ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable Webinar: Highlights from the Observational Medical Outcomes Partnership (OMOP) Annual Symposium

Patrick Ryan, Associate Director, Analytical Epidemiology, Johnson & Johnson Pharmaceutical Research and Development and Co-Investigator, Observational Medical Outcomes Partnership

March 17, 2011

Brookings Roundtable on Active Medical Product Surveillance

Some Initial Housekeeping

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or '*6'. (To unmute, press '*7' as well.)
- **There will be opportunities for questions and discussion throughout today's session. Please use the Q&A tab at the top of your screen to submit your questions into the queue at any point and we will call upon you to state your question.**
- We will open up the lines for questions from those participating only by phone at the end of each Q&A session.
- Call the Brookings IT Help Desk at 202-797-6193 with technical problems.

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Brookings Roundtable on Active Medical Product Surveillance: **Highlights from the OMOP Annual Symposium**

Patrick Ryan, on behalf of OMOP research team

March 17, 2011

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

Observational Medical Outcomes Partnership

Established to inform the appropriate use of observational healthcare databases for active surveillance by:

- **Conducting methodological research** to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues
- **Developing tools and capabilities** for transforming, characterizing, and analyzing disparate data sources
- **Establishing a shared resource** so that the broader research community can collaboratively advance the science

Methodological challenges for active surveillance

- A traditional pharmacoepidemiology study may conduct an analysis to estimate association of ONE drug and ONE outcome in ONE database at ONE point in time
- A national active surveillance system is envisioned to enable ONGOING monitoring of ANY medical product and ANY health outcome of interest across ALL databases in the network
- Methodological issues to be evaluated:
  - Precision
  - Accuracy
  - Value of information

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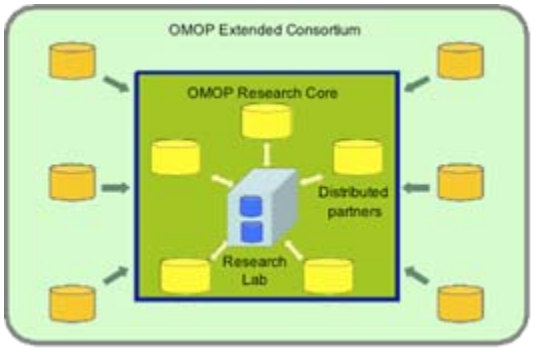
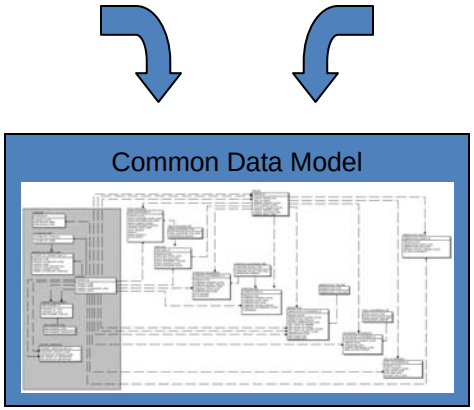
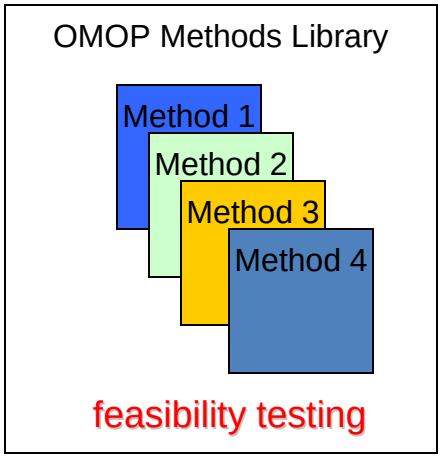
OMOP research experiment workflow







Drug

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

OMOP 2011 Symposium Agenda

- Method Performance Results from the Health Outcomes of Interest Experiment Presentation and Panel Discussion
- Lessons Learned from Systematic Observational Analysis Presentations and Panel Discussion
  - Standardized Tools for Data Characterization and Utility of Exploratory Visualization
  - Managing Data Quality for an Active Surveillance System
  - Implications of Health Outcomes of Interest Definitions – Acute Liver Injury Case Study
- Future Research and Applications Beyond Drug Safety Signal Refinement
  - Opportunities for Signal Detection in an Active Surveillance System
  - OMOP Methods Application for Comparative Effectiveness
  - OMOP's Future
- Summary - How OMOP Informs the National Effort
- Open Q/A with the OMOP Research Investigators

