

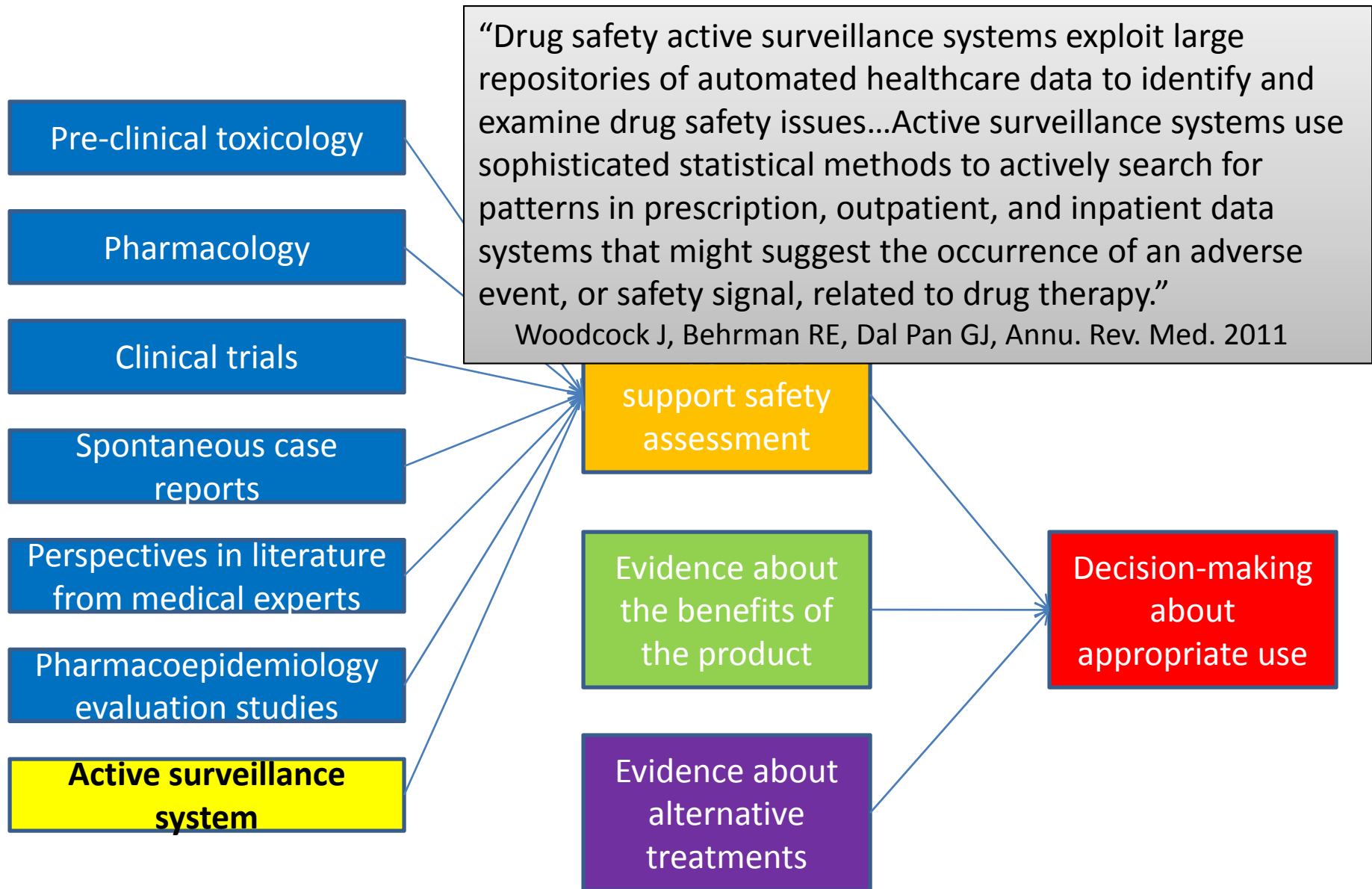
OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

