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The Observational Medical Outcomes Partnership: Overview of experimental results

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on behalf of OMOP Research Team
April 14, 2011

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

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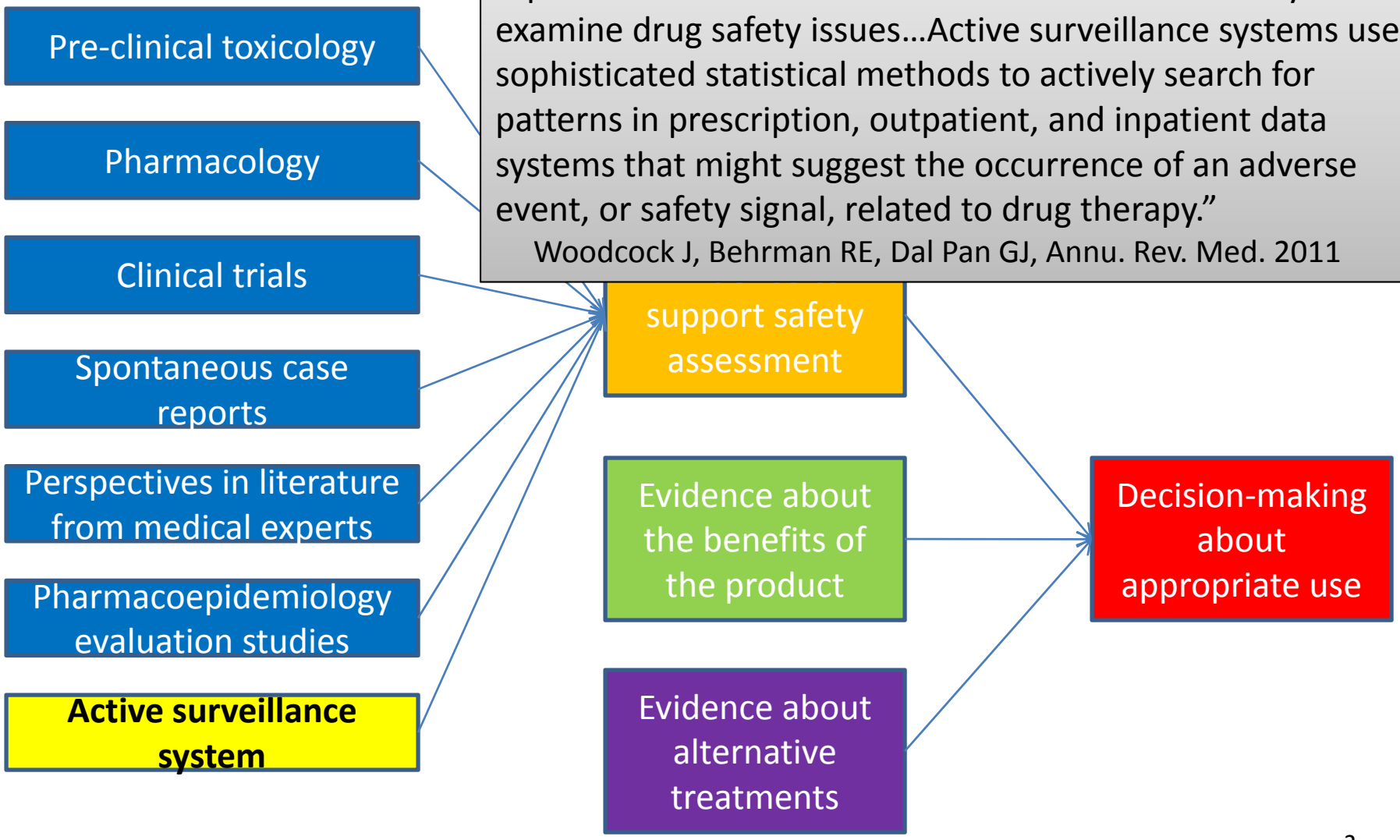
Active surveillance: One additional piece of evidence to inform medical decision-making

"Drug safety active surveillance systems exploit large repositories of automated healthcare data to identify and examine drug safety issues…Active surveillance systems use sophisticated statistical methods to actively search for patterns in prescription, outpatient, and inpatient data systems that might suggest the occurrence of an adverse event, or safety signal, related to drug therapy."

