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Exploring Methodological Needs for Signal Refinement

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

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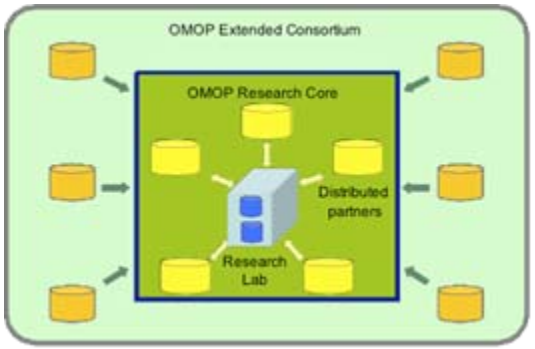
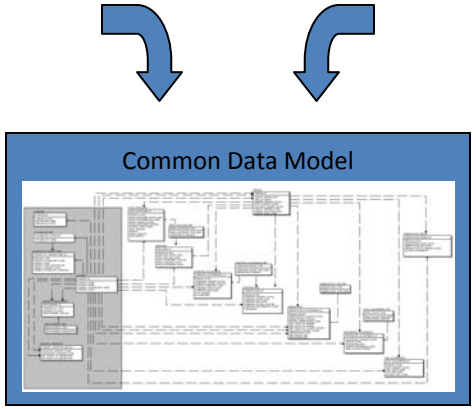
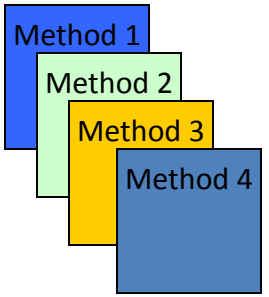
OMOP research experiment workflow





OMOP Methods Library



feasibility testing

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

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

Method name	Parameter combinations	Release date
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

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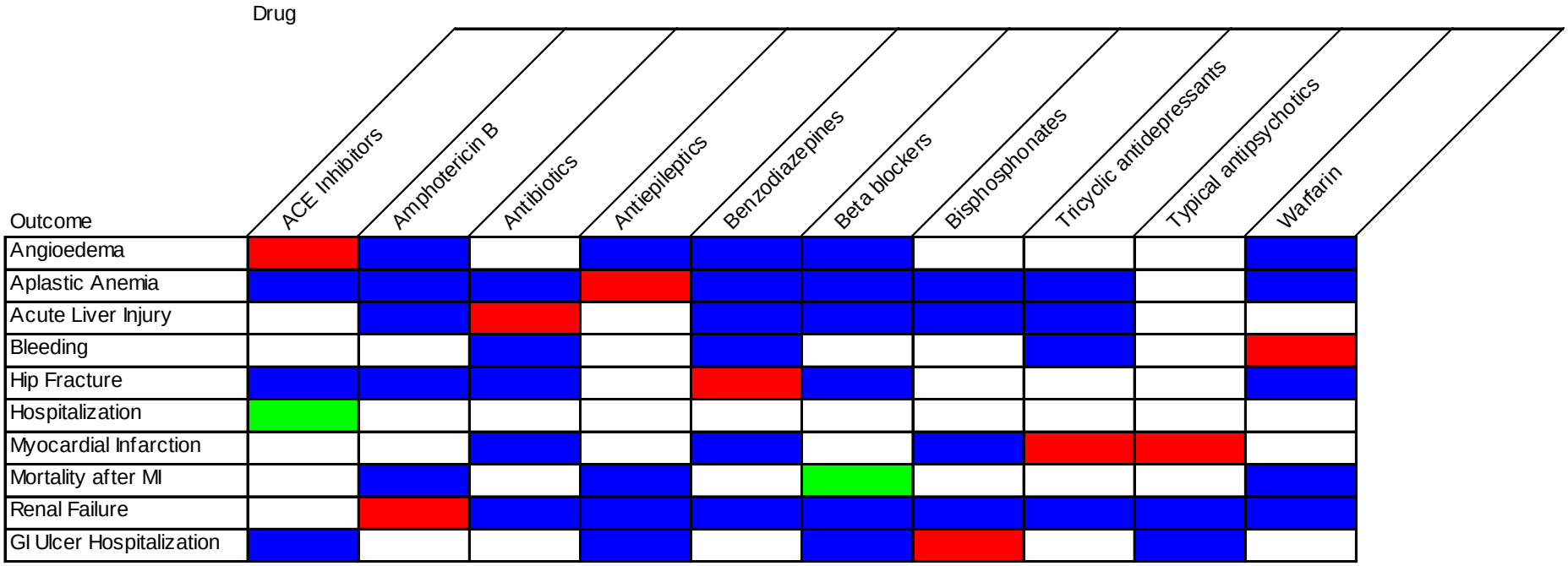
‘Ground truth’ for Monitoring Health Outcomes of Interest



