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Establishing Operating Characteristics of Active Surveillance Approaches

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on behalf of OMOP Research Team
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Full results and audio presentations from OMOP Symposium available at:
http://omop.fnih.org/OMOP2011Symposium

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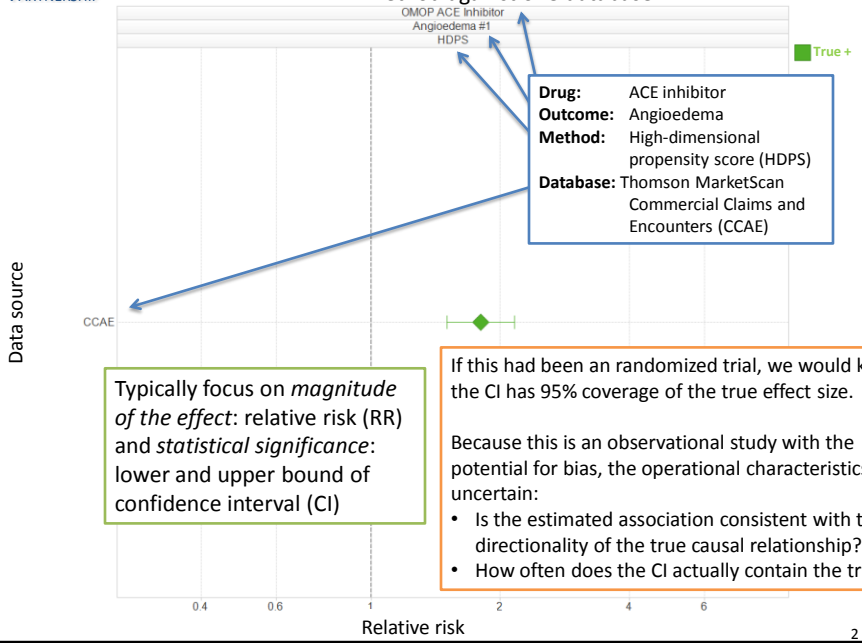
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



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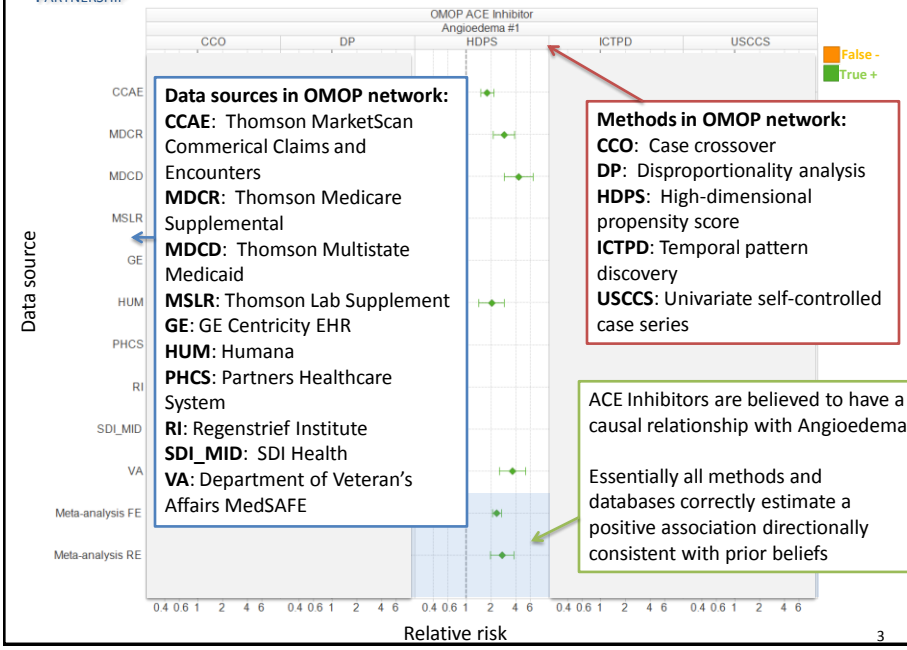
Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



