ENGELBERG CENTER for Health Care Reform at BROOKINGS

Overview of Additional Sentinel Initiative Activities:

Federal Partners Collaboration
The Observational Medical Outcomes Partnership
Brookings Institution's Convening Activities

Melissa Robb, U.S. Food and Drug Administration
Paul Stang, Johnson & Johnson and the Observational Medical Outcomes Partnership
Joshua Benner, Engelberg Center for Health Care Reform at Brookings

September 21, 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 several 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.

Federal Partners' Collaboration

Melissa Robb
Project Director, Sentinel Initiative
U.S. Food and Drug Administration

Safe Rx Project

- Collaboration between CMS and FDA
- Launched in 2008 at the time Medicare Part D data (prescription benefit) became available with support from HHS ASPE
- Evolved from earlier collaborations between CMS and FDA, primarily related to medical products covered by Medicare Part B
- Investigating ways to utilize Medicare and Medicaid medical product exposures and outcomes for active surveillance and full epidemiological studies

Scope

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- Small distributed system
  - Each Partner has unique data infrastructure
  - No common data model being utilized
- FDA proposes medical product – AE pairs
- Develop a shared protocol
- Assess interpretability of query findings resulting from a decentralized analytic approach

Planning Template

- CMS contractor Acumen has developed a template for planning the assessment
  - Phase 1: Define treatments, outcomes, and related health circumstances and medical interventions for analysis
  - Phase 2: Describe analysis populations and compare populations for outcome events

- Template has been refined through discussions with Federal Partners and use in active surveillance assessments

Examples of Assessments

- Antiviral drugs and neuropsychiatric adverse events
- Dronedarone and heart failure

Ongoing Challenges

- Limits to analysis approaches with rare outcomes
- Develop approaches to make most of claims data to enhance outcome validation given limited access to source data
- Interpretation of findings given diverse Federal Partner populations and differences in clinical guidelines and practice

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Overview of Recent Work from the Observational Medical Outcomes Partnership

Paul Stang
on behalf of OMOP Research Team
September, 2011

Note that all OMOP work products are posted on our website:
http://omop.fnih.org

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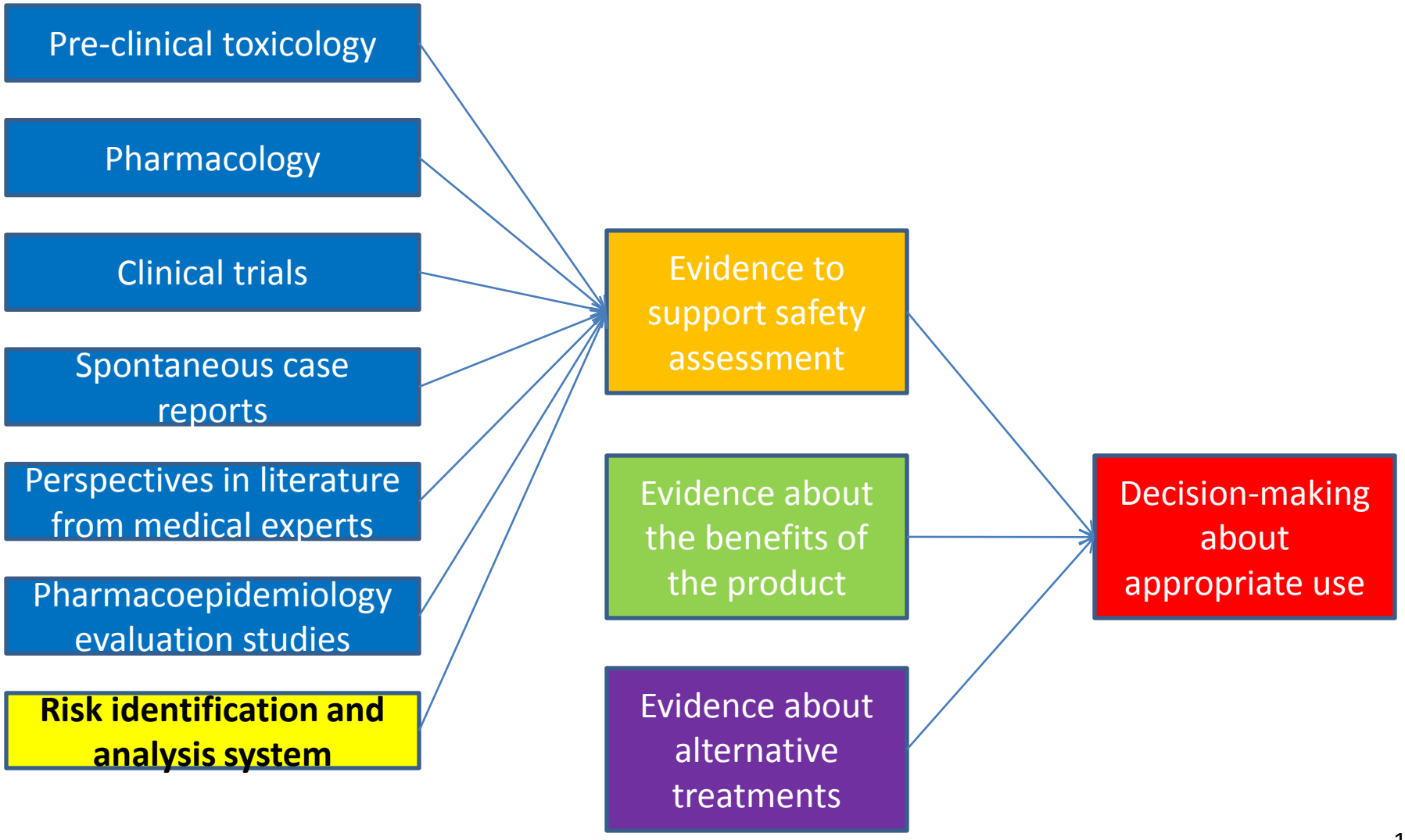
Risk identification and analysis system: One additional piece of evidence to inform medical decision-making