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’

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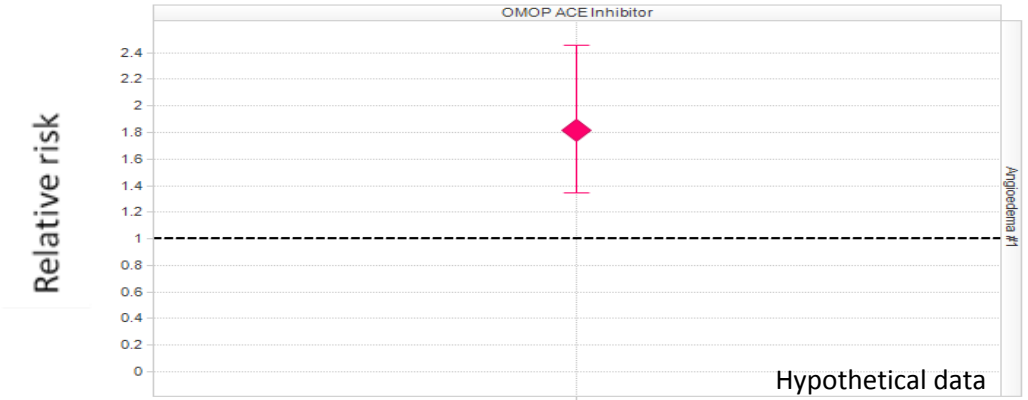
Studying method performance for 'signal refinement'

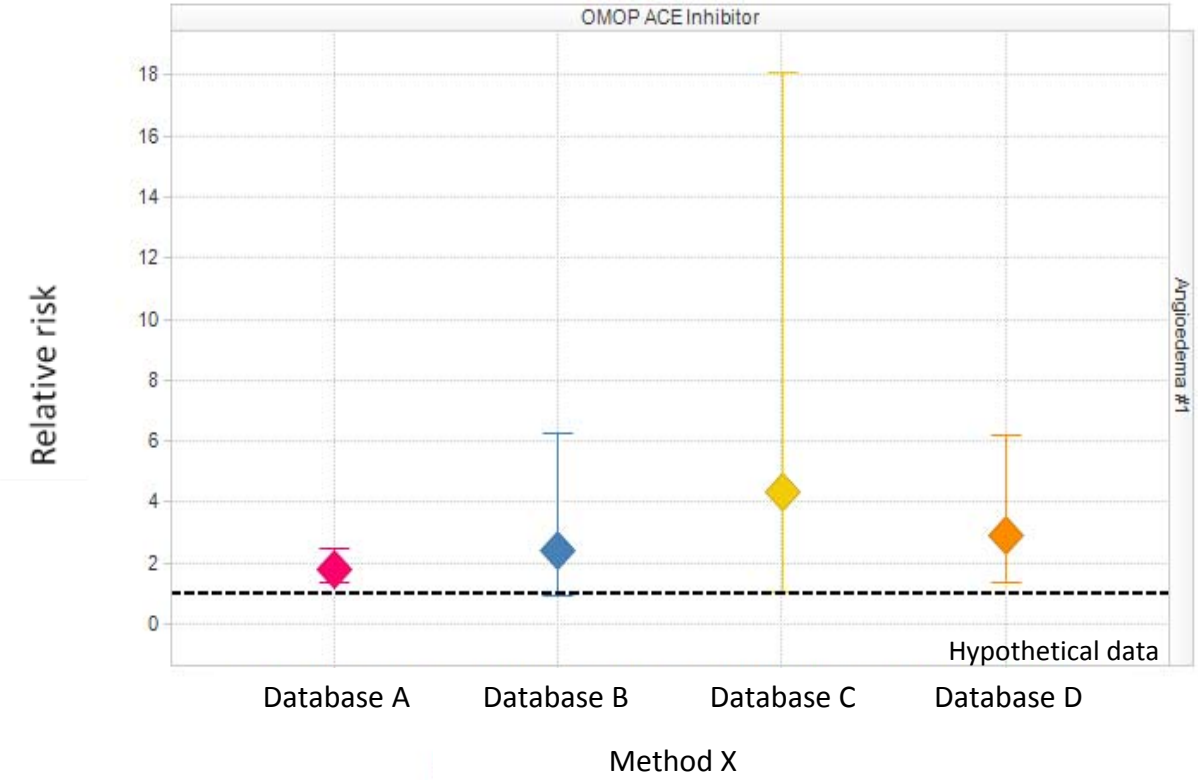
- Apply method with specific set of parameter settings to a database for a drug-outcome pair that has a prior suspicion of being potentially related
- Example: Run method X on database A for ACE inhibitors – Angioedema