Woodcock J, Behrman RE, Dal Pan GJ, Annu. Rev. Med. 2011



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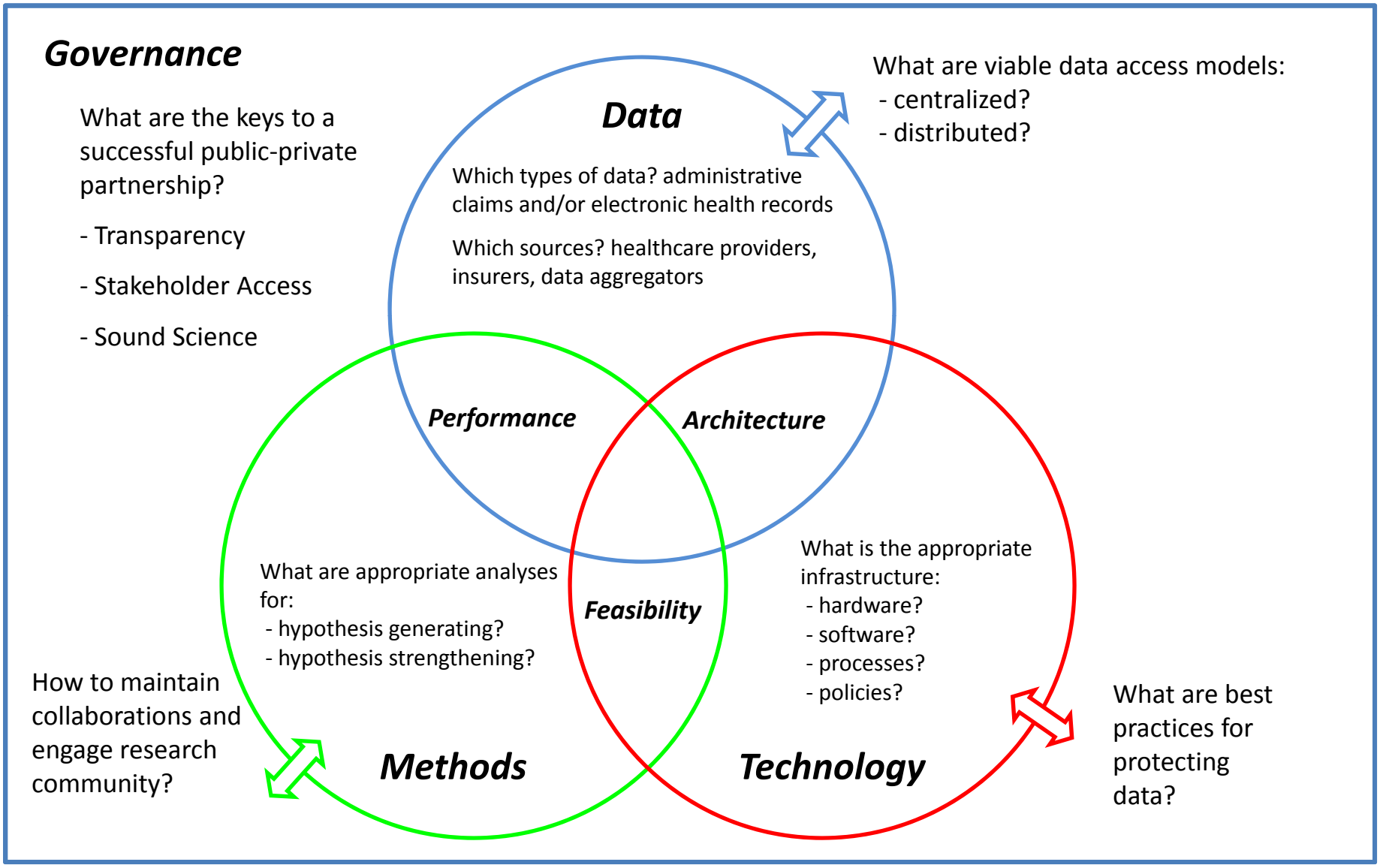
Outstanding Questions For Active Surveillance



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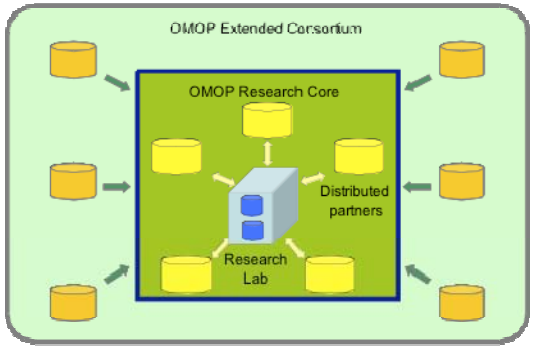
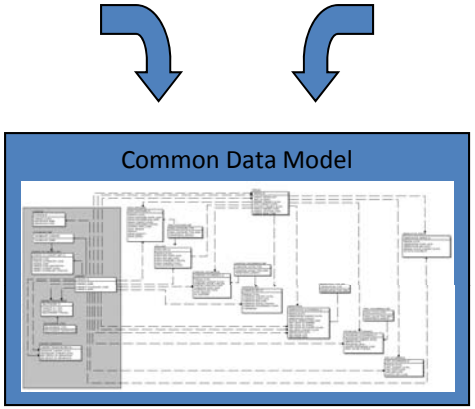
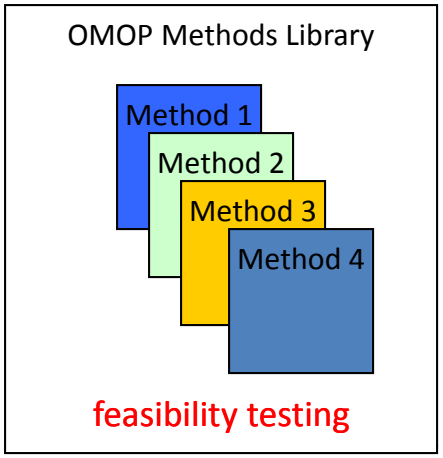
OMOP research experiment workflow







Outcome \ Drug	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'			Negative control'		True positive' risk
Hip Fracture	Negative control'	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