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Observational Medical Outcomes Partnership

Public-Private Research Partnership established to inform the appropriate use of observational healthcare databases for studying the effects of medical products:

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

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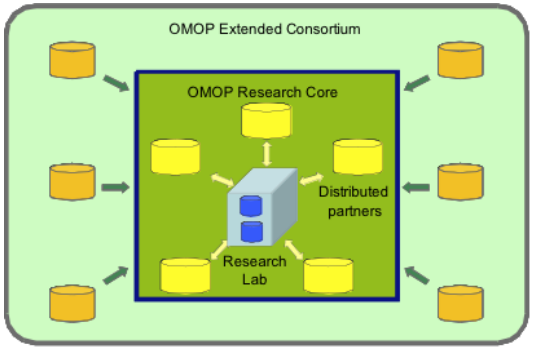
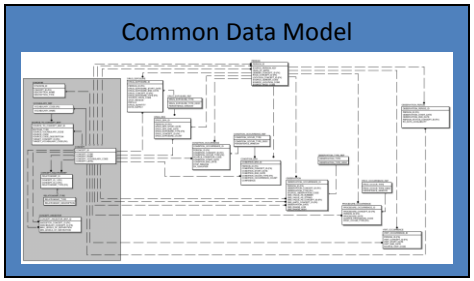
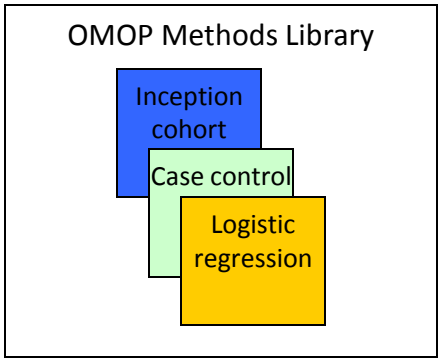
OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 200M+ lives

- Open-source
- Standards-based





- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data

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										

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Summary of OMOP's Efforts to Date

- Governance structure of public-private partnership
- Tools
  - Data: Common Data Model, Vocabulary mappings
  - Summarization: standardized programs providing disease natural history, data characteristics, data quality, cohort identification
  - Literature search strategy for definitions, studies
- Simulator (OSIM2) that can create research datasets
- Identification and coding of library of potential methods
- Initial findings from applying multiple configurations of the methods across databases in a small number of test cases

Variability and Diversity

- In data sources and across them
- In methods and the 'parameter settings' that can be used
- In how we define
  - population,
  - comparators,
  - exposures, and
  - outcomes

Challenge is whether we can empirically identify the best combination of these choices