Database A - Method X

- 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

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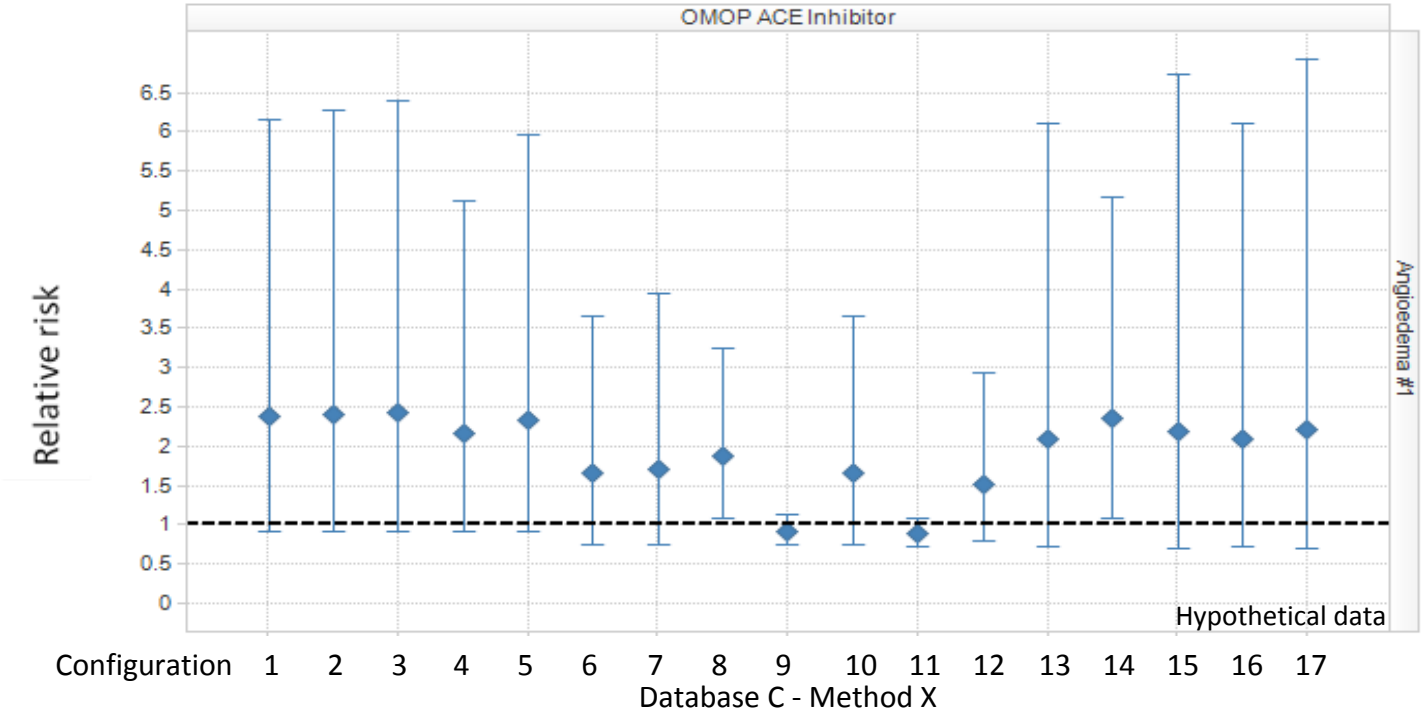
How do estimates vary by method parameter settings?