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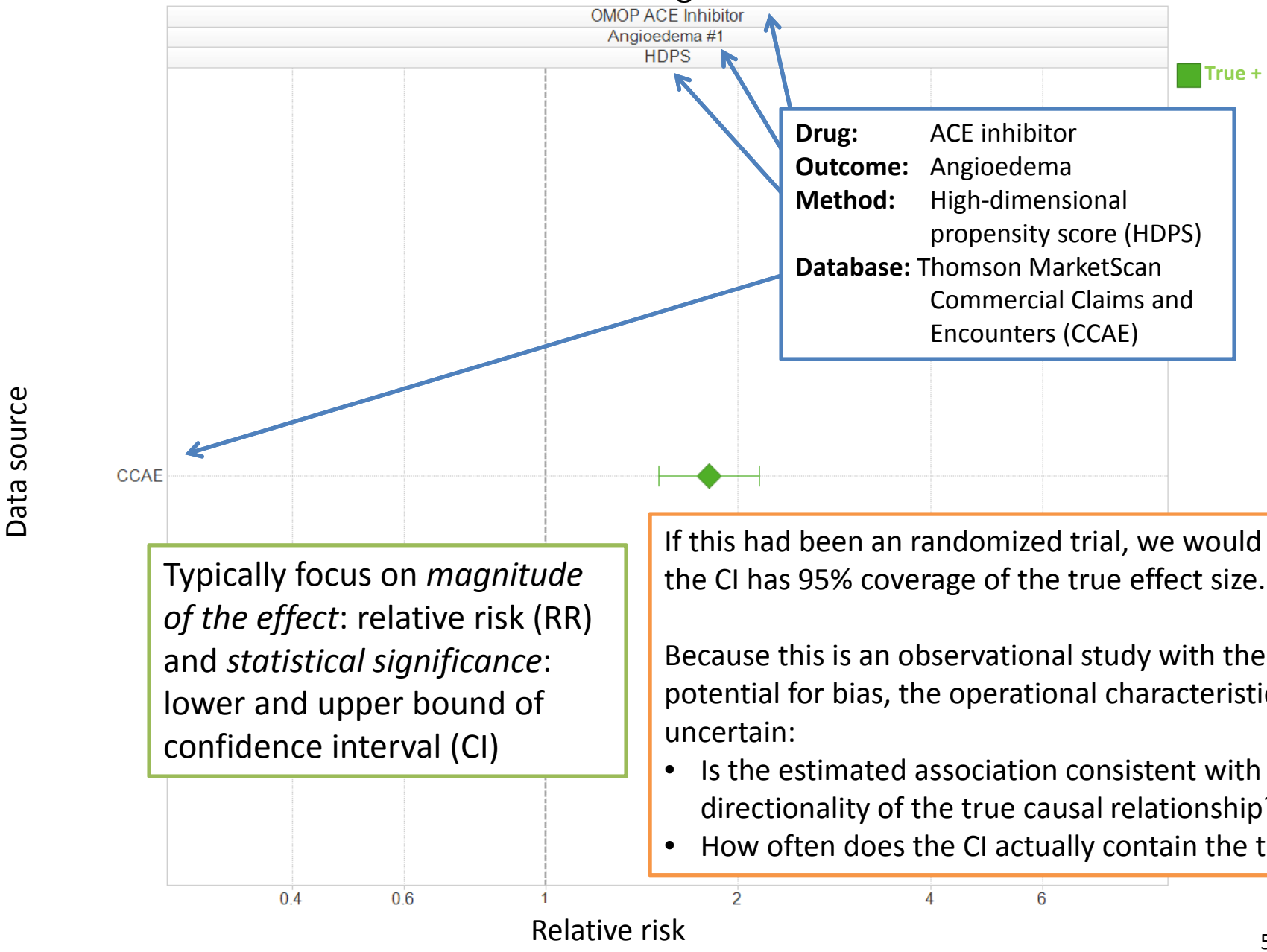
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



Drug: ACE inhibitor
Outcome: Angioedema
Method: High-dimensional propensity score (HDPS)
Database: Thomson MarketScan Commercial Claims and Encounters (CCAE)

Typically focus on *magnitude of the effect*: relative risk (RR) and *statistical significance*: lower and upper bound of confidence interval (CI)

If this had been an randomized trial, we would know the CI has 95% coverage of the true effect size.

Because this is an observational study with the potential for bias, the operational characteristics are uncertain:

- Is the estimated association consistent with the directionality of the true causal relationship?
- How often does the CI actually contain the truth?