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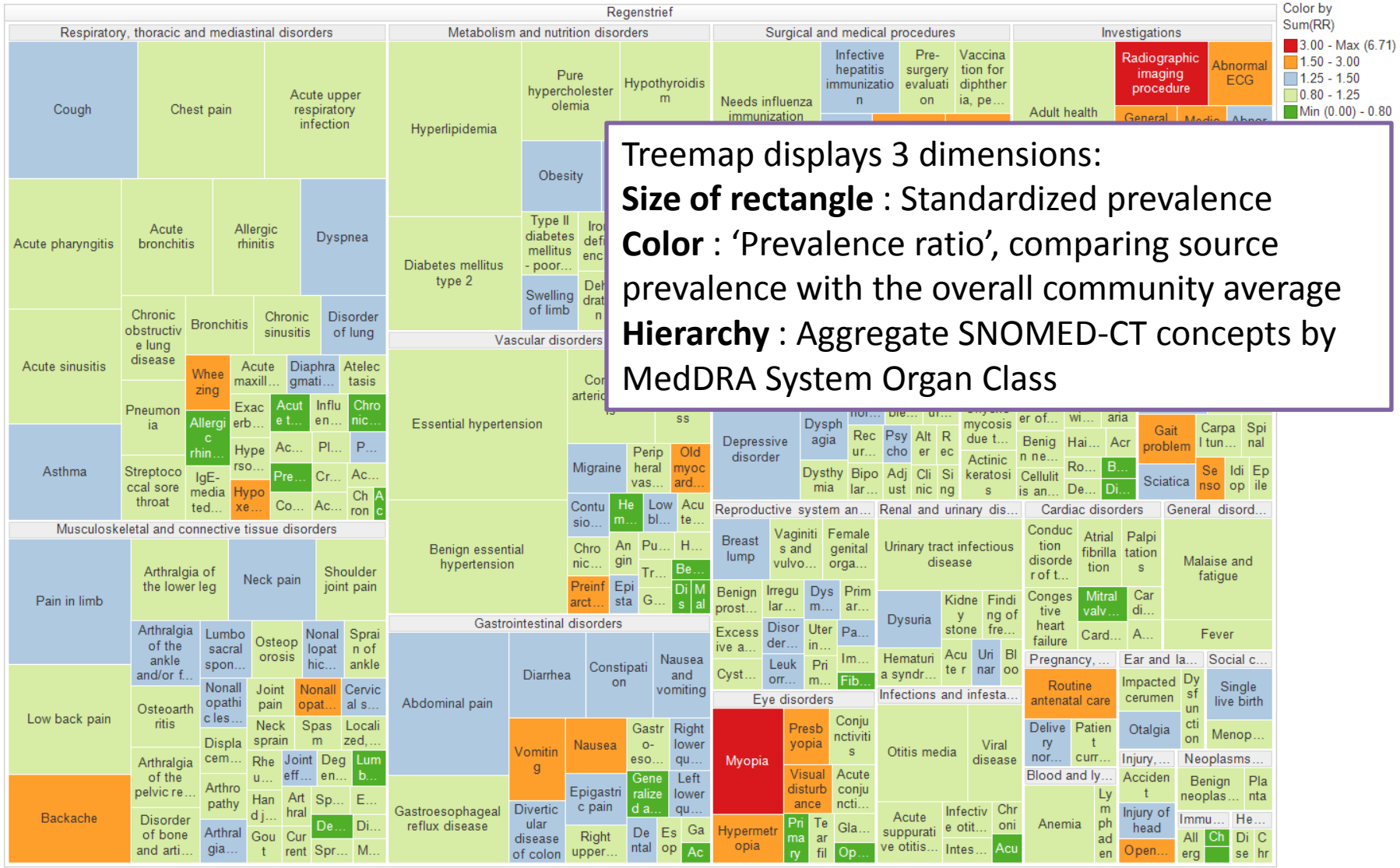
Variation across data sites: prevalence of all diseases in one site vs. the 'network'



Treemap displays 3 dimensions:

Size of rectangle : Standardized prevalence

Color : 'Prevalence ratio', comparing source prevalence with the overall community average

Hierarchy : Aggregate SNOMED-CT concepts by MedDRA System Organ Class

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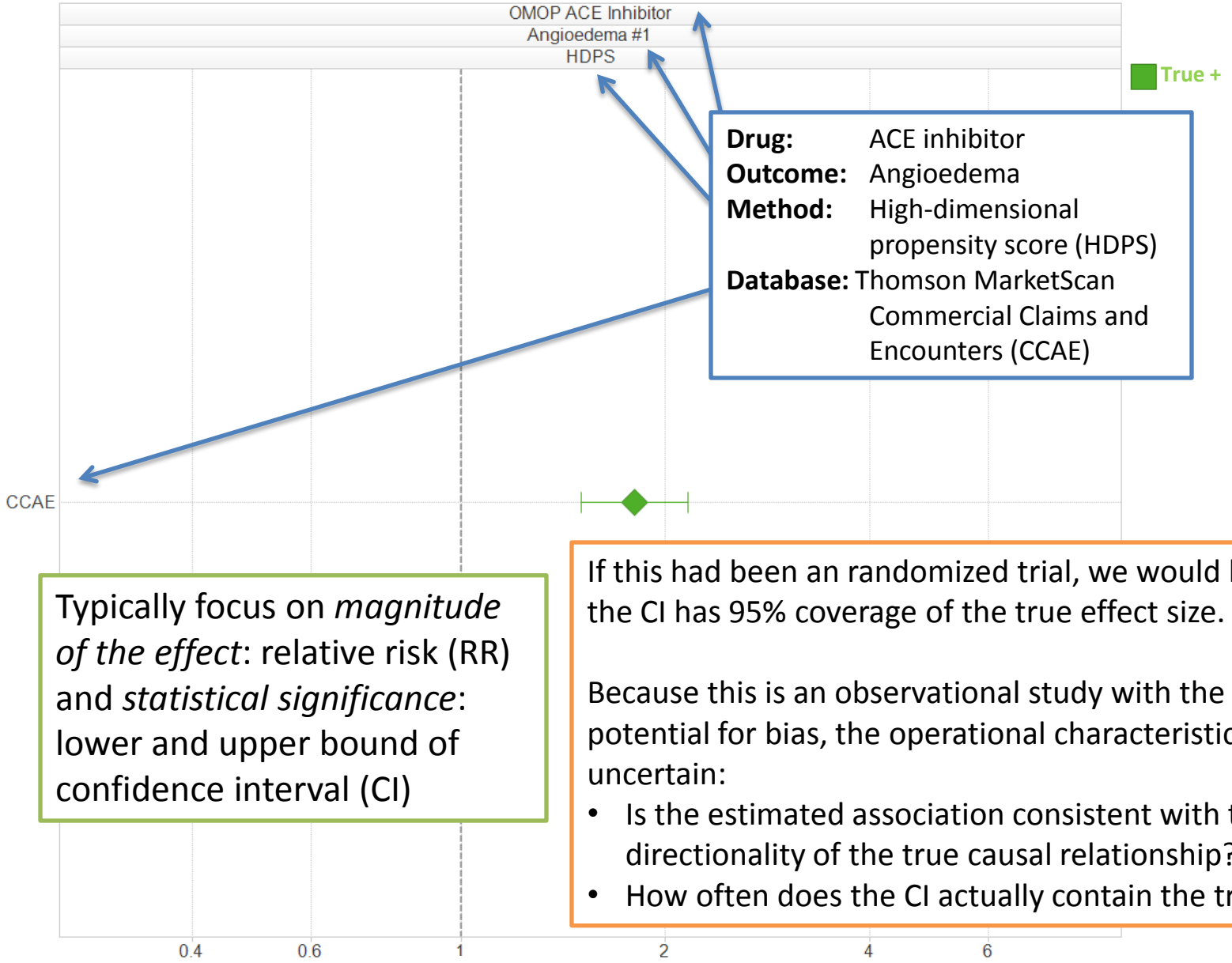
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