The Observational Medical Outcomes Partnership: Overview of experimental results

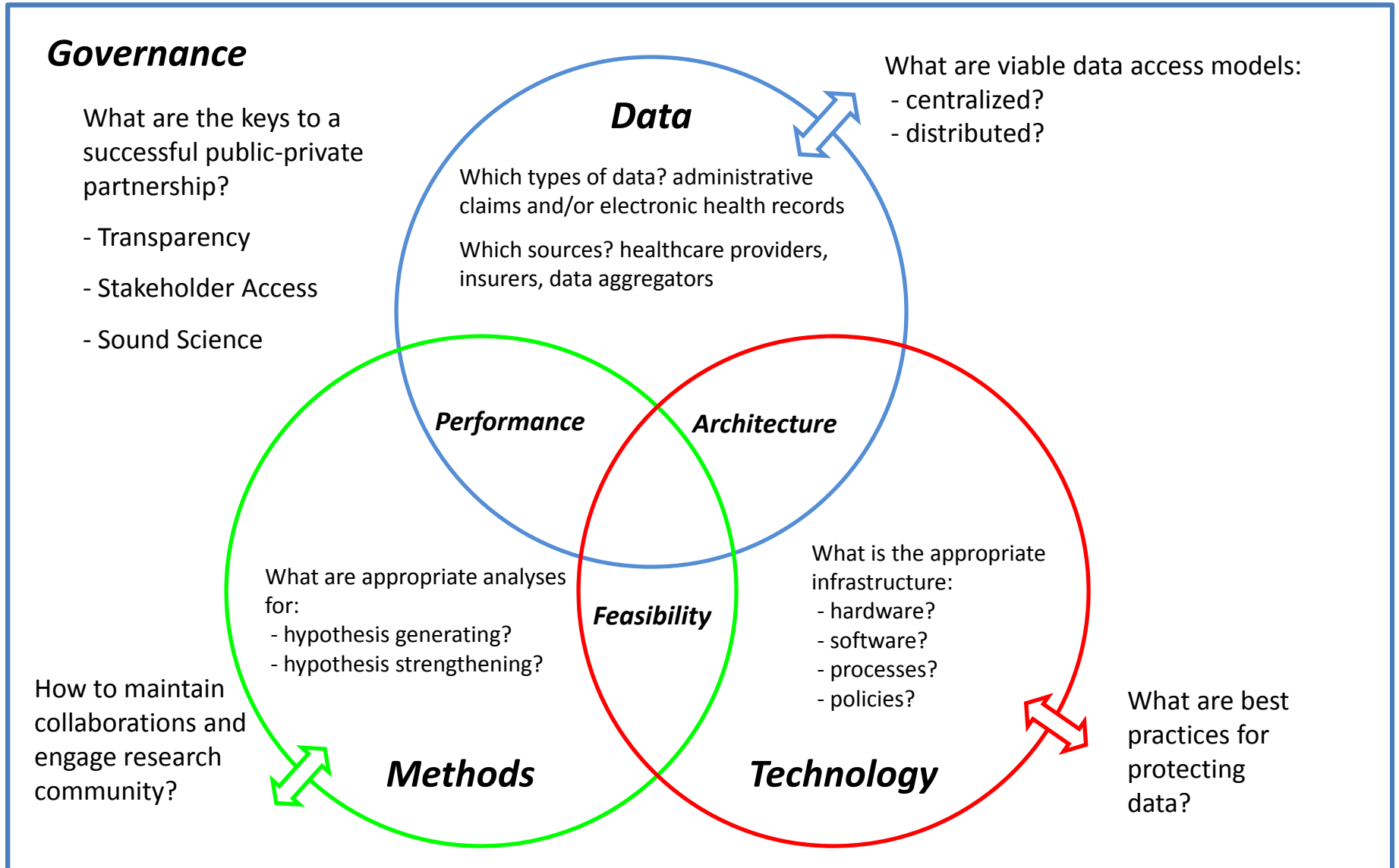
Patrick Ryan, David Madigan
on behalf of OMOP Research Team
April 14, 2011

Full results and audio presentations from OMOP Symposium available at:
<http://omop.fnih.org/OMOP2011Symposium>

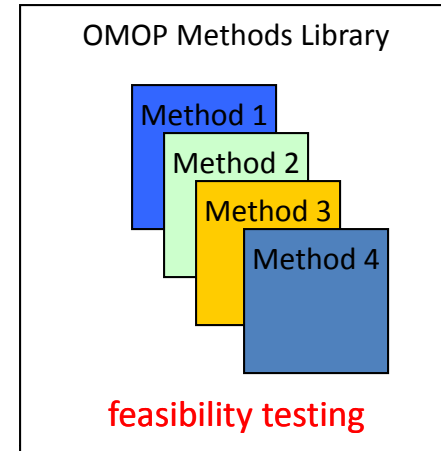
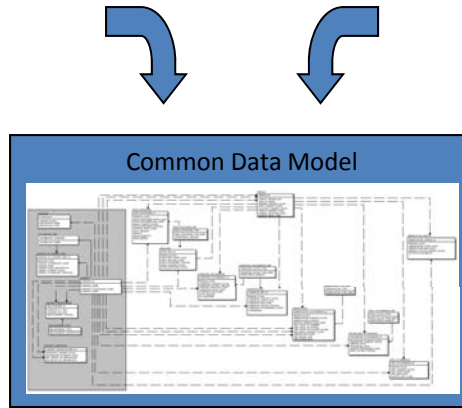
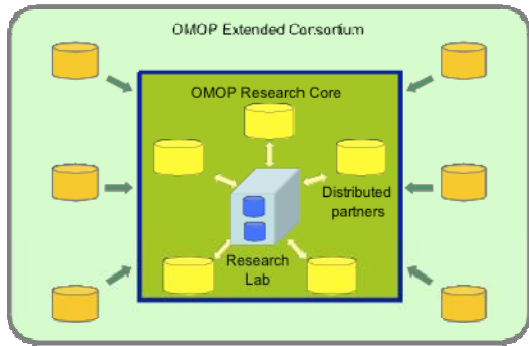
Active surveillance: One additional piece of evidence to inform medical decision-making