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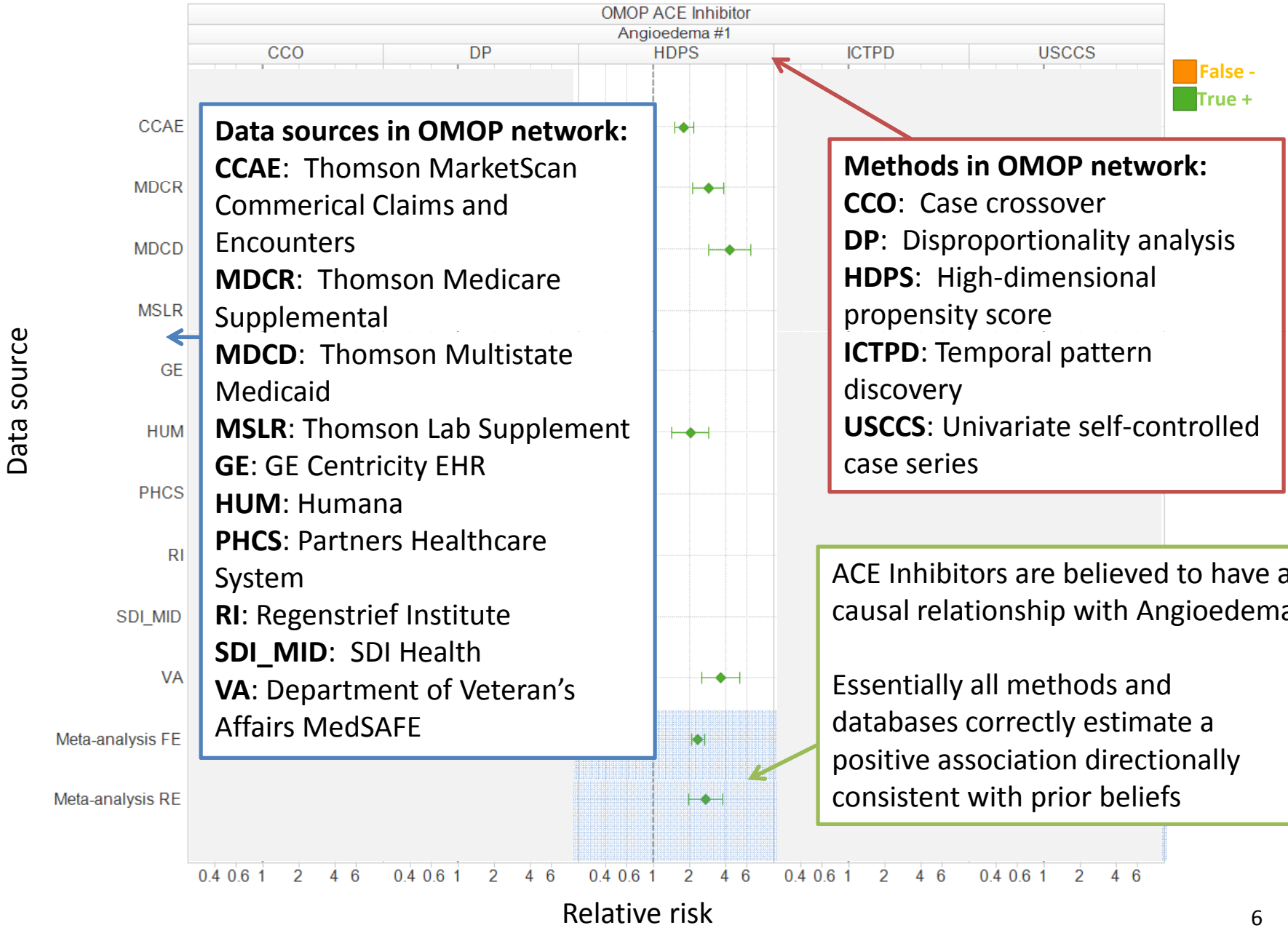
Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



Data sources in OMOP network:
CCAE: Thomson MarketScan Commerical Claims and Encounters
MDCR: Thomson Medicare Supplemental
MDCD: Thomson Multistate Medicaid
MSLR: Thomson Lab Supplement
GE: GE Centricity EHR
HUM: Humana
PHCS: Partners Healthcare System
RI: Regenstrief Institute
SDI_MID: SDI Health
VA: Department of Veteran's Affairs MedSAFE

Methods in OMOP network:
CCO: Case crossover
DP: Disproportionality analysis
HDPS: High-dimensional propensity score
ICTPD: Temporal pattern discovery
USCCS: Univariate self-controlled case series

ACE Inhibitors are believed to have a causal relationship with Angioedema

Essentially all methods and databases correctly estimate a positive association directionally consistent with prior beliefs

