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Exploring Methodological Needs for Signal Refinement

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on behalf of OMOP Research Team
September 21, 2010

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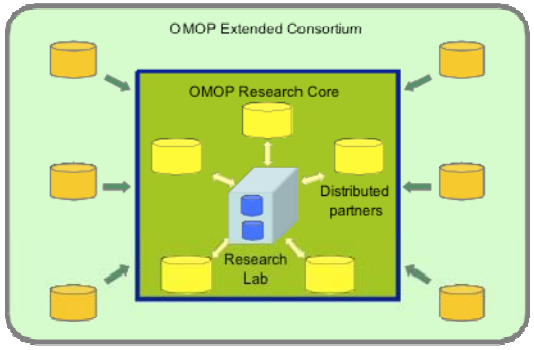
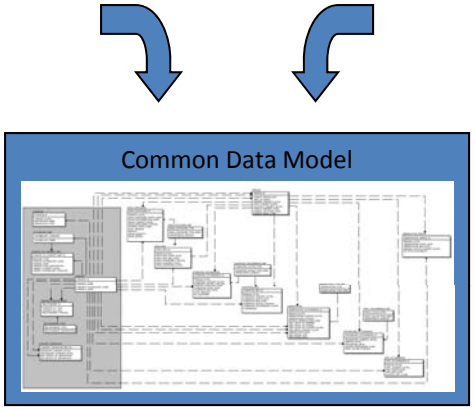
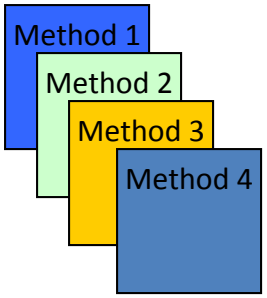
OMOP research experiment workflow





OMOP Methods Library



feasibility testing

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

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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

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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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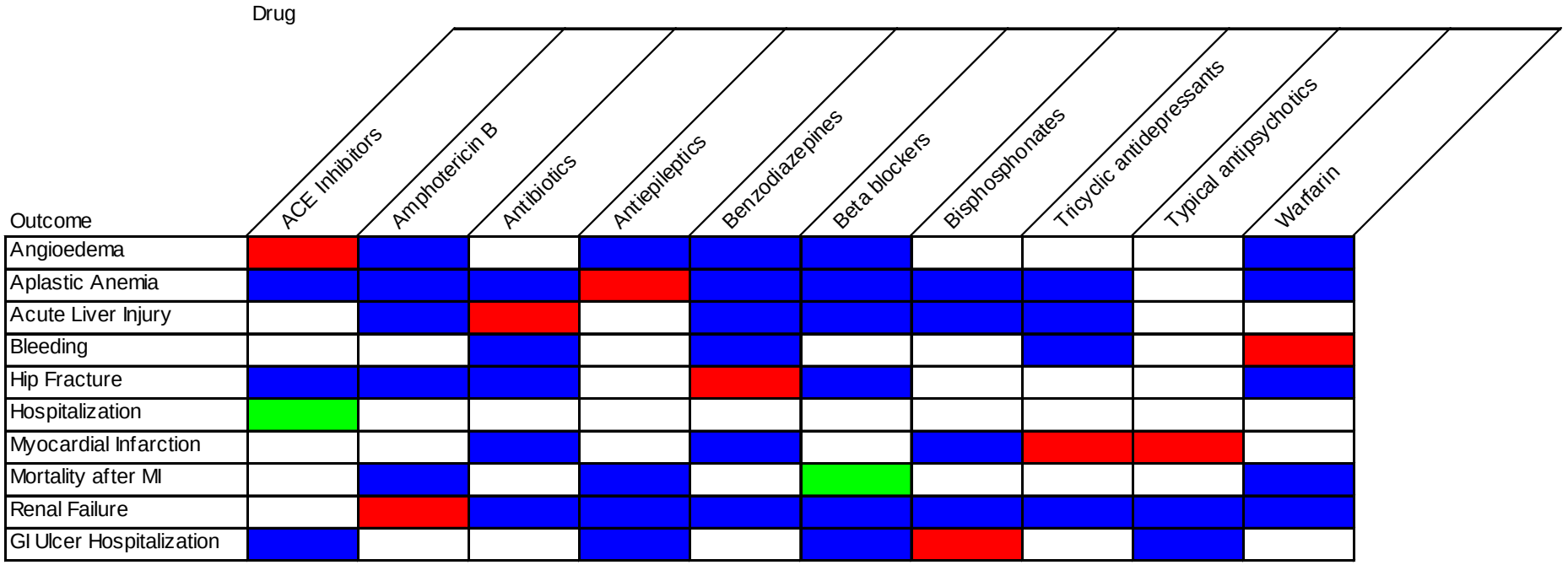
‘Ground truth’ for Monitoring Health Outcomes of Interest