Outstanding Questions For Active Surveillance



OMOP research experiment workflow



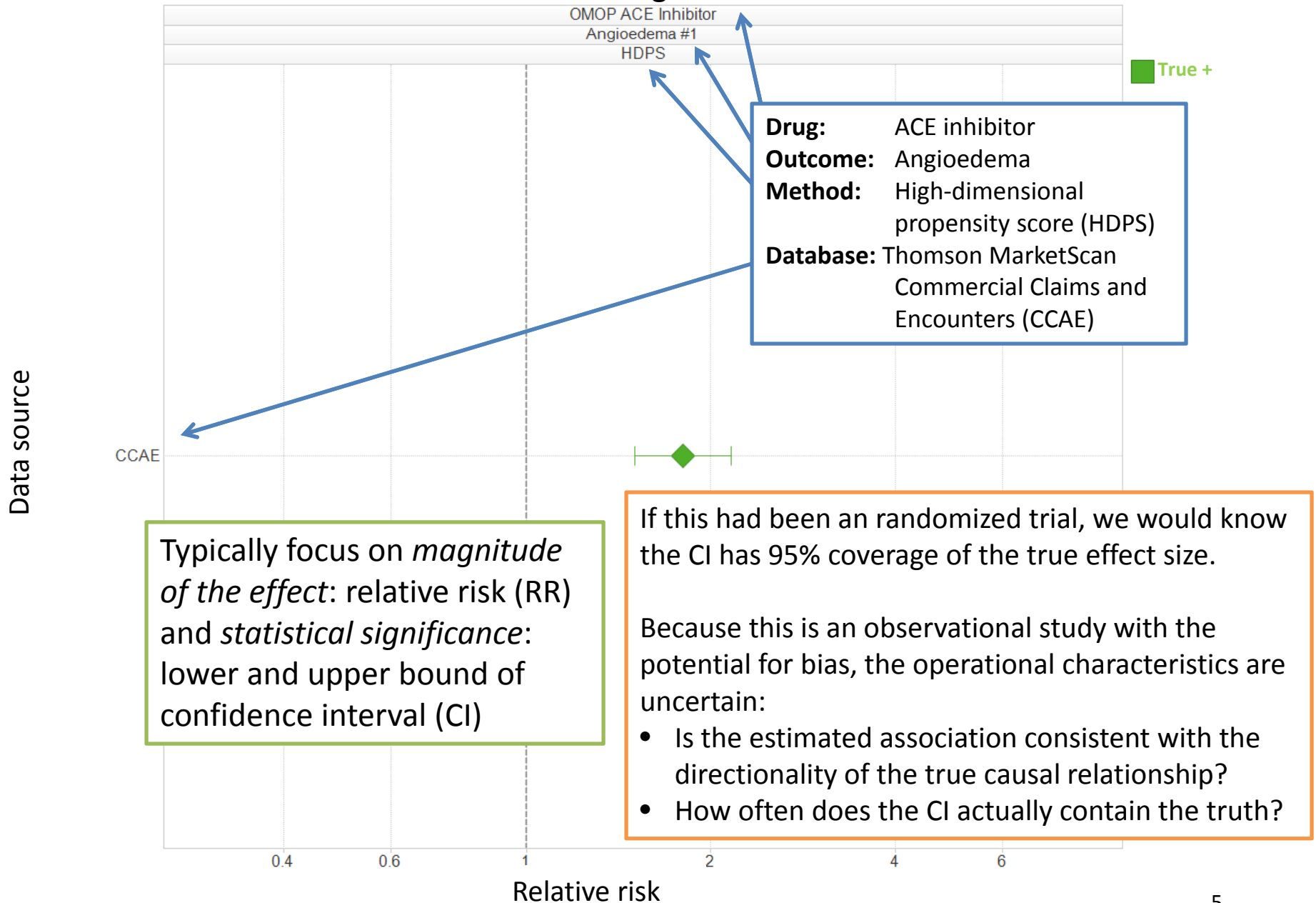
Drug

Outcome	ACE inhibitors	Amphotericin B	Antibiotics: erythromycin, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, phenytoin	Benzodiazepines	Beta blockers	Bisphosphonates: aenrononate	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema	True positive' benefit	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Aplastic Anemia	Negative control'	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Acute Liver Injury	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Bleeding	Negative control'	Negative control'	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	True positive' risk
Hip Fracture	Negative control'	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Hospitalization	True positive' benefit	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Myocardial Infarction	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	True positive' risk	True positive' risk	Negative control'	Negative control'
Mortality after MI	Negative control'	Negative control'	Negative control'	Negative control'	True positive' benefit	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
Renal Failure	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'
GI Ulcer Hospitalization	Negative control'	Negative control'	Negative control'	Negative control'	Negative control'	True positive' risk	Negative control'	Negative control'	Negative control'	Negative control'