From OMOP 2011 Symposium
What You Will Hear Today…

- Patrick Ryan and David Madigan: **"Method Performance Results from the HOI Experiment"**
- No one clear 'best' method, as it depends on tolerance for false positives vs. false negatives
- Systematic pharmacoepidemiology can achieve
  - 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

- You need a relative risk > 2 to have confidence in result ….detecting effects smaller than 2 will incur higher risk of false positives

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Method Performance Results from the HOI Experiment:

- Method performance can vary by data source, drug, and outcome
- Method estimates are sensitive to outcome definitions and parameter settings
- Need to develop strategies for principled parameter selection and implement comprehensive sensitivity analyses for evaluating the robustness of any findings
- Additional research across a broader array of test cases is needed to fully characterize expected method behavior to improve confidence in the results that are obtained

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From OMOP 2011 Symposium
What You Will Hear Today…

- Paul Stang: **"Standardized Tools for Data Characterization and Utility of Exploratory Visualization"**
  - Overview of the characteristics of the databases used in OMOP - Detailed understanding of the characteristics of datasets is a prerequisite for active drug safety surveillance
  - Standardized methods, e.g. OSCAR and NATHAN, have been developed in OMOP to characterize data sources
  - Visualizations of data can provide additional insights and is useful in the interpretation of findings
  - The OMOP drugs of interest and HOIs are made up of a large set of drugs and conditions, each of which could have unique behavior that should be considered. We need a comprehensive view of these populations.

From OMOP 2011 Symposium
What You Will Hear Today…

- Christian Reich: **"Managing Data Quality for an Active Surveillance System "** which is about data processing and issues, quality of ETL, quality of vocabulary mapping, and detection of data anomalies.
  - Drug surveillance relies on high quality of data
  - OMOP has manipulated data in two ways: conversion to CDM and changing terminologies
  - Christian will discuss the development of standardized tools used for managing data quality

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From OMOP 2011 Symposium
What You Will Hear Today…

- Judy Racoosin: "**Implications of Health Outcomes of Interest Definitions – Acute Liver Injury Case Study"**
  - Use of administrative claims data for active drug safety surveillance requires using algorithms of codes to identify cases of given HOIs
  - The systematic review for the HOI "acute liver injury" did not identify algorithms that had good PPV
  - Requirement for relevant procedures and labs was added to some of the definitions to investigate the potential for improved capability for identifying true cases
  - NATHAN can help refine a potential HOI definition by optimizing selection of pertinent inclusion and exclusion criteria