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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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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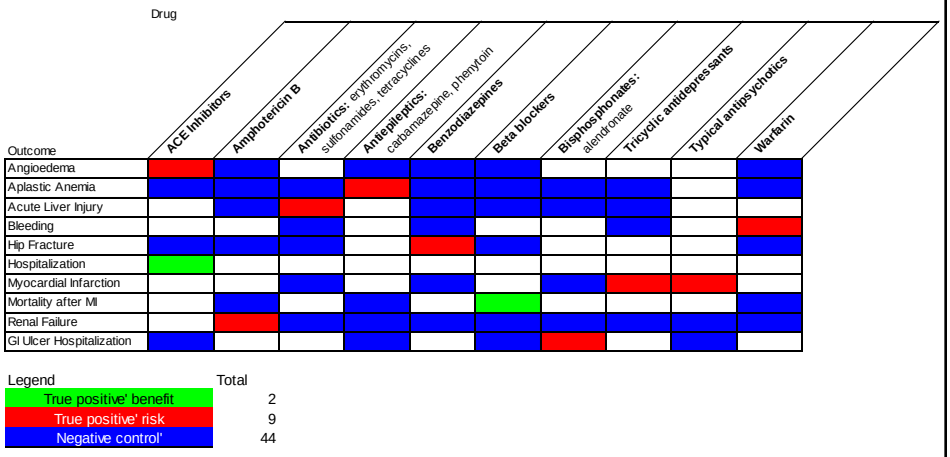
'Ground truth' assumed for Monitoring Health Outcomes of Interest



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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)	Harvard Medical School / 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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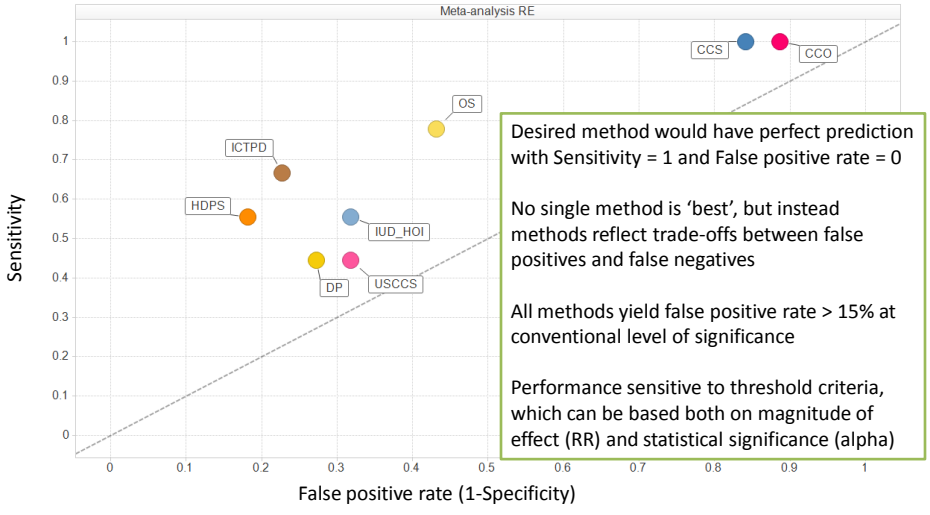
Comparing methods by sensitivity and specificity at alpha=0.05