- 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

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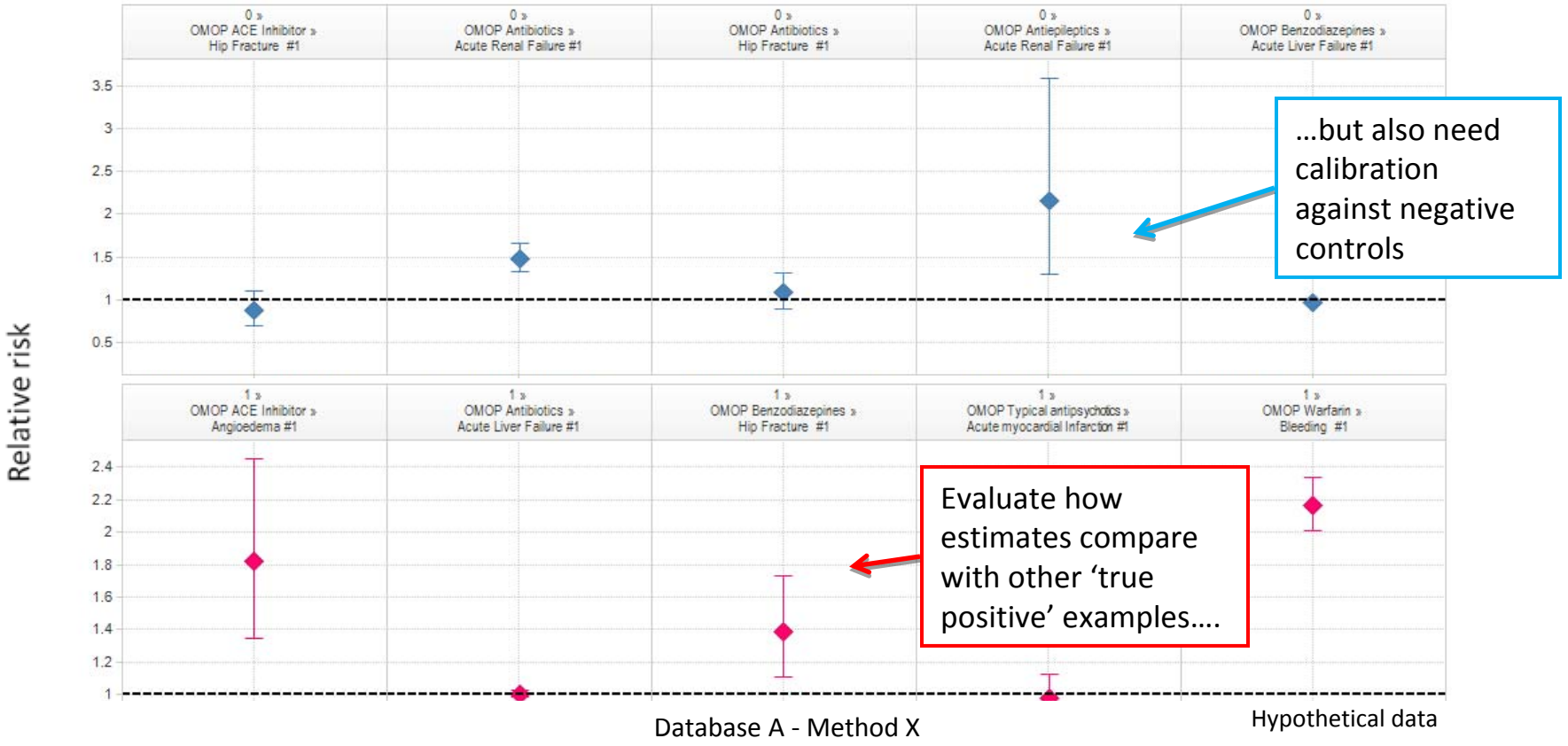
How does method perform against other 'benchmark' true positives and negative controls?



- 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'