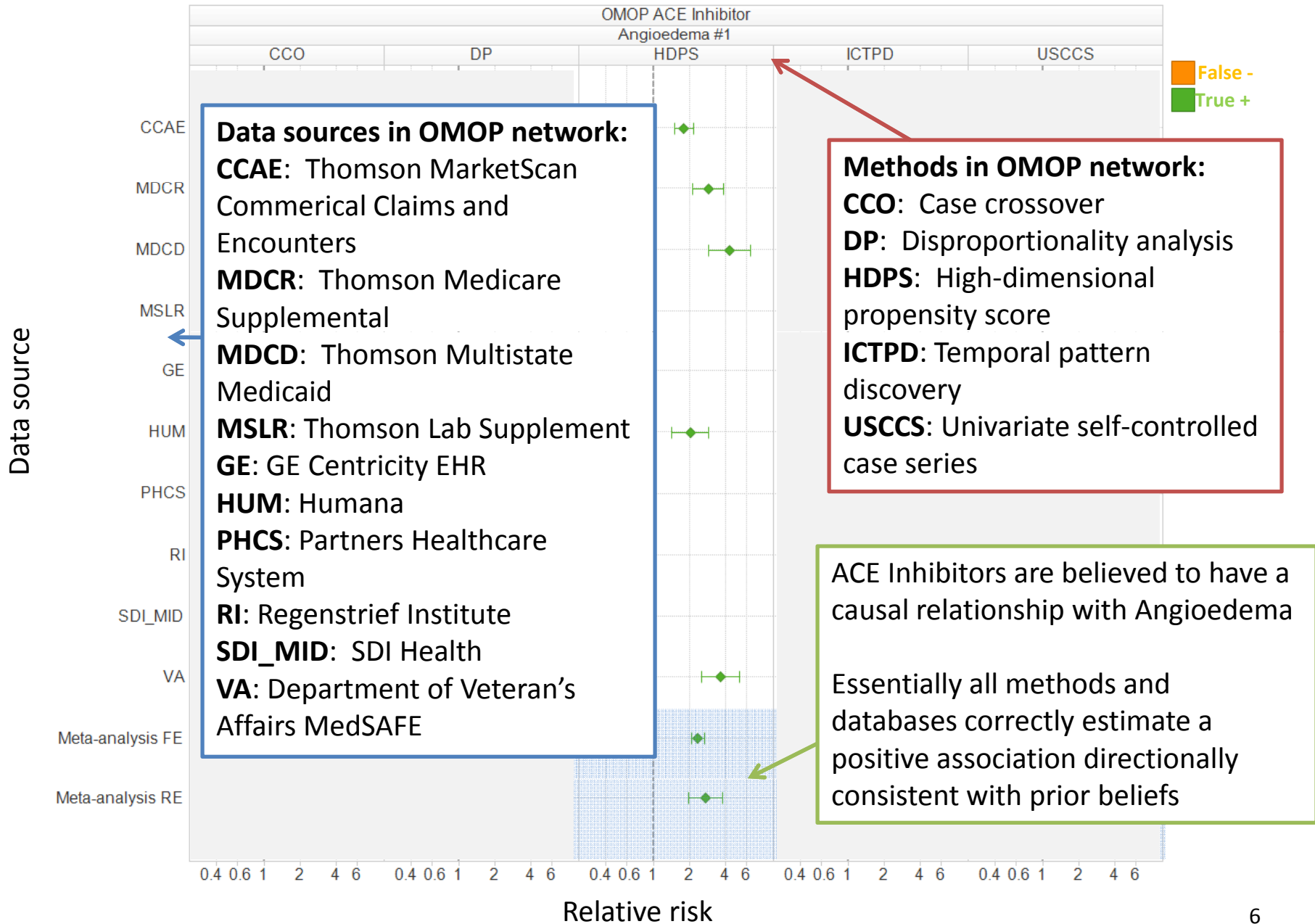
Legend

True positive' benefit	2
True positive' risk	9
Negative control'	44

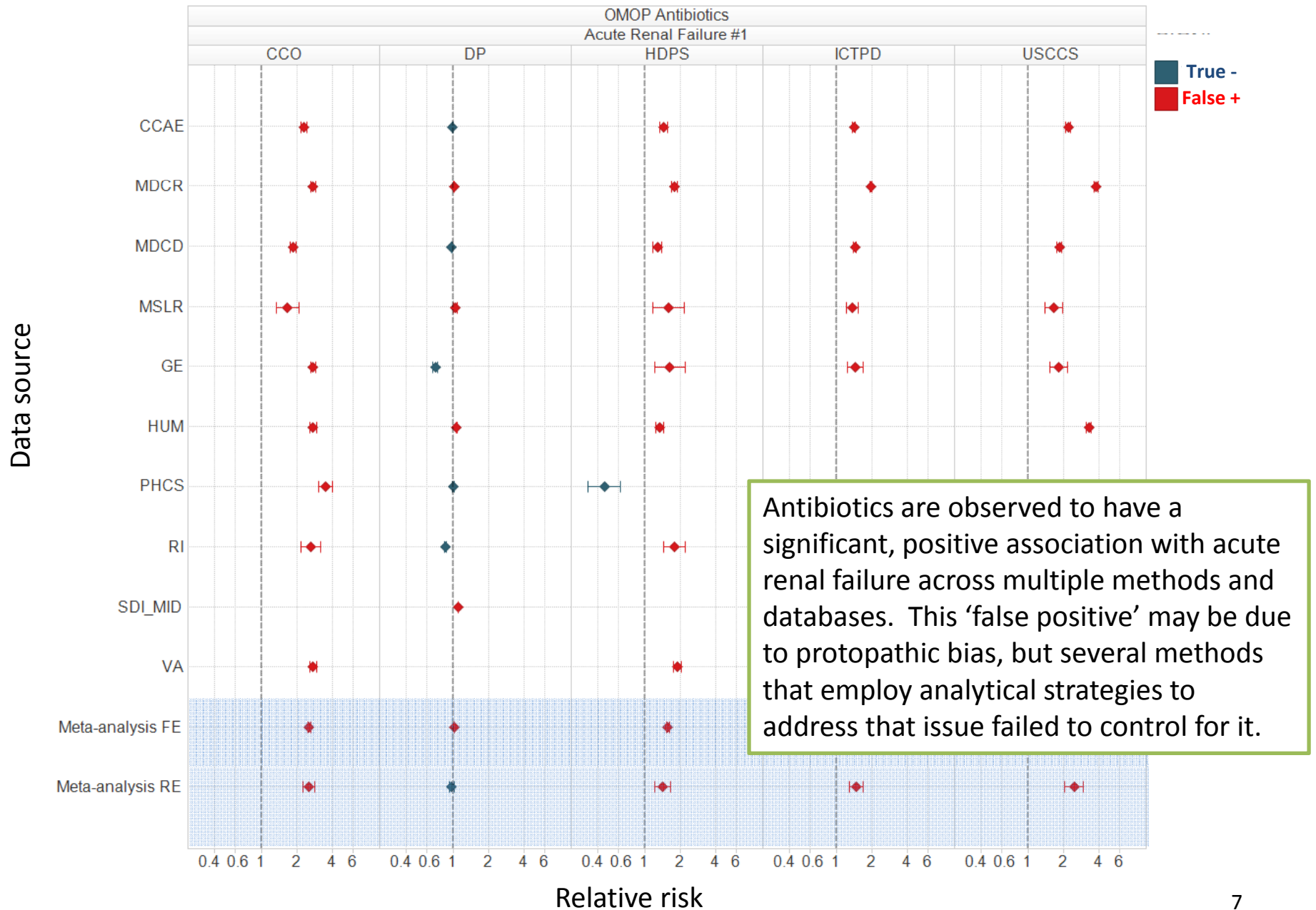
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