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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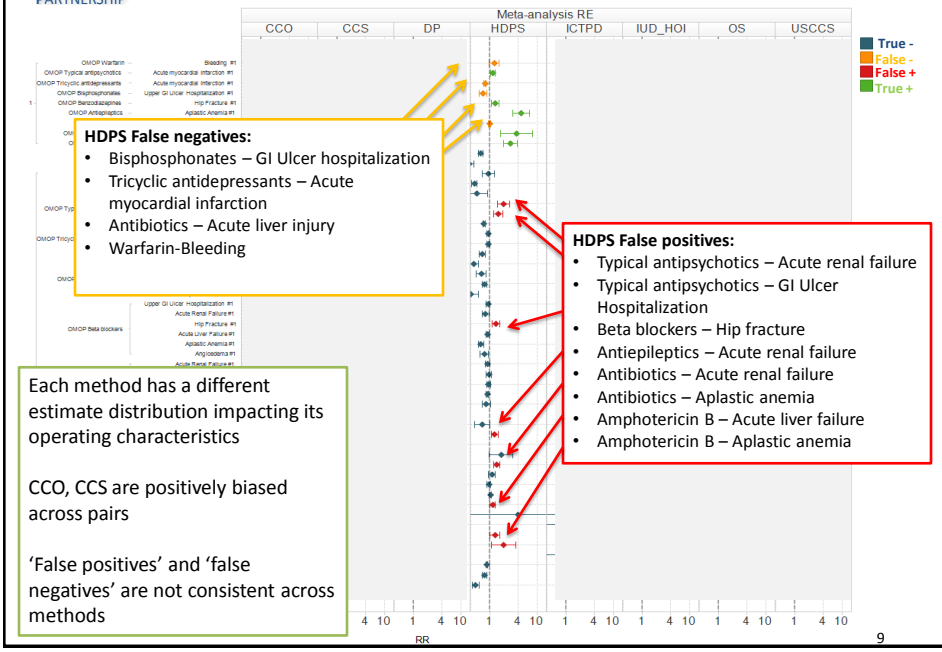
Distribution of estimates across all drug-outcome pairs



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

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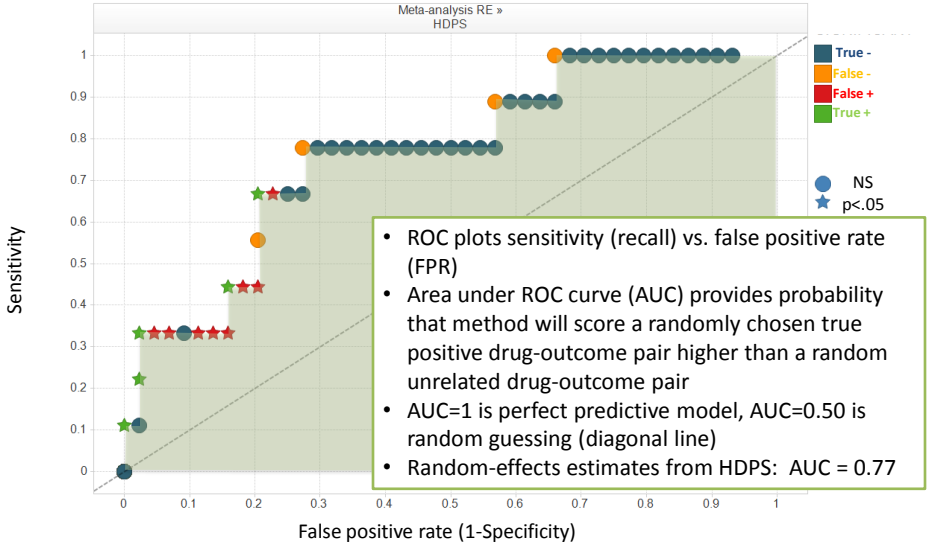
Receiver Operating Characteristic (ROC) curve



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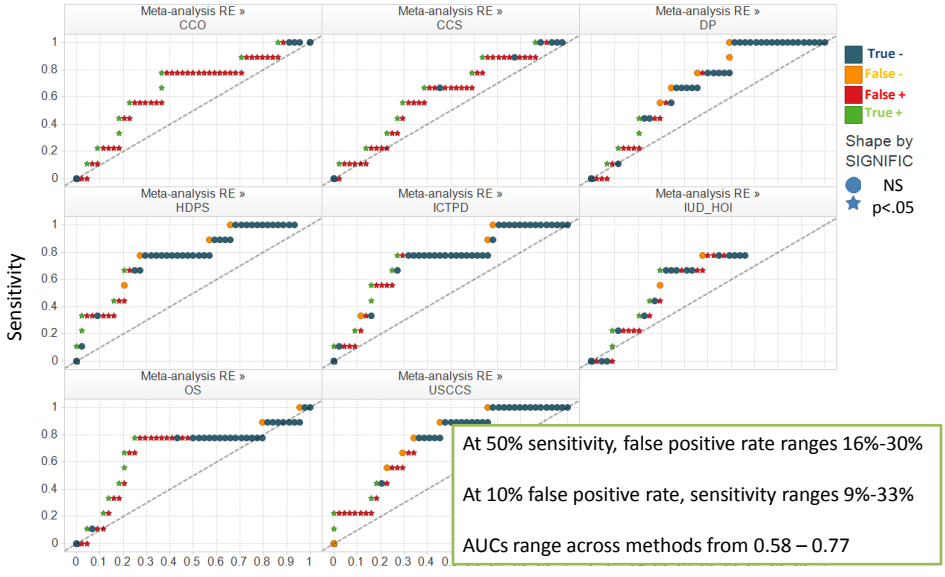
ROC curves of random-effects meta-analysis estimations for all methods