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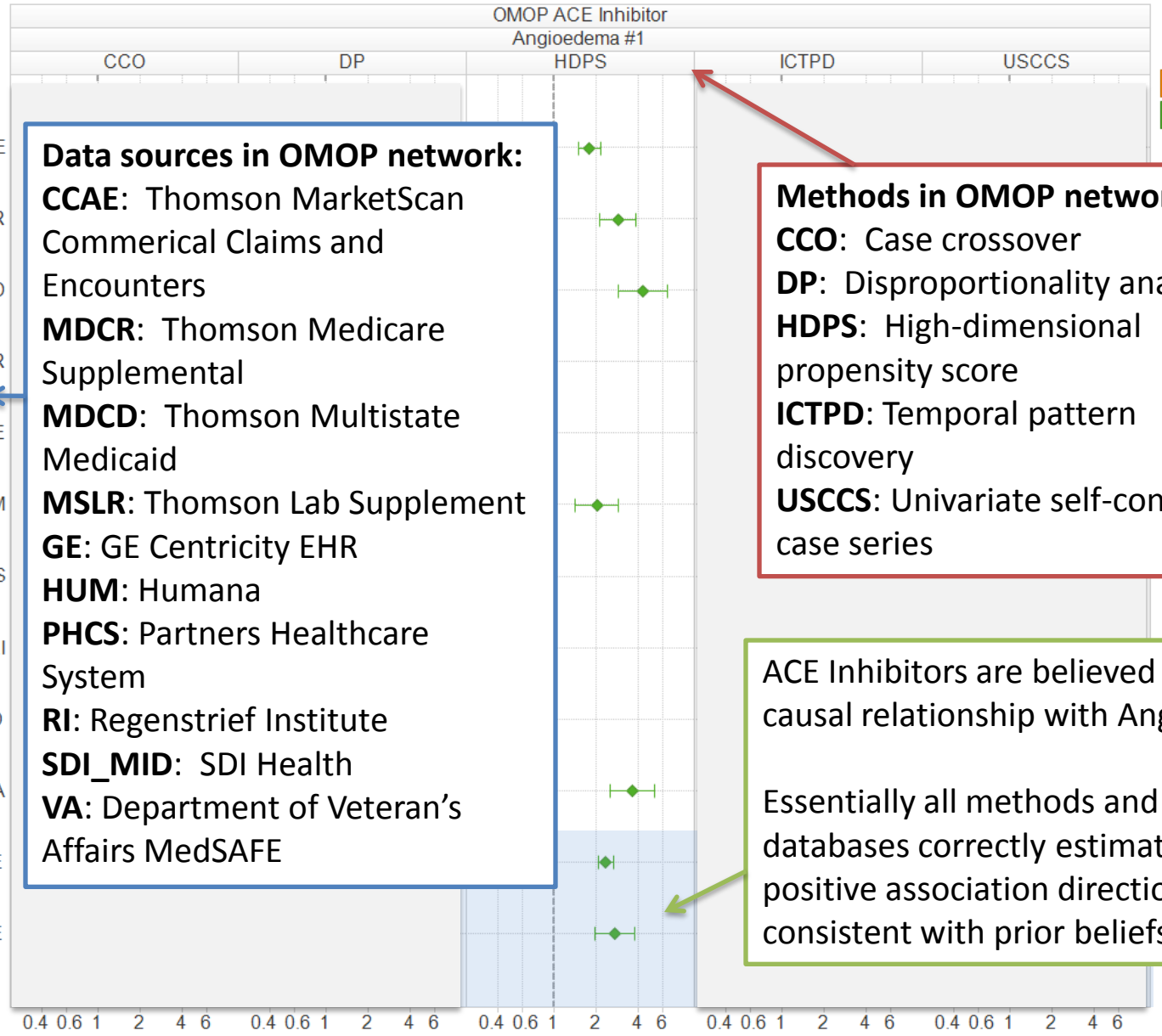
Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