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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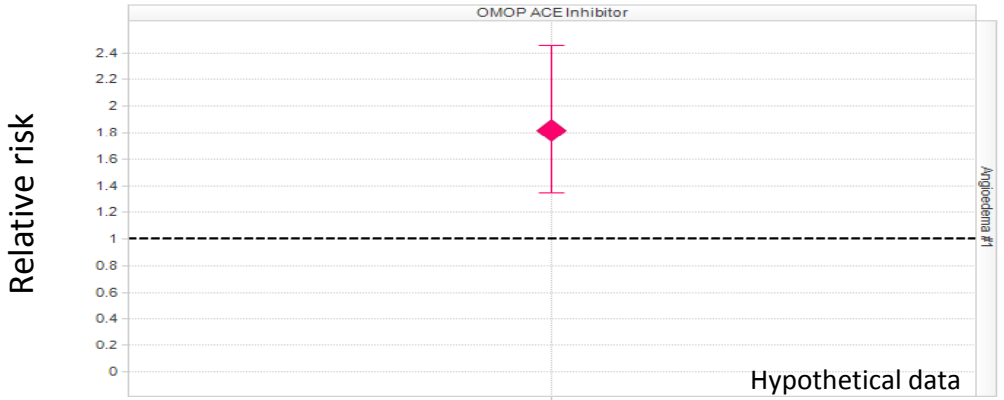
Studying method performance for 'signal refinement'

- 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?

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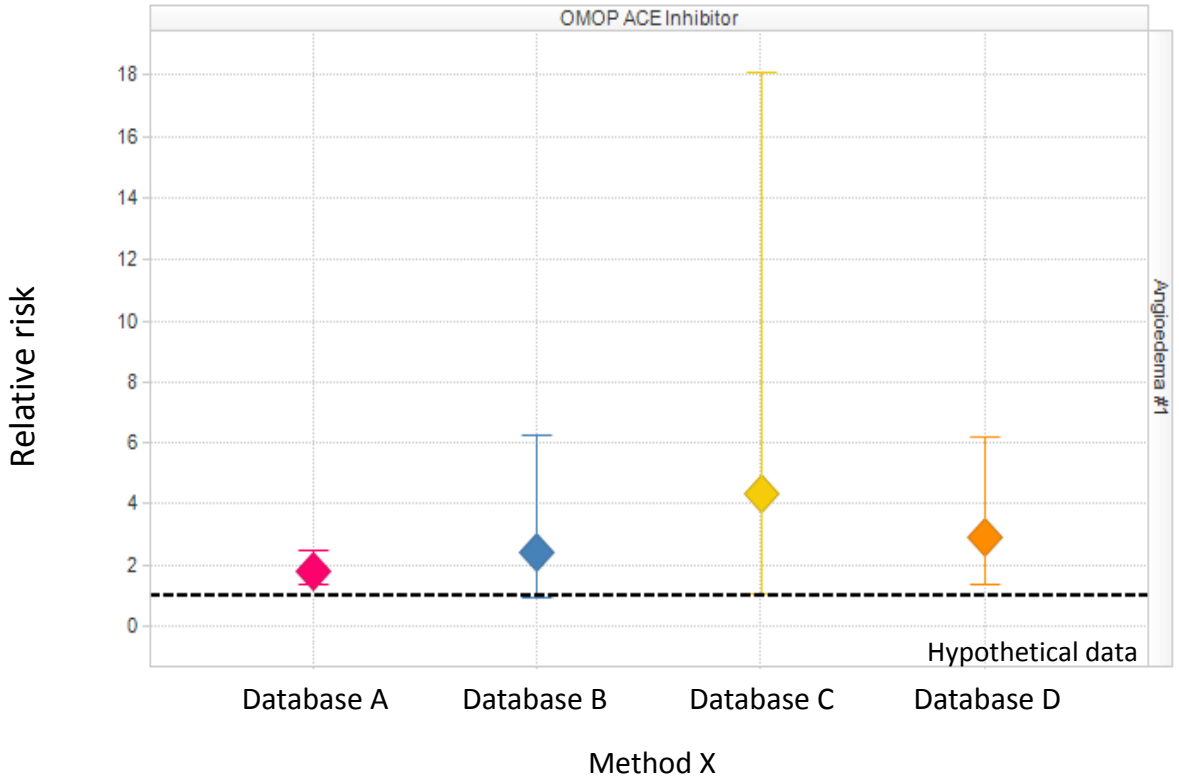
How do effect estimates vary by database?