Consistent 'false positive' observed for 'negative control' of Antibiotics and Acute Renal Failure



Measuring method performance

Drug-condition association status

Y – ‘true association’,

N – ‘negative control’

Y

N

Method prediction:
Drug-condition
pair met a
specific
threshold

Y

True positives

False positives

N

False negatives

True negatives

Question: For any method applied to any data source, what are the expected operating characteristics?

'Ground truth' assumed for Monitoring Health Outcomes of Interest

Outcome	ACE Inhibitors	Amphotericin B	Antibiotics: erythromycins, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, phenytoin	Benzodiazepines	Beta blockers	Bisphosphonates: alendronate	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema	True positive risk	Negative control		Negative control	Negative control	Negative control				Negative control
Aplastic Anemia	Negative control	Negative control	Negative control	True positive risk	Negative control	Negative control	Negative control	Negative control		Negative control
Acute Liver Injury		Negative control	True positive risk		Negative control	Negative control	Negative control	Negative control		
Bleeding			Negative control				Negative control			True positive risk
Hip Fracture	Negative control	Negative control			True positive risk	Negative control				Negative control
Hospitalization	True positive benefit									
Myocardial Infarction			Negative control		Negative control		Negative control	True positive risk	True positive risk	
Mortality after MI		Negative control		Negative control		True positive benefit				Negative control
Renal Failure		True positive risk	Negative control	Negative control	Negative control	Negative control	Negative control	Negative control	Negative control	Negative control
GI Ulcer Hospitalization	Negative control			Negative control		Negative control	True positive risk		Negative control	

Legend	Total
True positive benefit	2
True positive risk	9
Negative control	44

Measuring method performance example: Random-effect meta-analysis of estimates from High-dimensional propensity score

Drug-condition association status

Y – ‘true association’,

N – ‘negative control’

Y

N

Method prediction:
Drug-condition pair met a specific threshold:
(LB 95% CI > 1)

Y

N

True positives: 5	False positives: 8
False negatives: 4	True negatives: 36

Positive predictive value
= precision
= $TP / (TP+FP)$
= $5 / (5+8) = 0.38$

Negative predictive value
= $TN / (FN+TN)$
= $36 / (4+36) = 0.90$

Sensitivity
= Recall
= $TP / (TP+FN)$
= $5 / (5+4) = 0.56$

Specificity
= $TN / (FP+TN)$
= $36 / (8+36) = 0.82$
False positive rate
= $1 - 0.82 = 0.18$

