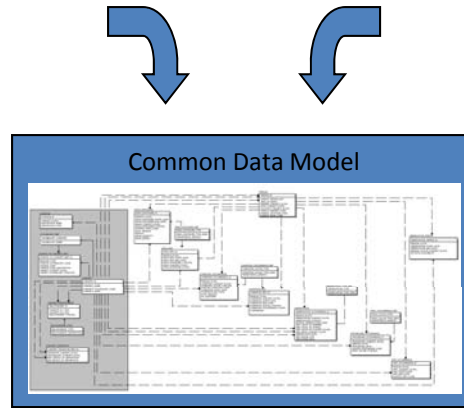
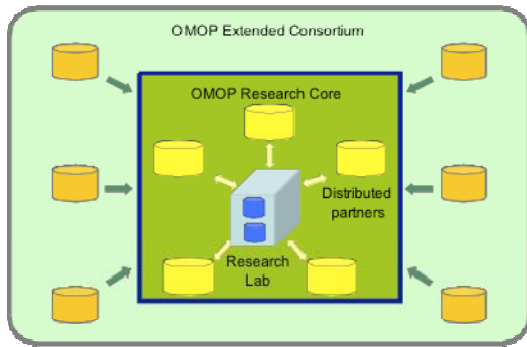


**OBSERVATIONAL  
MEDICAL  
OUTCOMES  
PARTNERSHIP**

**Exploring Methodological  
Needs for Signal Refinement**

Patrick Ryan  
on behalf of OMOP Research Team  
September 21, 2010

# OMOP research experiment workflow



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

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

- Non-specified conditions**
- All outcomes in condition terminology
  - 'Labeled events' as reference
    - Warning
    - Precautions
    - Adverse Reactions
    - Postmarketing Experience

What methods are most appropriate for signal refinement?  
Multiple alternative approaches identified that deserve empirical testing to measure performance

<b>Method name</b>	<b>Parameter combinations</b>	<b>Release date</b>
Disproportionality analysis (DP)	112	15-Mar-10
Univariate self-controlled case series (USCCS)	64	2-Apr-10
Observational screening (OS)	162	8-Apr-10
Multi-set case control estimation (MSCCE)	32	16-Apr-10
Bayesian logistic regression (BLR)	24	21-Apr-10
Case-control surveillance (CCS)	48	2-May-10
IC Temporal Pattern Discovery (ICTPD)	84	23-May-10
Case-crossover (CCO)	48	1-Jun-10
HSIU cohort method (HSIU)	6	8-Jun-10
Maximized Sequential Probability Ratio Test (MSPRT)	144	25-Jul-10
High-dimensional propensity score (HDPS)	144	6-Aug-10
Conditional sequential sampling procedure (CSSP)	144	30-Aug-10
Statistical relational learning (SRL)		
Incident user design (IUD-HOI)		

<http://omop.fnih.org/MethodsLibrary>

## Attributes that could influence method performance

- Drug attributes
  - Background prevalence
  - Duration of exposure
- Condition attributes
  - Background prevalence
  - Occurrences recorded
- Drug-condition attributes
  - Time-to-event
  - Strength of association
  - Degree of confounding
- Database attributes
  - Population size
  - Data available (claims, clinical)
  - Longitudinal capture

When addressing a specific drug-outcome pair, such as ‘oral diabetic-AMI’ and ‘injectable antibiotic-liver injury’, one can consider how the pairs relates to these attributes, but some may not be known at the time of study

# 'Ground truth' for Monitoring Health Outcomes of Interest

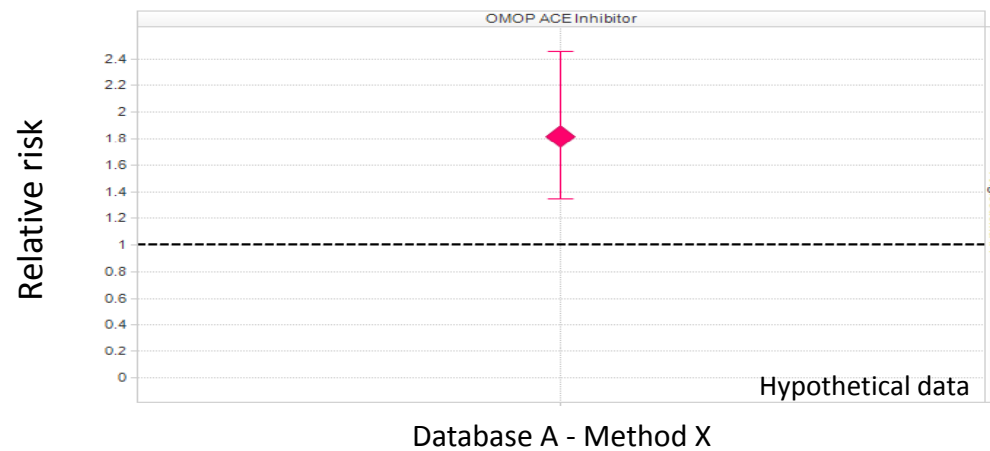
Outcome	ACE Inhibitors	Amphotericin B	Antibiotics	Antiepileptics	Benzodiazepines	Beta blockers	Bisphosphonates	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema	R	N	N	N	N	N	N	N	N	N
Aplastic Anemia	N	N	N	R	N	N	N	N	N	N
Acute Liver Injury	N	N	R	N	N	N	N	N	N	N
Bleeding	N	N	N	N	N	N	N	N	N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