- 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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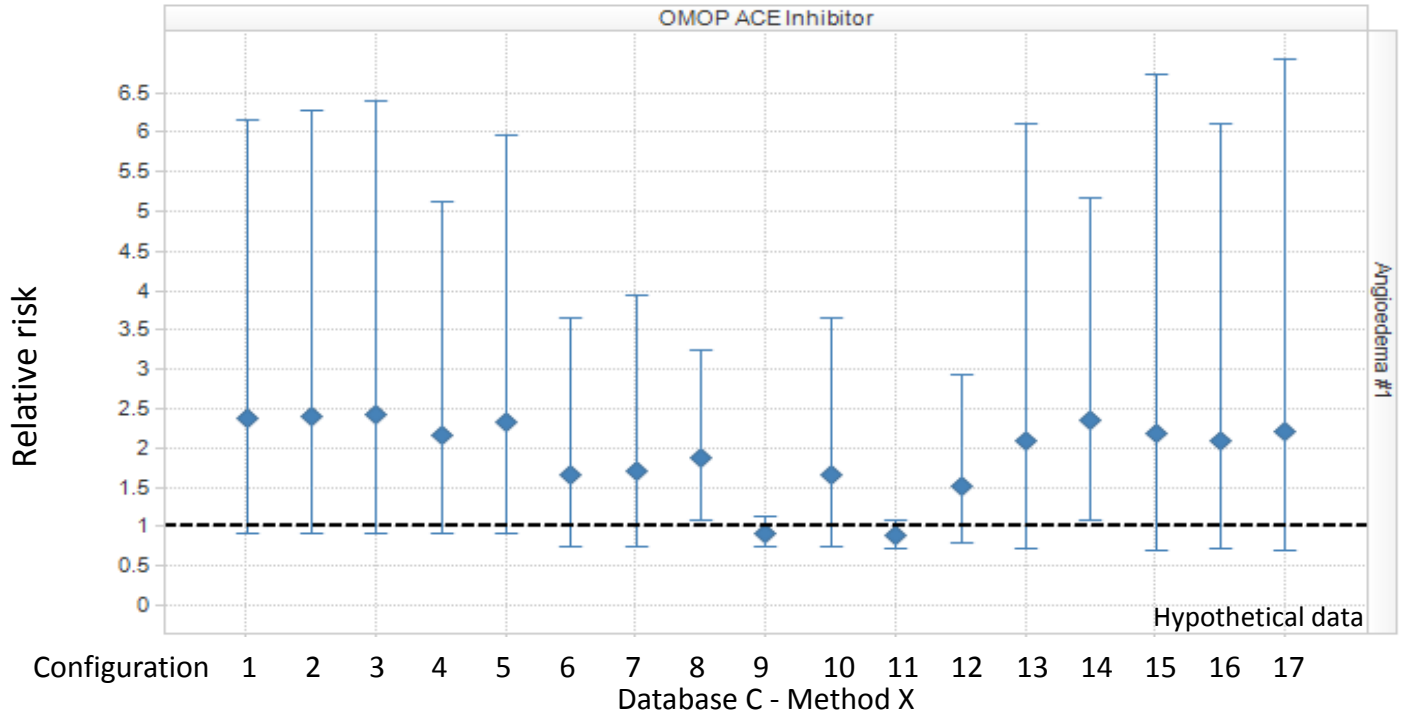
How do estimates vary by method parameter settings?