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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So given these operating characteristics, what can we expect to do in practice….

- Use case: An emerging safety concern is raised for a new medical product. The association between the drug and outcome could be estimated by running an OMOP active surveillance method across the network of observational databases
  - The method will produce a relative risk and standard error from each participating data source, which can then be pooled together in a meta-analytic framework
  - Hypothetical scenario: The random-effects meta-analysis yields an RR=2.0 with SE=0.06.
  - Question: what is the probability that there is a true causal relationship given this observed association?
- Bayes rule enables such calculation…
  - p(true|RR,SE) ~ p(RR,SE|true)*p(true)
  - p(true) is the prior probability of true association; consider a family of priors: skeptical (0.1), indifferent (0.5), enthusiastic (0.9)
  - p(RR,SE|true) can be estimated from empirical data (OMOP experimental results)

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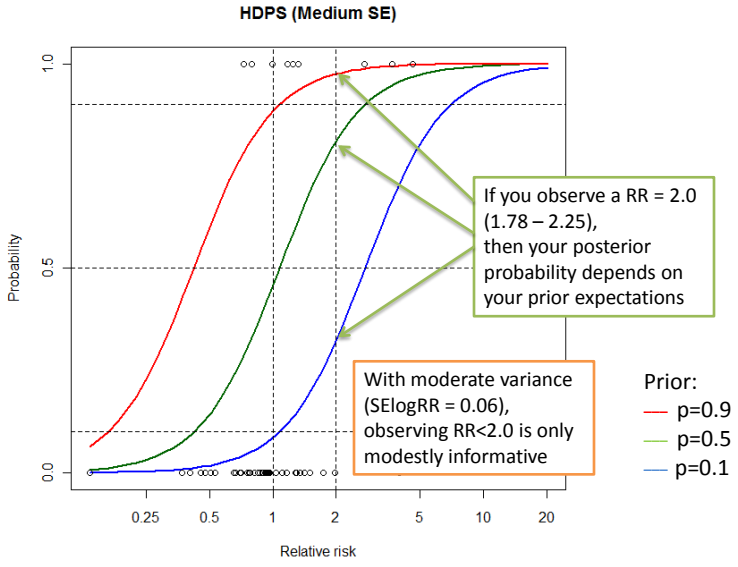
Revising prior expectations in light of new evidence from an active surveillance system



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Concluding thoughts

- Operating characteristics are fundamental to understanding how an active surveillance system can complement current practice to support a comprehensive safety assessment
- No one clear 'best' method, as it depends on tolerance for false positives vs. false negatives, but current evidence suggests system can achieve:
  - At 50% sensitivity, false positive rate ranges 16%-30%
  - At 10% false positive rate, sensitivity ranges 9%-33%
- Accuracy of a method when applied to all available data is only the start and may be optimistic
  - Newly marketed medical products accumulate exposures over time and the population exposed may shift
  - Timeliness of detection is an additional desired performance metric, but first depends on accuracy to know that timely findings are correct and stable
- Further empirical research needed to have more complete understanding of operating characteristics before widespread adoption
  - More test cases needed to describe overall performance and identify specific limitations of methods
  - Experiments need to be conducted in both real data and simulated data to provide a complete summary of method behavior

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