Legend	Total
B- 'True positive' benefit	2
R- 'True positive' risk	9
N- 'Negative control'	44

One potential goal: establish a reference set that sufficiently covers the anticipated scenarios so results can be generalized to new pairs such as 'oral diabetic- AMI' and 'injectable antibiotic-liver injury'

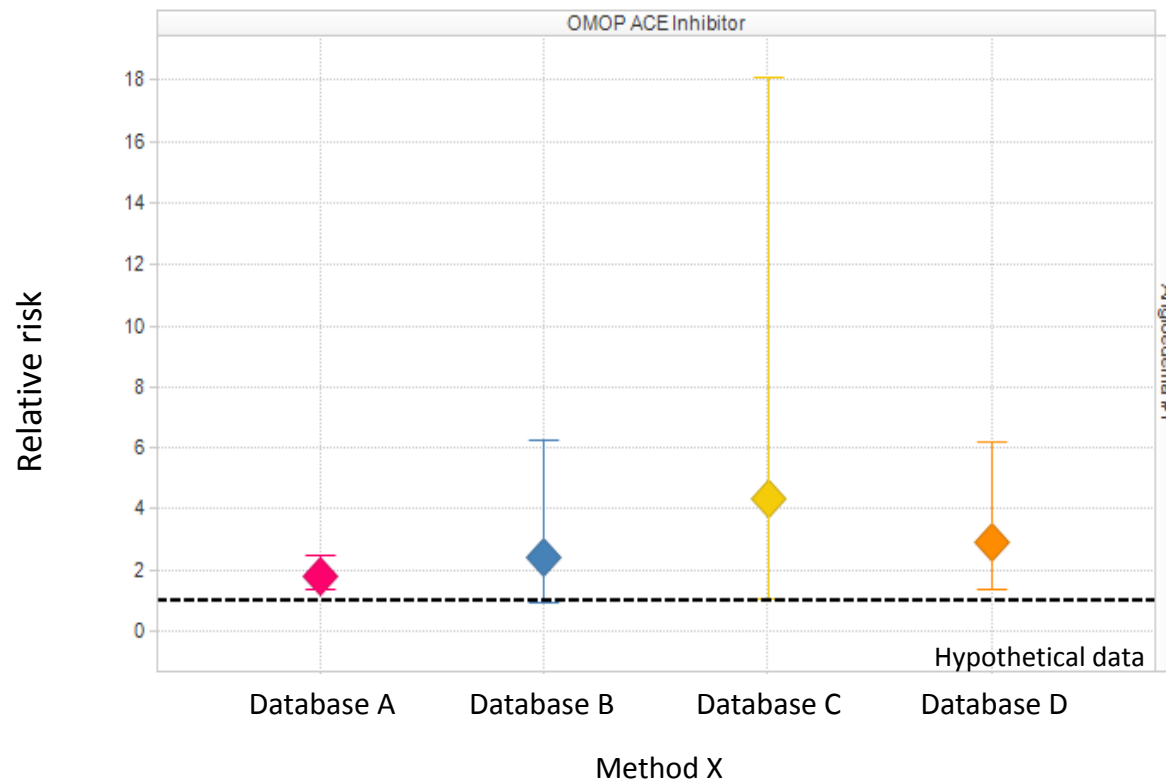
## Studying method performance for ‘signal refinement’

- Apply method with specific set of parameter settings to a database for a drug-outcome pair that has a prior suspicion of being potentially related
- Example: Run method X on database A for ACE inhibitors – Angioedema