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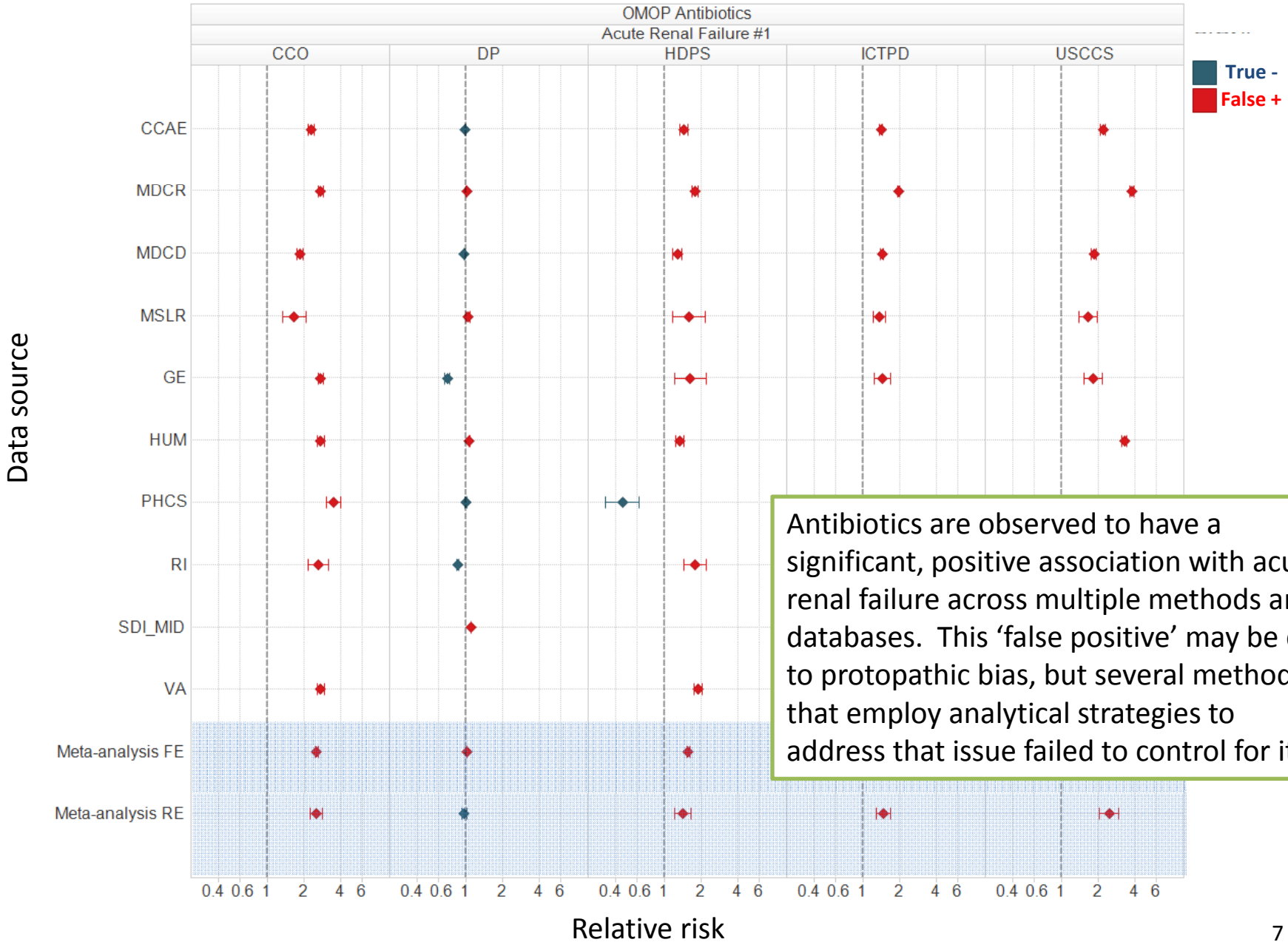
Consistent 'false positive' observed for 'negative control' of Antibiotics and Acute Renal Failure



Antibiotics are observed to have a significant, positive association with acute renal failure across multiple methods and databases. This 'false positive' may be due to protopathic bias, but several methods that employ analytical strategies to address that issue failed to control for it.

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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**

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

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‘Ground truth’ assumed for Monitoring Health Outcomes of Interest

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

Legend	Total
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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'

Method prediction: Drug-condition pair met a specific threshold:

(LB 95% CI > 1)

	Y	N
Y	True positives: 5	False positives: 8
N	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

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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