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OMOP Methods Evaluation

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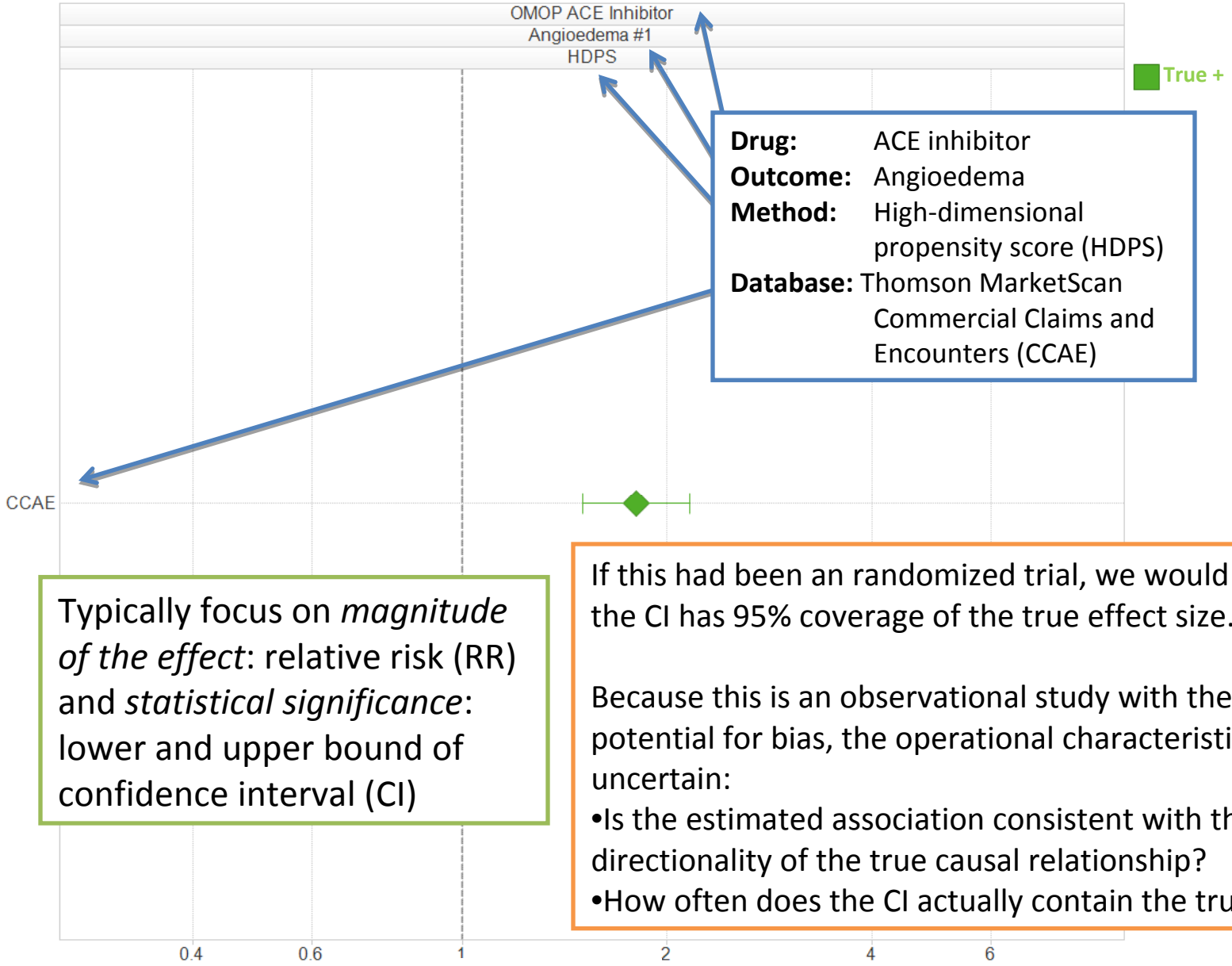
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



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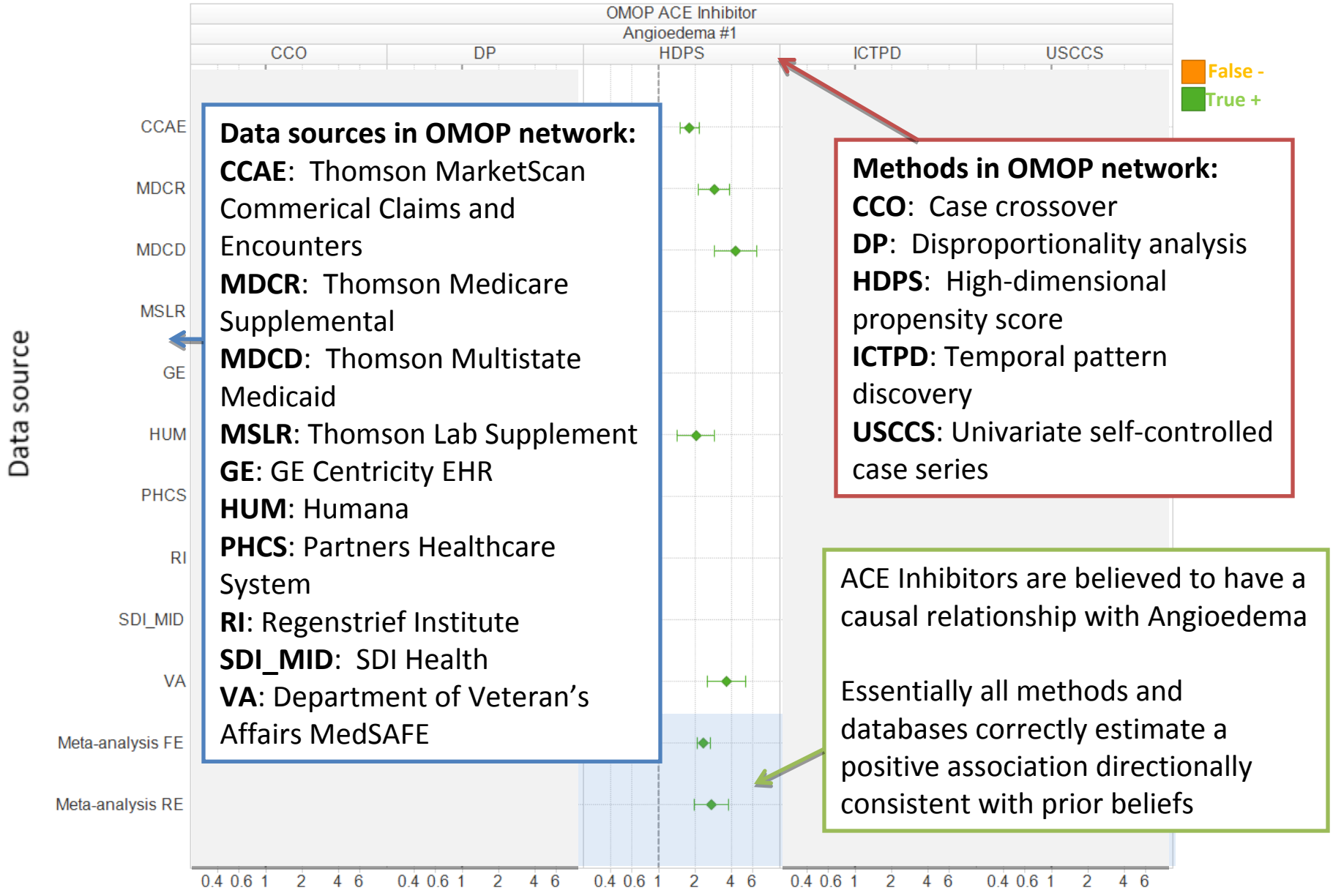
Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