Accuracy
= $(TP+TN) / (TP+TN+FP+FN)$
= $(5+36) / (9+44) = 0.77$

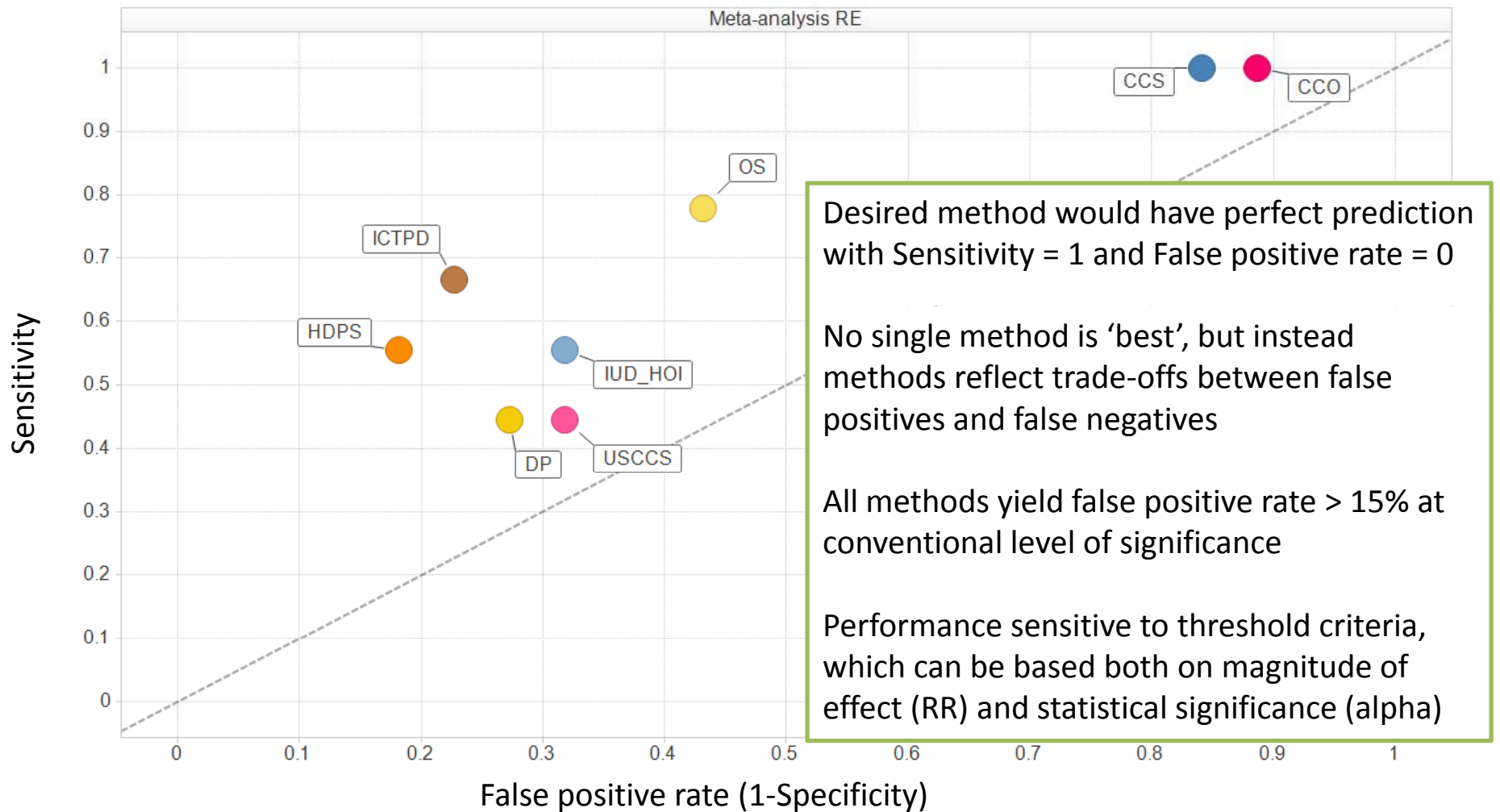
Active surveillance methods under evaluation in OMOP experiment

Method name	Contributor	Release date
Disproportionality analysis		
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10
Case-based methods		
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10
Case-control surveillance (CCS)	Lilly	2-May-10
Case-crossover (CCO)	University of Utah	1-Jun-10
Exposure-based methods		
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10
High-dimensional propensity score (HDPS)	Columbia	6-Aug-10
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10
Sequential testing methods		
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10

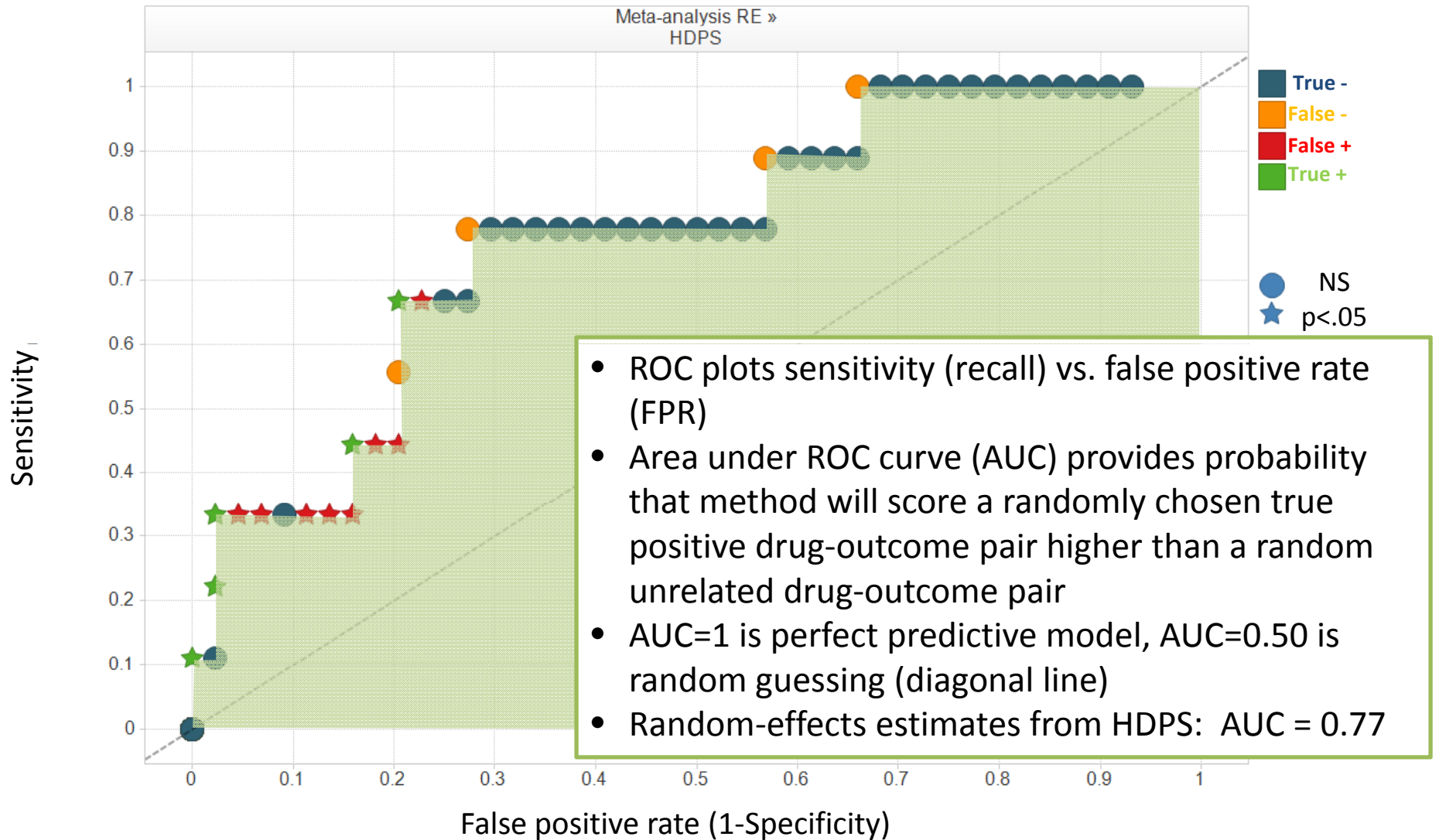
In what follows, we have chosen one parameter combination for each method that performs best for the meta-analysis estimates