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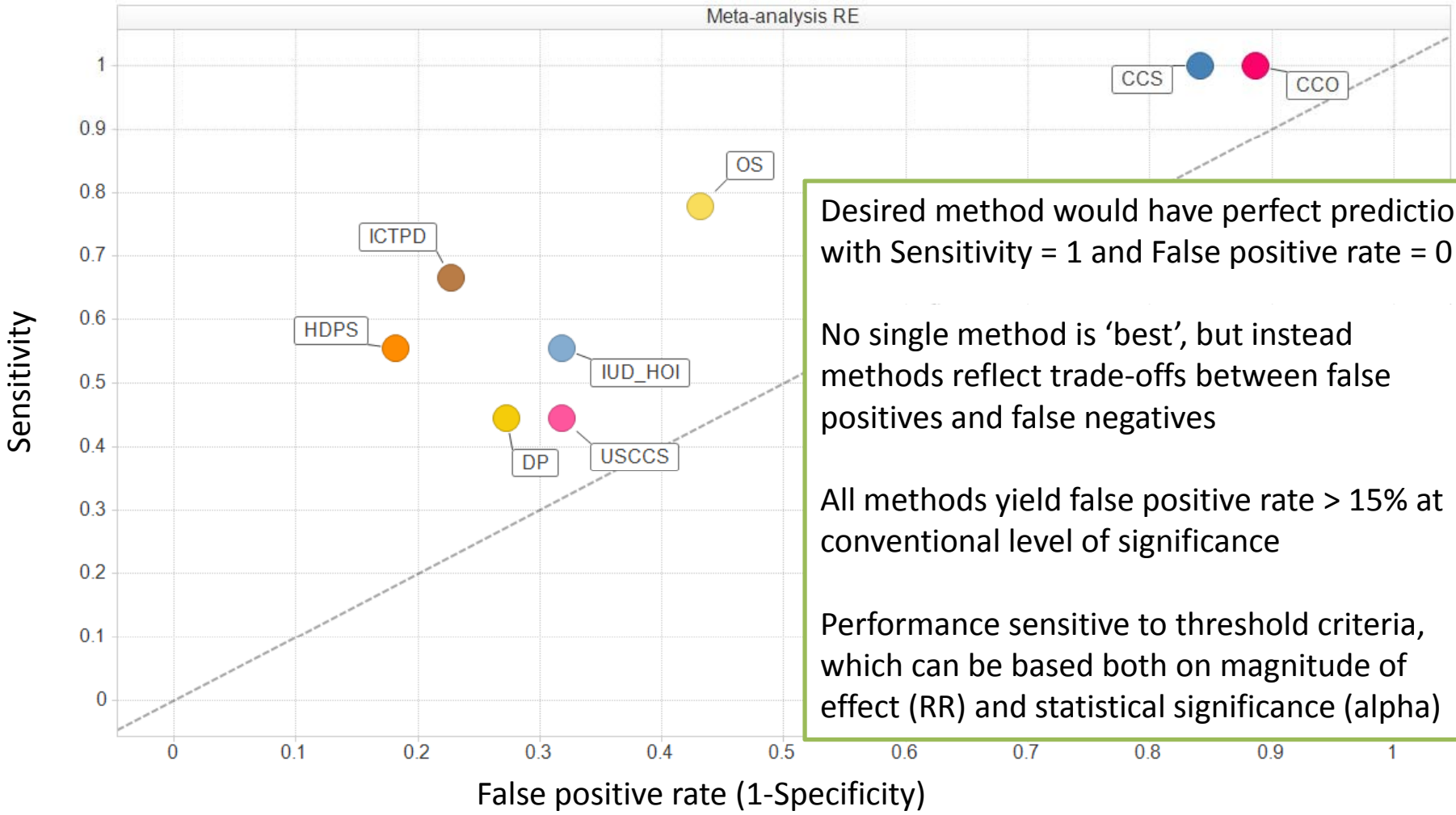
Comparing methods by sensitivity and specificity at alpha=0.05



Desired method would have perfect prediction with Sensitivity = 1 and False positive rate = 0

No single method is 'best', but instead methods reflect trade-offs between false positives and false negatives

All methods yield false positive rate > 15% at conventional level of significance

Performance sensitive to threshold criteria, which can be based both on magnitude of effect (RR) and statistical significance (alpha)

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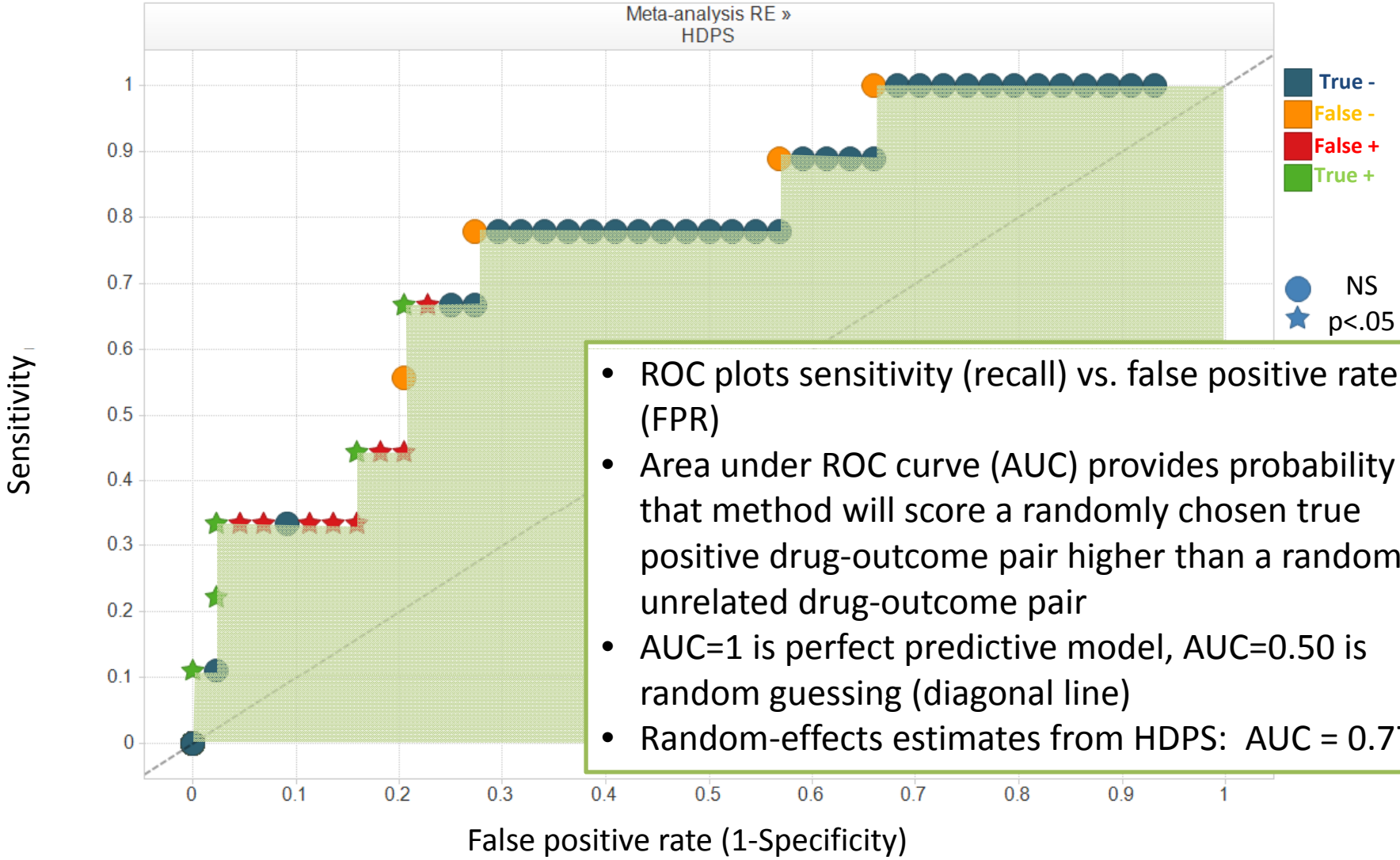
Receiver Operating Characteristic (ROC) curve