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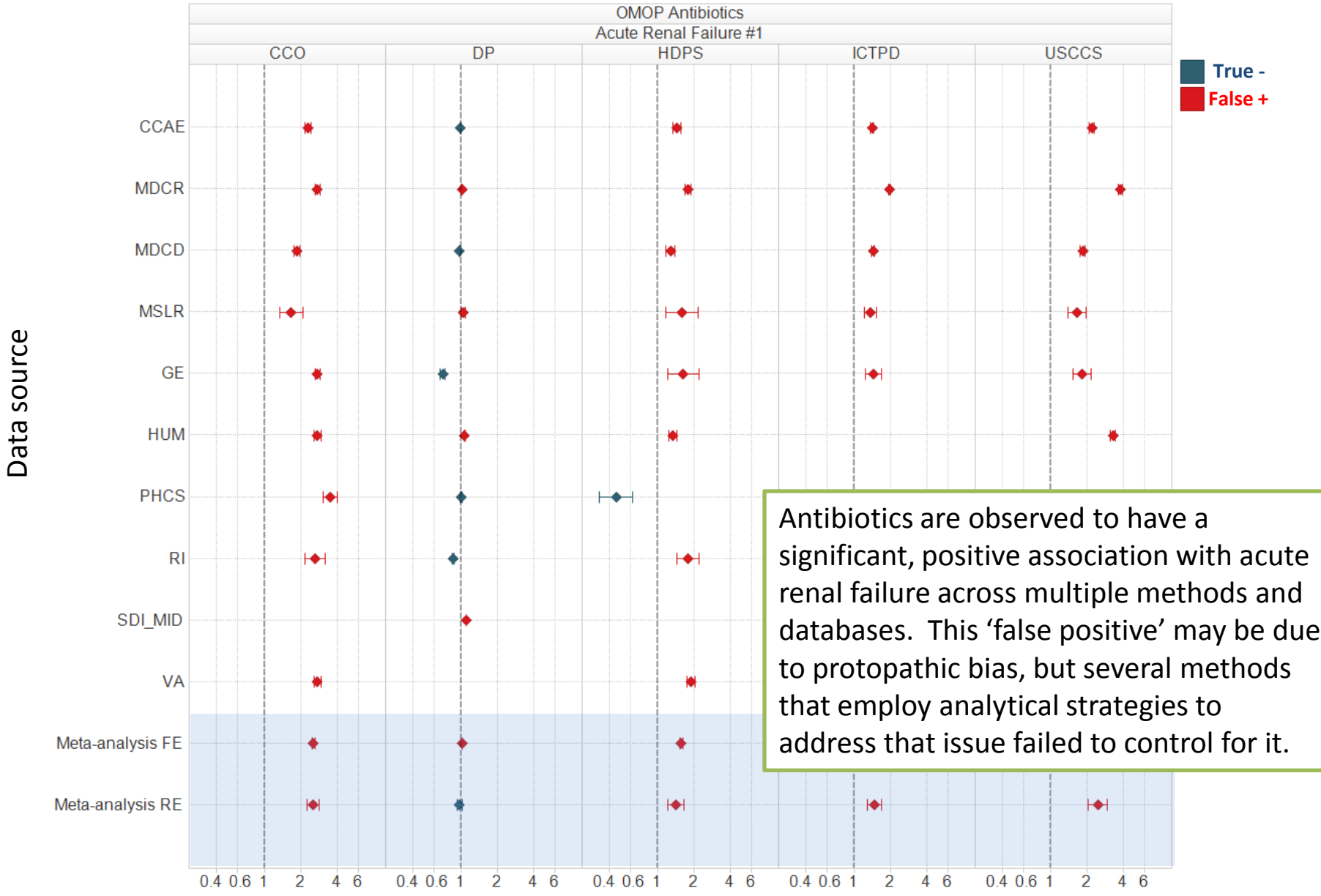
Consistent ‘false positive’ observed for ‘negative control’ of Antibiotics and Acute Renal Failure



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.