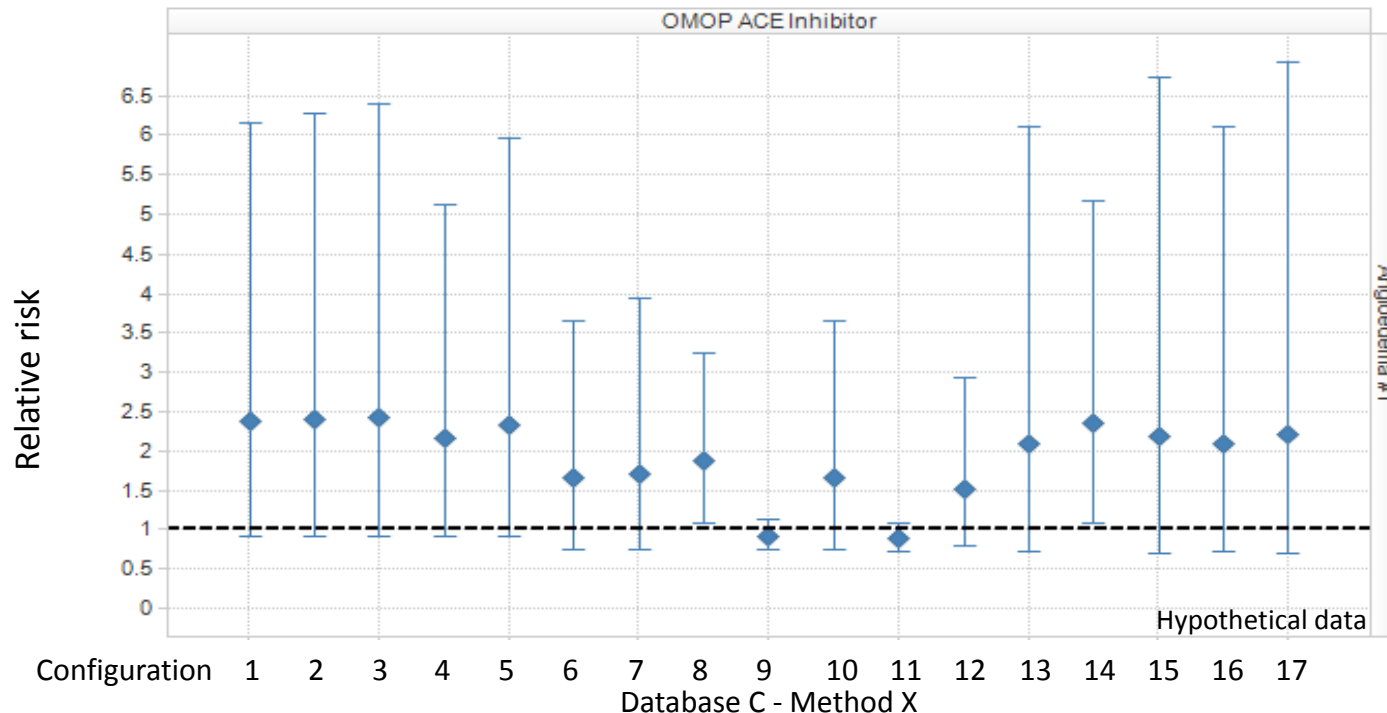
- Challenges:
  - How to put the resulting score in context?
  - What if we modified one of the methods parameters?
  - What if we applied the method to a different database?
  - If we had applied the same method to other drug-outcome pairs, what types of scores would we expect?
    - How many other true positives would get a  $RR > 1.8$ ?
    - How many false positives would be identified with a threshold of 1.8?

## How do effect estimates vary by database?



- Each database may have unique source population characteristics that can influence method behavior, including:
  - Sample size
  - Length and type of longitudinal data capture
  - Population demographics, such as age, gender
  - Disease severity, including comorbidities, concomitant medications and health service utilization patterns

## How do estimates vary by method parameter settings?



- Performance can be sensitive to various factors, including:
  - Length of washout period to identify incident use
  - Definition of time-at-risk
  - Choice of comparator
  - Number and types of covariates to include in propensity score modeling
  - Statistical approach for adjustment: matching vs. stratification vs. multivariate modeling
- ‘Optimal’ settings may vary by database and/or the drug-outcome pair in question