- ROC plots sensitivity (recall) vs. false positive rate (FPR)
- Area under ROC curve (AUC) provides probability that method will score a randomly chosen true positive drug-outcome pair higher than a random unrelated drug-outcome pair
- AUC=1 is perfect predictive model, AUC=0.50 is random guessing (diagonal line)
- Random-effects estimates from HDPS: AUC = 0.77

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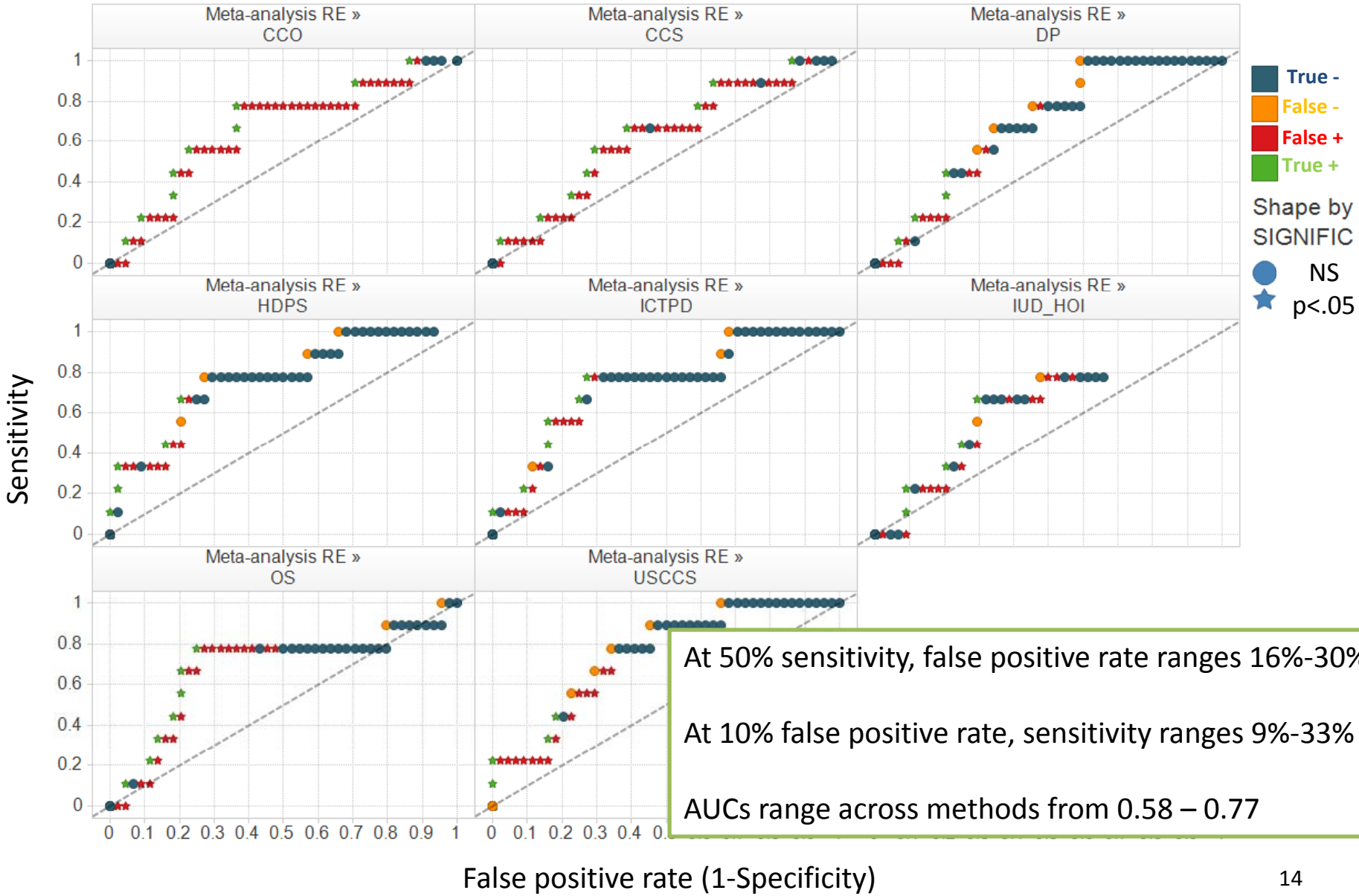
ROC curves of random-effects meta-analysis estimations for all methods