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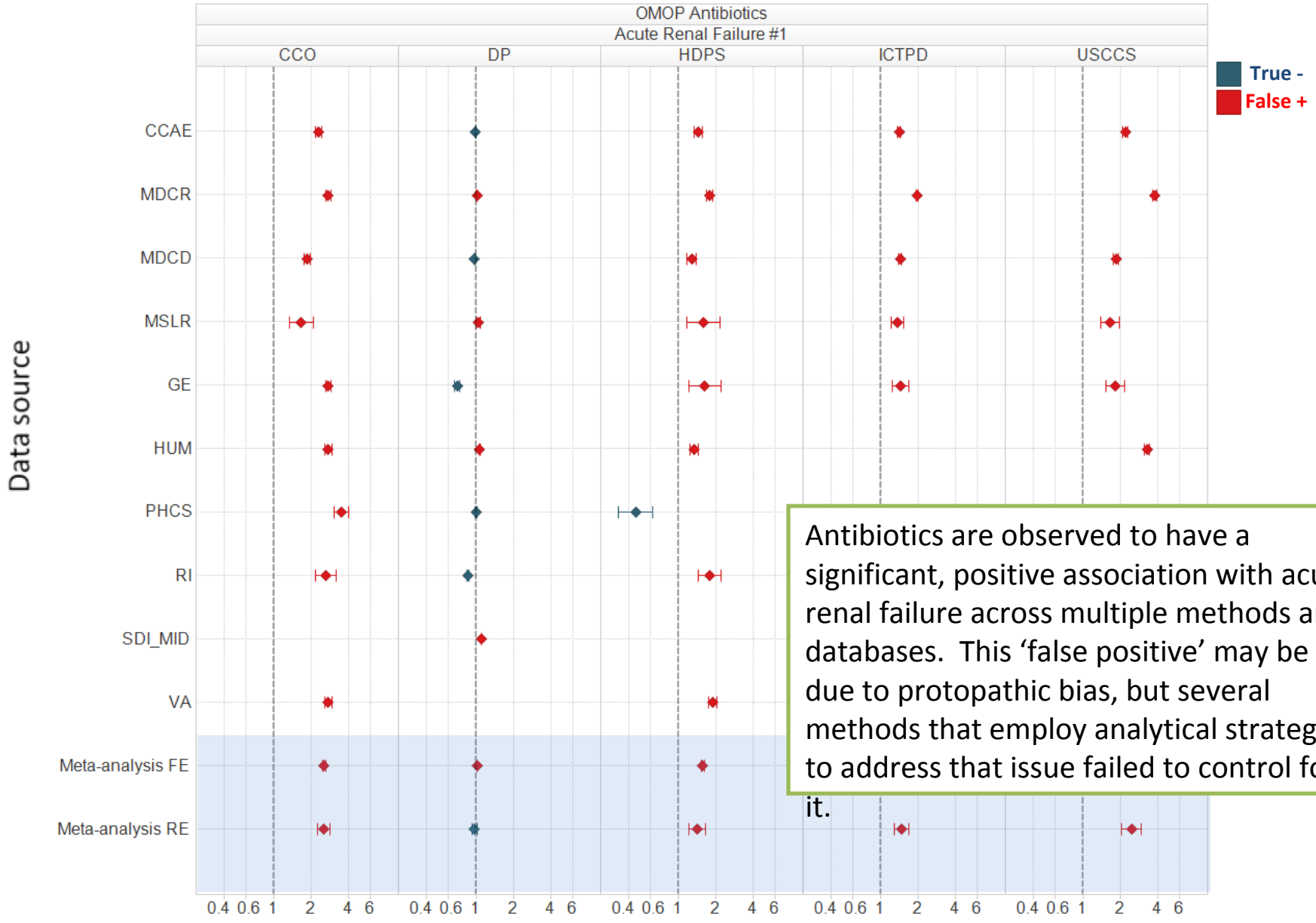
Consistent ‘false positive’ observed for ‘negative control’ of Antibiotics and Acute Renal Failure