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

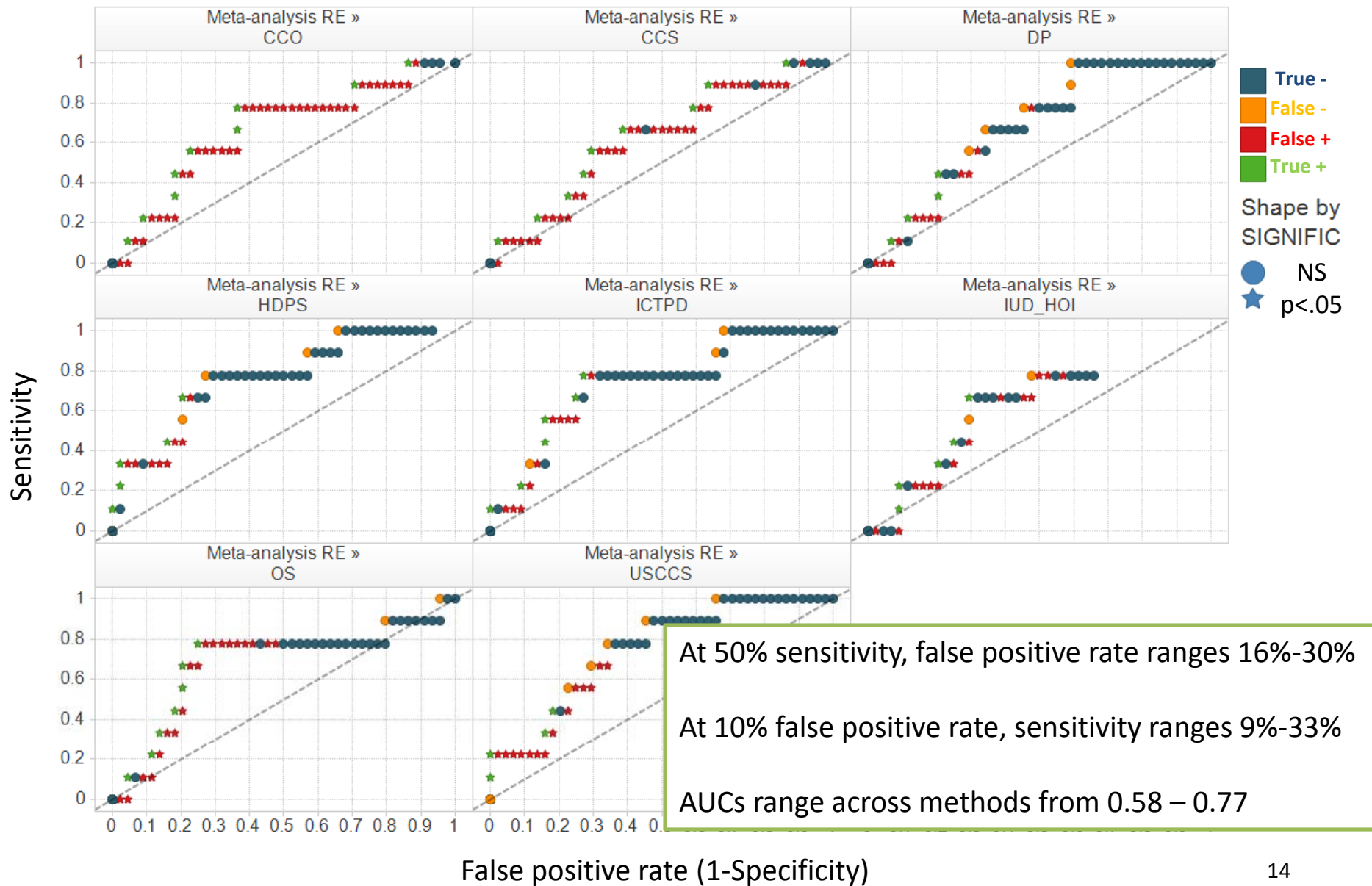
Comparing methods by sensitivity and specificity at alpha=0.05