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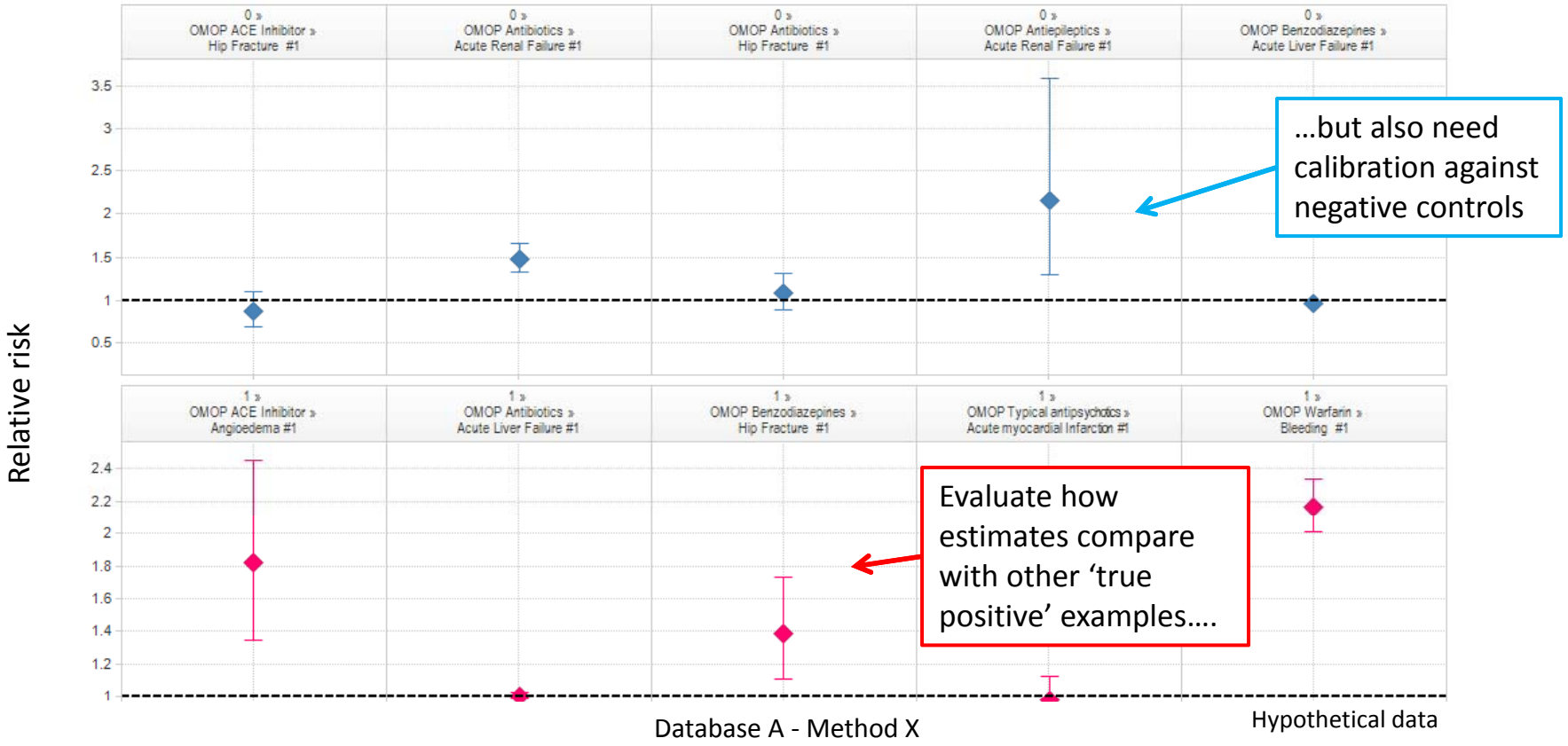
How does method perform against other 'benchmark' true positives and negative controls?