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.

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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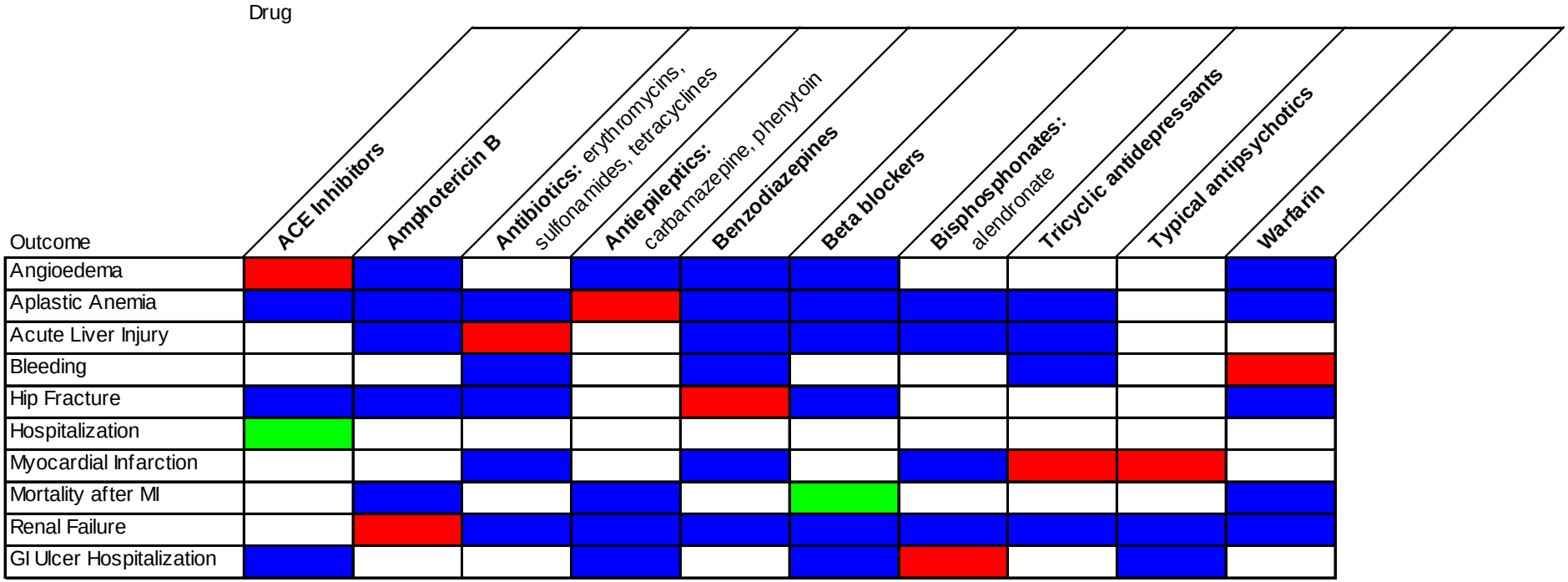
‘Ground truth’ assumed for Monitoring Health Outcomes of Interest