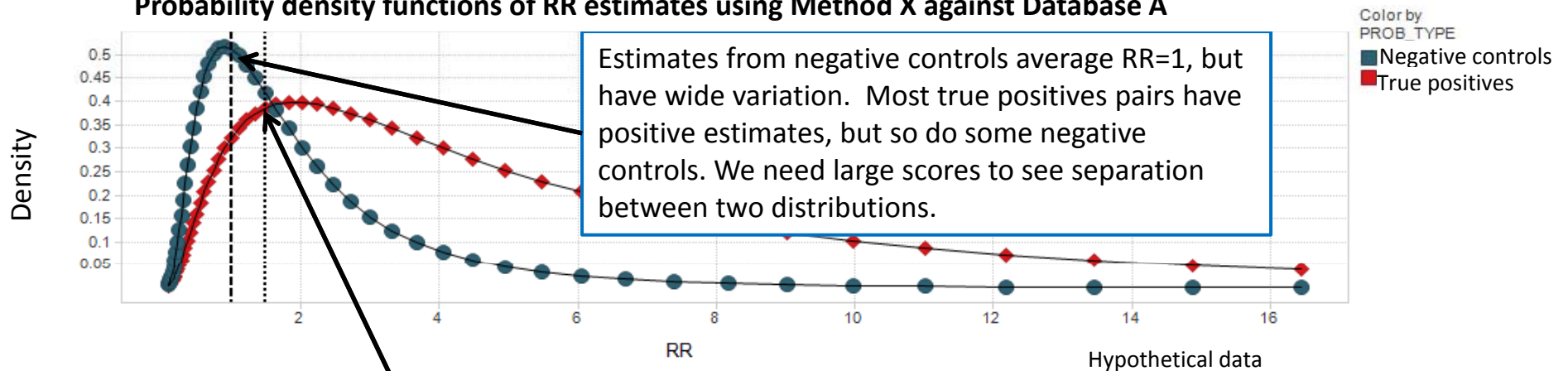
# How does method perform against other 'benchmark' true positives and negative controls?



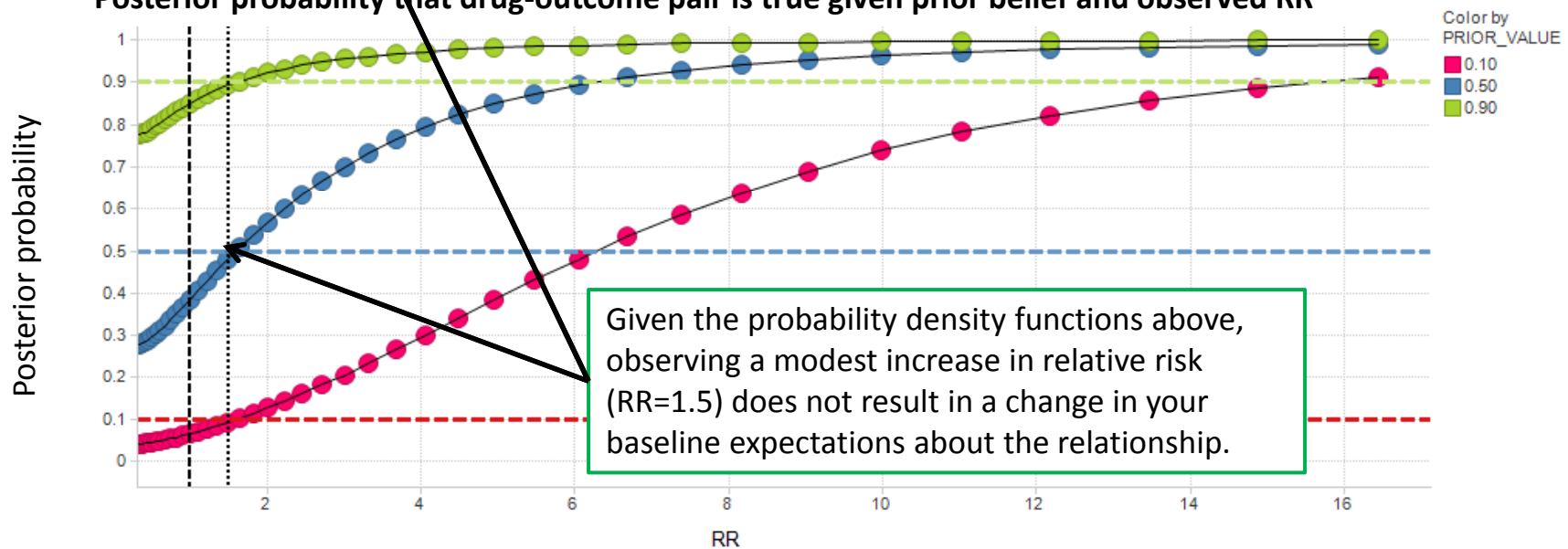
- It is important to establish operating characteristics of any method, when applied across a network of databases, as part of the 'validation before adoption for signal refinement'

Probabilistic framework for interpreting active surveillance results:  
In light of the observed evidence, how confident are we that there is a true association between medical product exposure and outcome?

Probability density functions of RR estimates using Method X against Database A



Posterior probability that drug-outcome pair is true given prior belief and observed RR



## Concluding thoughts

- Many viable methods to consider for active surveillance
- Method performance may vary by parameter settings, database, and characteristics of the drug-outcome pair
- Empirical testing, using both true positives and negative controls, is needed to establish operating characteristics of methods and data sources prior to adoption
- Bias presents a significant methodological challenge unlikely to be overcome by any one method or one database
- Probabilistic framework offers another way of interpreting findings from an active surveillance system

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