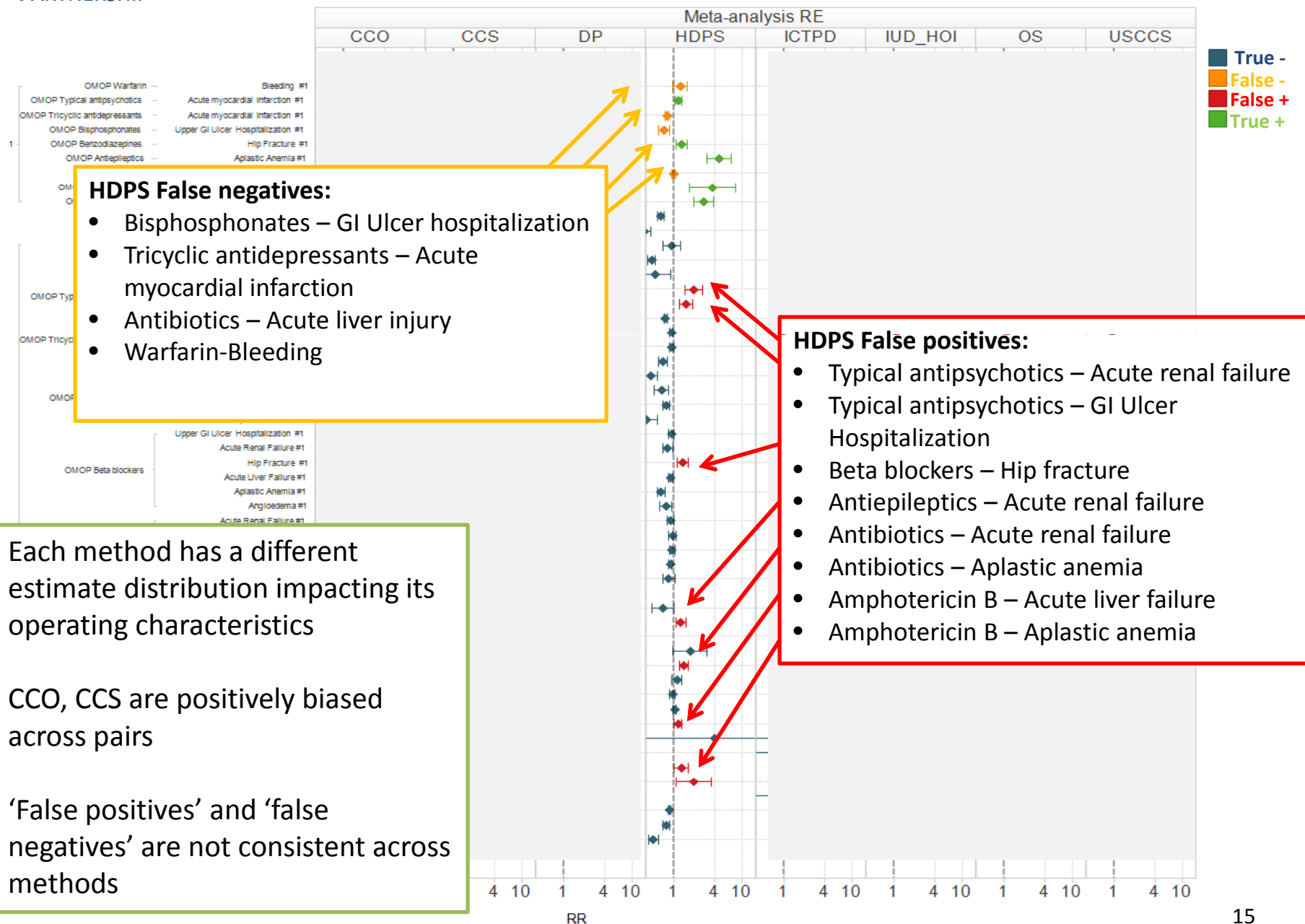
Receiver Operating Characteristic (ROC) curve



ROC curves of random-effects meta-analysis estimations for all methods



Distribution of estimates across all drug-outcome pairs



Further exploration after lunch

- 1pm: How do study design choices impact effect estimates from observational analyses?
- 2pm: Given these operating characteristics, how can we integrate observational evidence into our decision-making?
- The emerging interest of observational data for evidence generation for medical products demand increased statistical rigor to facilitate the appropriate use of these data
- Active drug safety surveillance and comparative effectiveness research require active participation by biostatisticians in industry, government, and academia
- Afternoon sessions will discuss opportunities for statistical leaders to take a more prominent role in designing observational analyses and interpreting results to inform activities throughout the drug development lifecycle

Concluding thoughts

- An active surveillance system can complement current practice by providing evidence to support a comprehensive safety assessment
- No one clear 'best' method, as it depends on tolerance for false positives vs. false negatives
- In this experiment, active surveillance methods achieved:
 - At 50% sensitivity, false positive rate ranges 16%-30%
 - At 10% false positive rate, sensitivity ranges 9%-33%
- Need to be cautious in interpreting results from single method in single database
 - Replication does not necessarily provide complete confidence
- Further empirical research needed to have more complete understanding of operating characteristics before widespread adoption