Legend	Total
True positive' benefit	2
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http://omop.fnih.org/OMOPWhitePapers

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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

http://omop.fnih.org/MethodsLibrary

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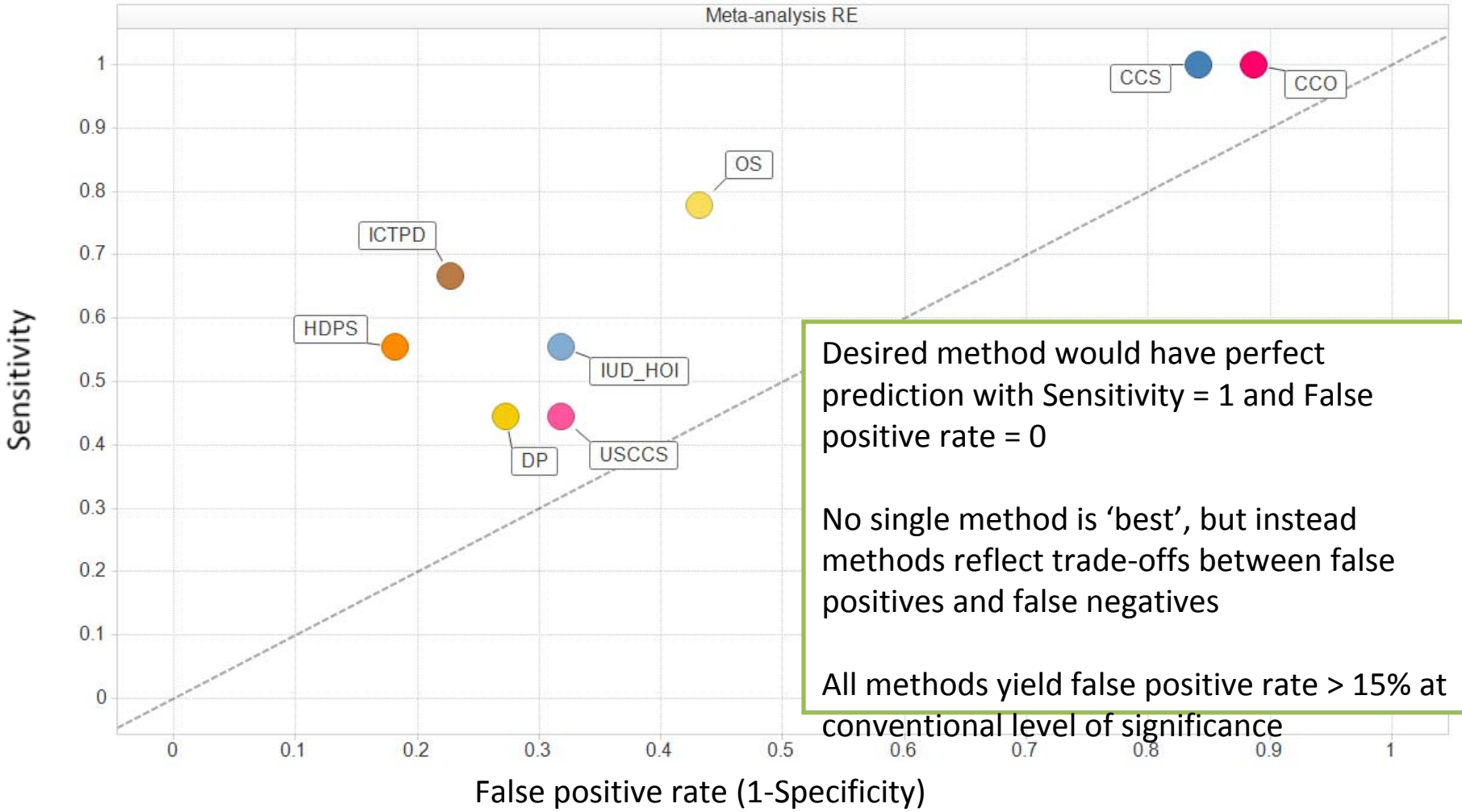
Comparing methods by sensitivity and specificity at alpha=0.05