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Measuring method performance example: Random-effect meta-analysis of estimates from one Method

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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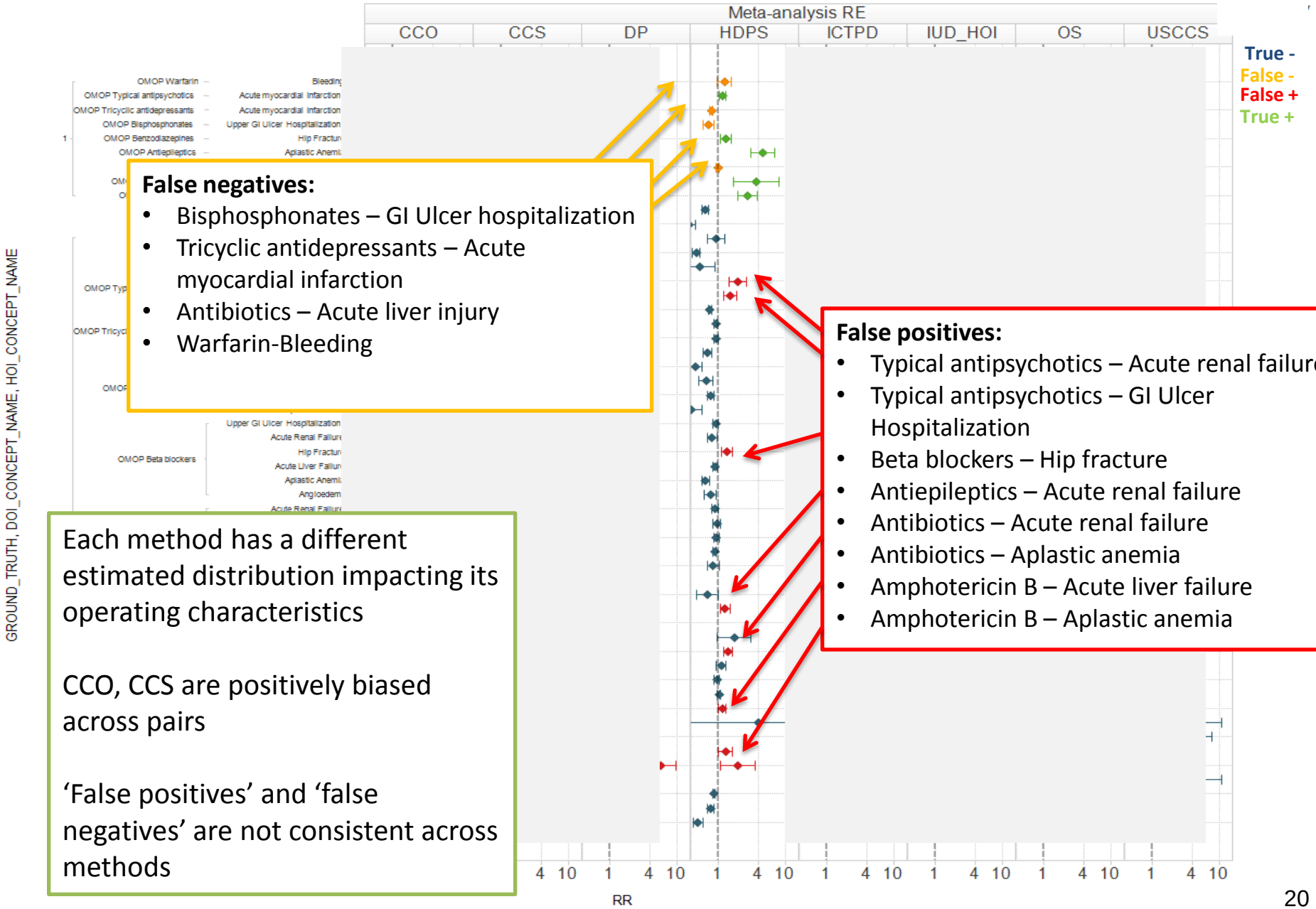
Distribution of estimates across all drug-outcome pairs



False negatives:

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

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 estimated 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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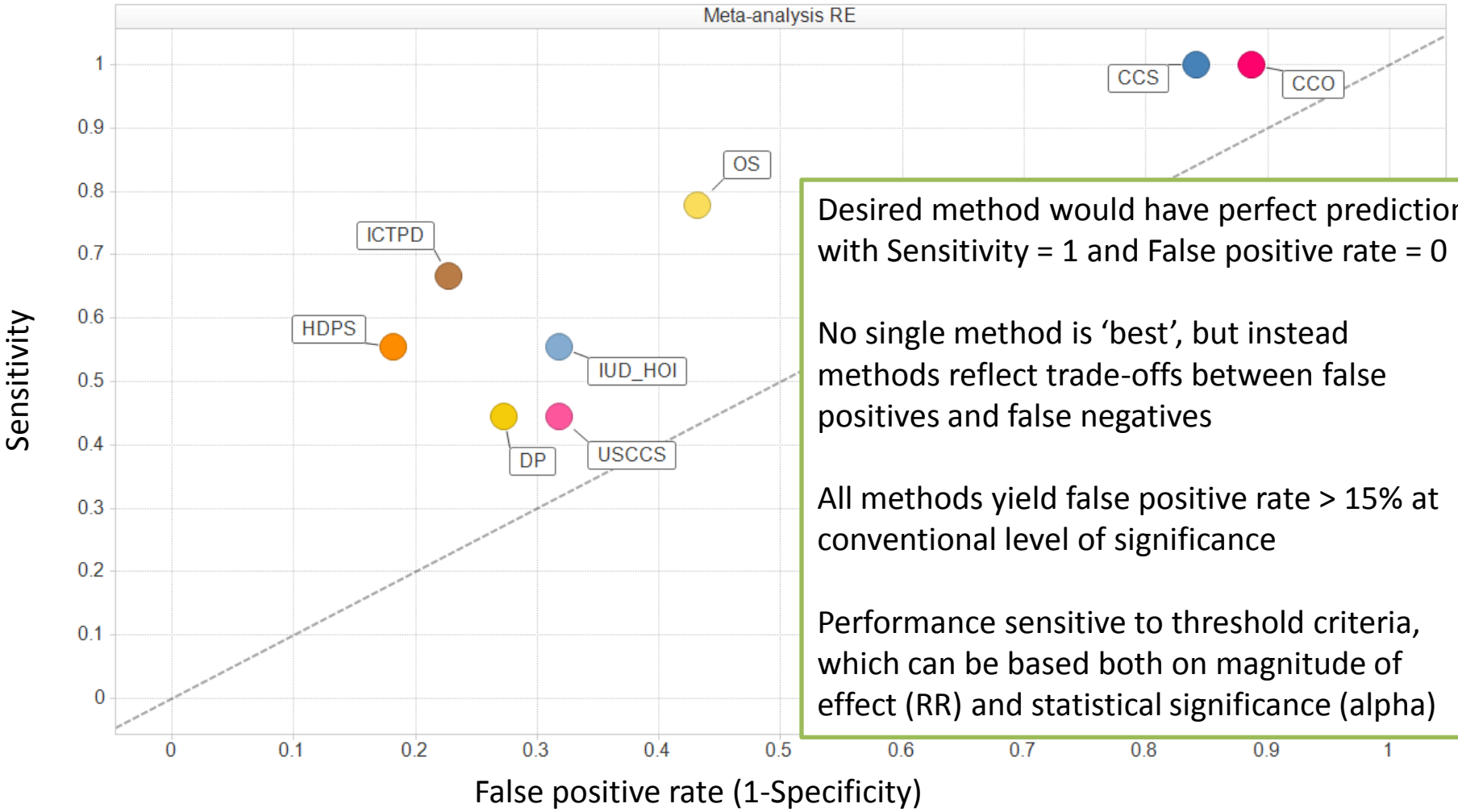
Comparing methods by sensitivity and specificity at alpha=0.05



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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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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OMOP 2011/2012 Research Agenda

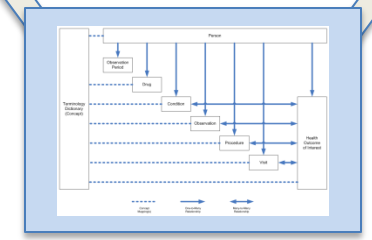
Drug-outcome pairs

	Positives	Negatives
Total	166	375
Myocardial Infarction	37	102
Upper GI Bleed	24	105
Acute Liver Injury	81	64
Acute Renal Failure	24	104

+ EU-ADR replication

- Improve HOI definitions
- Explore false positives

• Evaluate study design decisions (EDDIE)



Methods development

Methods enhancements
- *Multivariate self-controlled case series*

Increased parameterization
- *Case-control, new user cohort designs*

Application of existing tools
- *ICTPD, OS, LGPS, DP*

• Expand CDM for additional use cases

Observational data

Real-world performance:

+ OMOP Distributed Partners
+ EU-ADR network

Simulated data:

signal
- Strength (RR)
- Type (timing)