At 50% sensitivity, false positive rate ranges 16%-30%

At 10% false positive rate, sensitivity ranges 9%-33%

AUCs range across methods from 0.58 – 0.77

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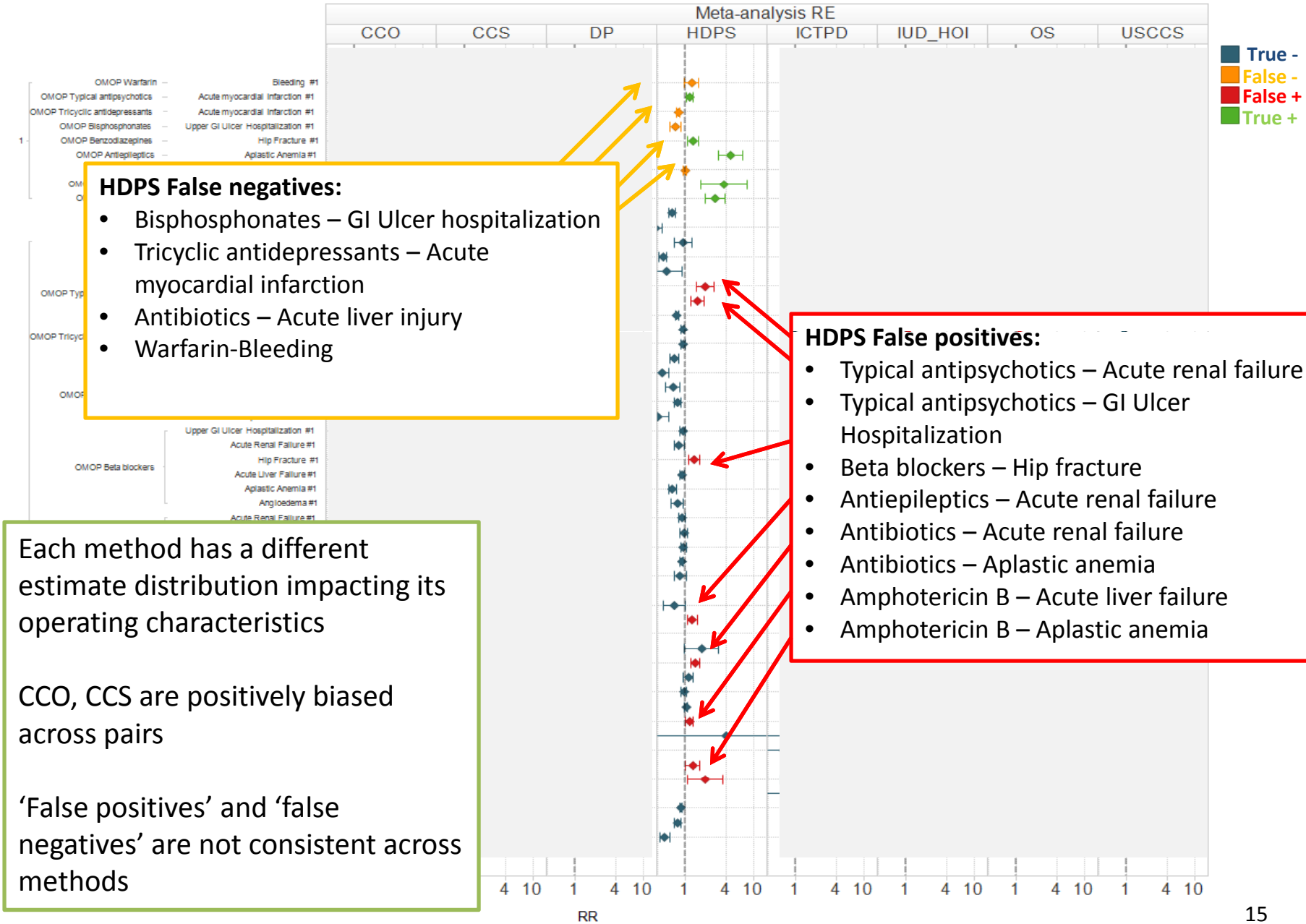
Distribution of estimates across all drug-outcome pairs



HDPS False negatives:

- Bisphosphonates – GI Ulcer hospitalization
- Tricyclic antidepressants – Acute myocardial infarction
- Antibiotics – Acute liver injury
- Warfarin-Bleeding

HDPS False positives:

- Typical antipsychotics – Acute renal failure
- Typical antipsychotics – GI Ulcer Hospitalization
- Beta blockers – Hip fracture
- Antiepileptics – Acute renal failure
- Antibiotics – Acute renal failure
- Antibiotics – Aplastic anemia
- Amphotericin B – Acute liver failure
- Amphotericin B – Aplastic anemia

Each method has a different estimate distribution impacting its operating characteristics

CCO, CCS are positively biased across pairs

'False positives' and 'false negatives' are not consistent across methods

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