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

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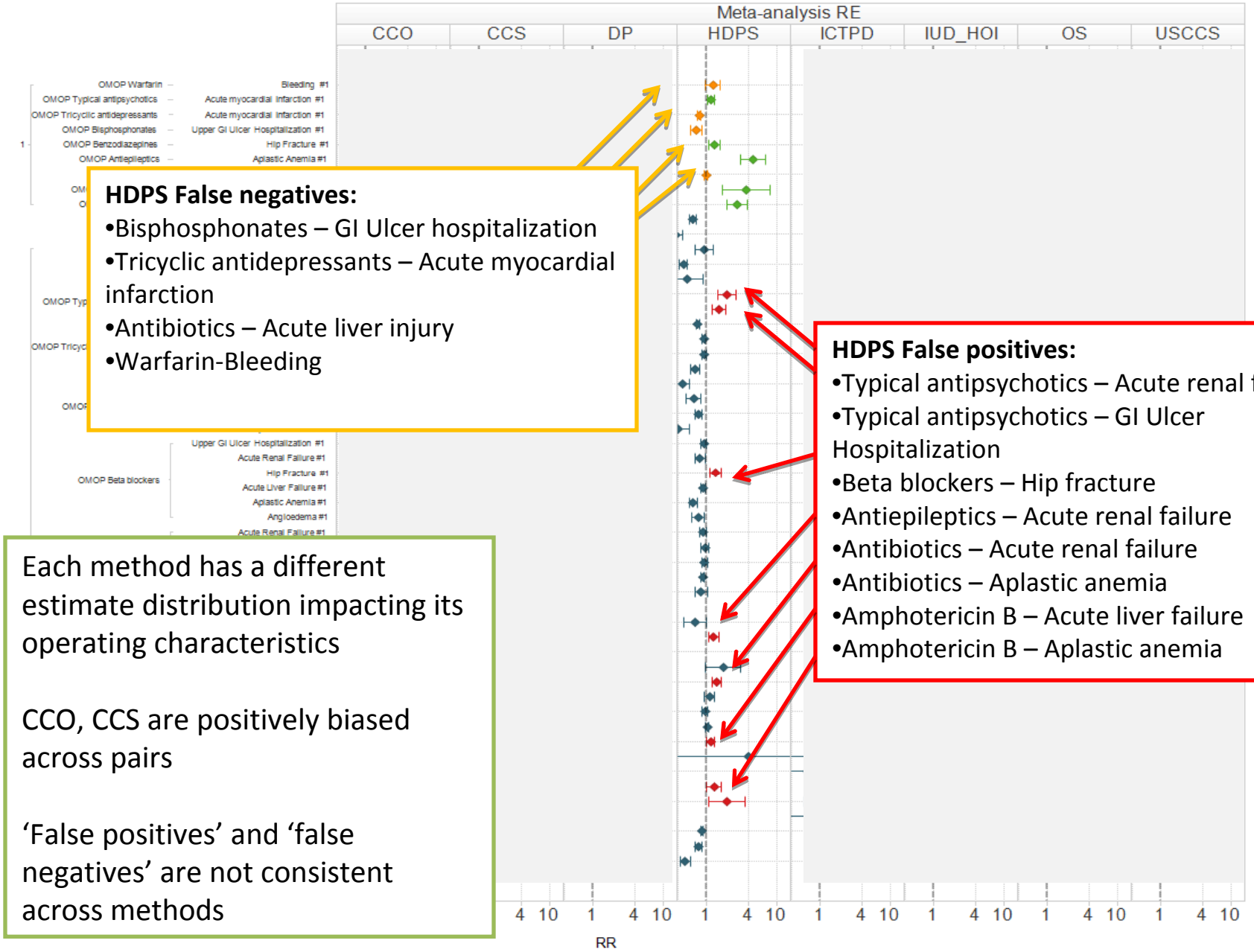
Distribution of estimates across all drug-outcome pairs



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

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
- Systematic pharmacoepidemiology can achieve:
  - 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
- You need a relative risk > 2 to have confidence in result ….detecting effects smaller than 2 will incur higher risk of false positives

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Roundtable Discussion and Questions

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