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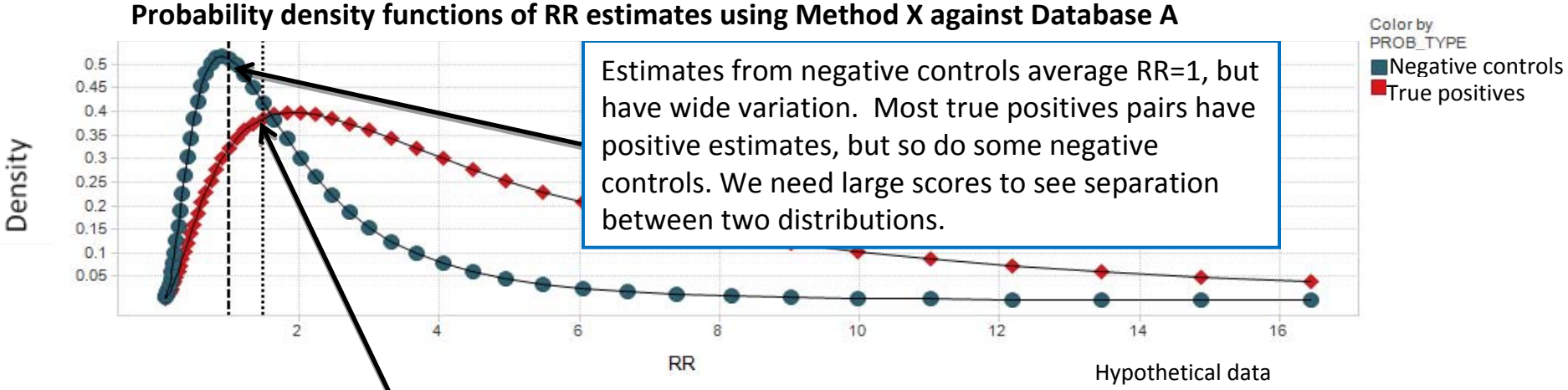
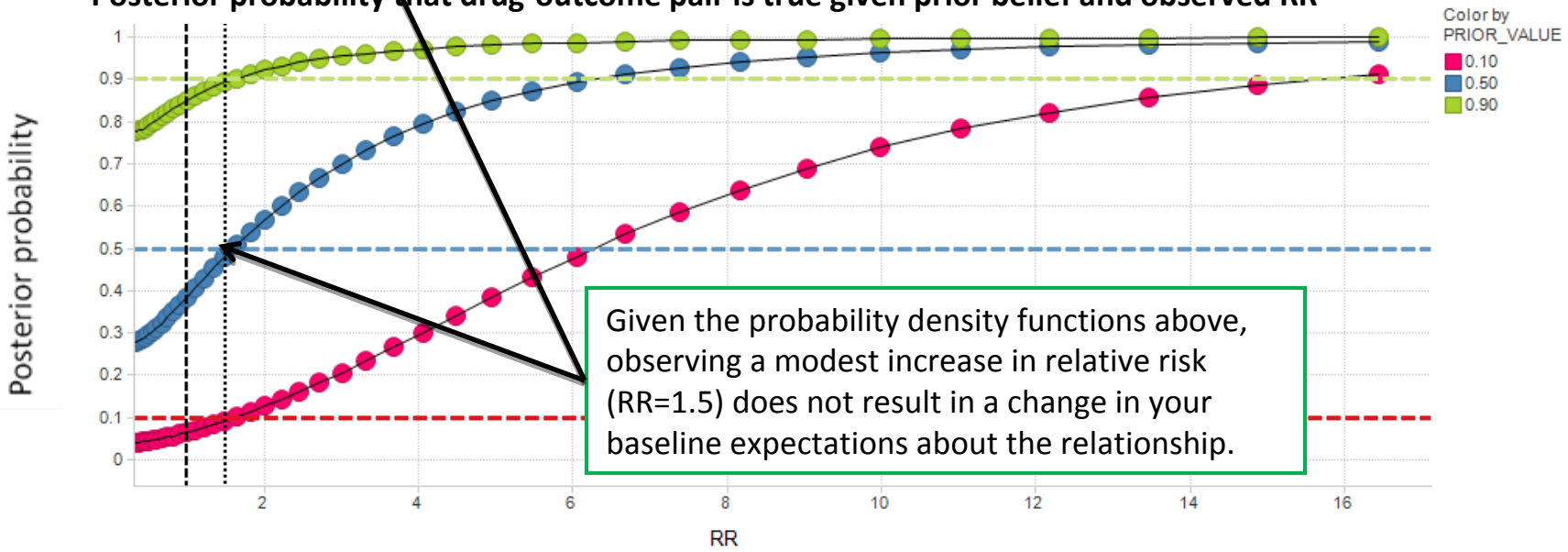
Probabilistic framework for interpreting active surveillance results: In light of the observed evidence, how confident are we that there is a true association between medical product exposure and outcome?

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



Estimates from negative controls average RR=1, but have wide variation. Most true positives pairs have positive estimates, but so do some negative controls. We need large scores to see separation between two distributions.

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



Given the probability density functions above, observing a modest increase in relative risk (RR=1.5) does not result in a change in your baseline expectations about the relationship.

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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Contact information

Patrick Ryan
Research Investigator
ryan@omop.org

David Madigan
OMOP Methods Lead
madigan@stat.columbia.edu

Thomas Scarnecchia
Executive Director
scarnecchia@omop.org

Emily Welebob
Senior Program Manager, Research
welebob@omop.org

OMOP website: http://omop.fnih.org