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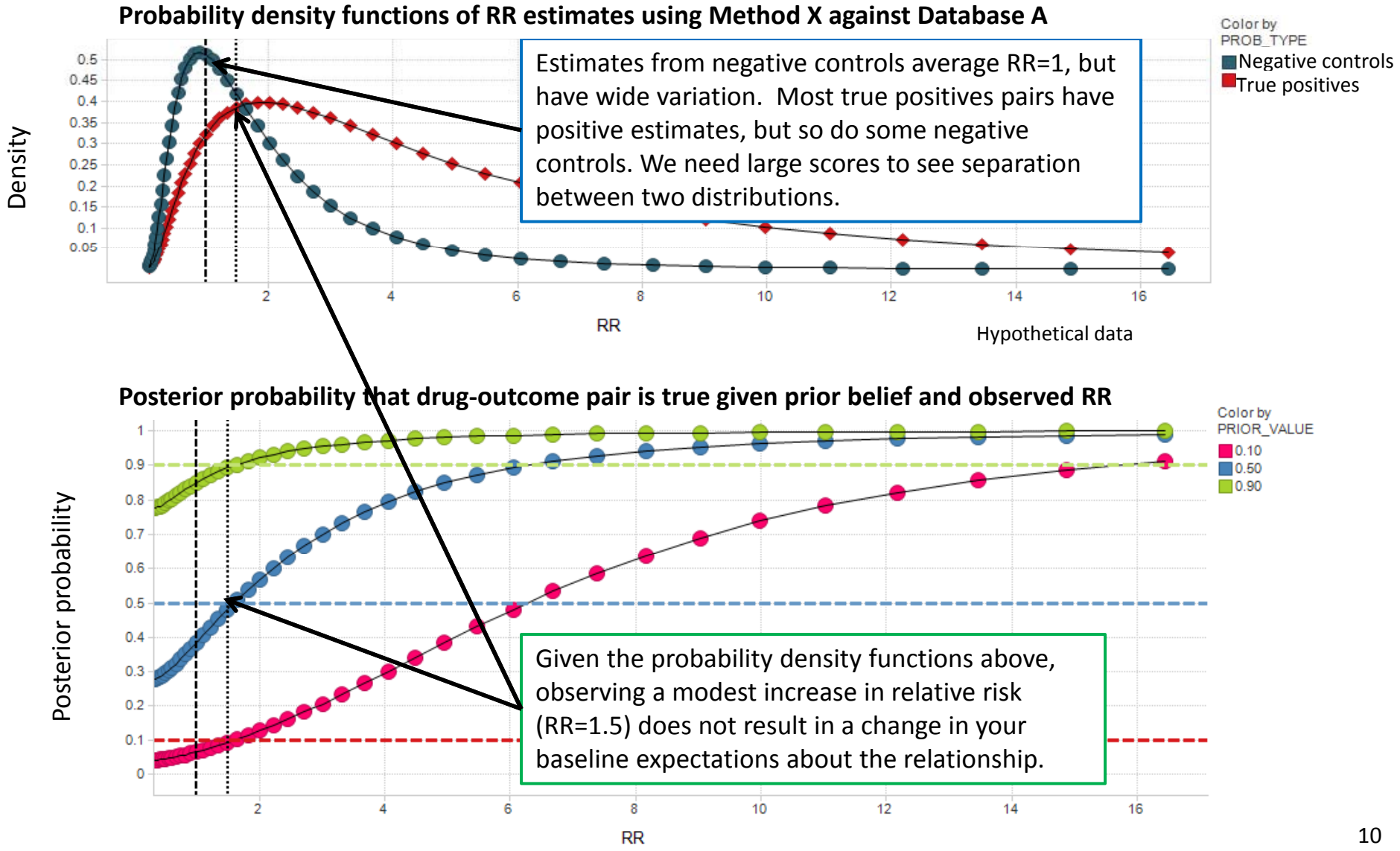
Probabilistic framework for interpreting active surveillance results: In light of the observed evidence, how confident are we that there is a true association between medical product exposure and outcome?



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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