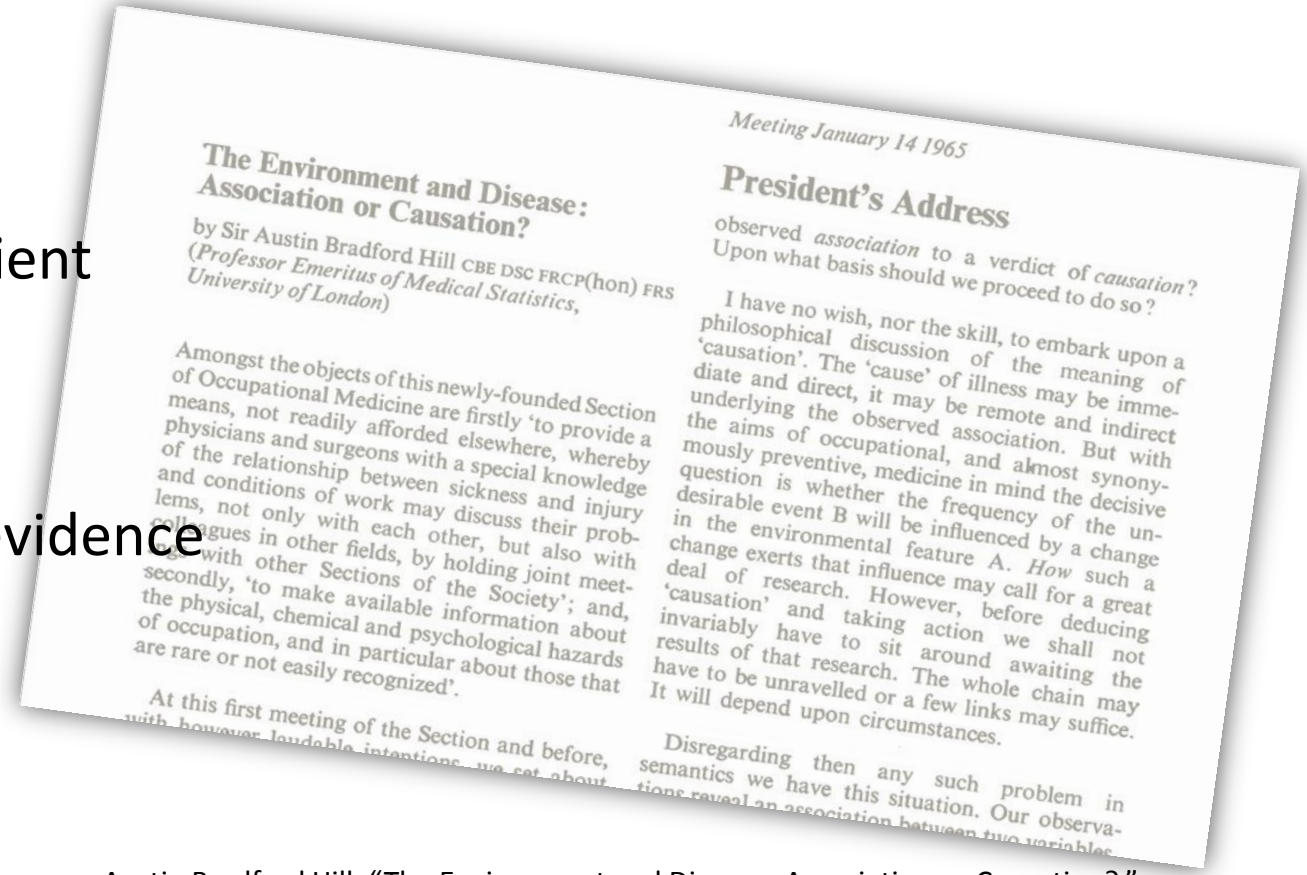
data type
- Claims vs. EHR
- Privately insured vs. Medicare vs. Medicaid

population size

1/10/50m patients

Hill's causality viewpoints

- Strength of association
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy



Meeting January 14 1965

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before,

President's Address

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observa-

Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

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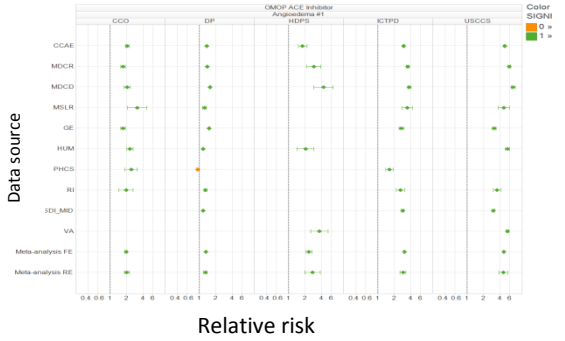
Vision for a risk identification and analysis system ‘causal dashboard’

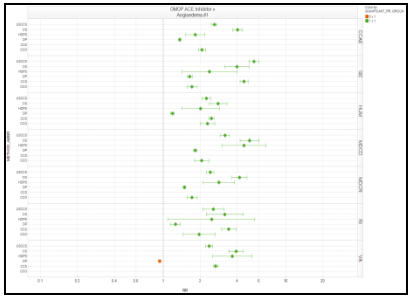
Drug Tricyclic antidepressants ▼ **Outcome** Acute myocardial infarction ▼

Strength of association

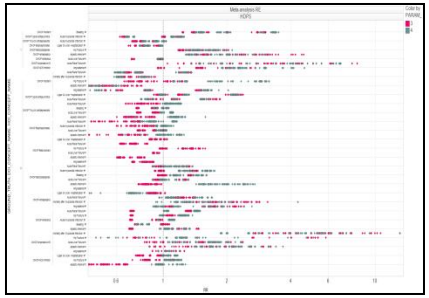


Consistency

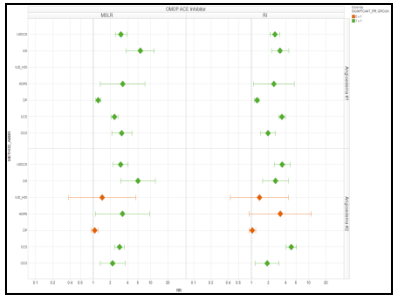
by data source



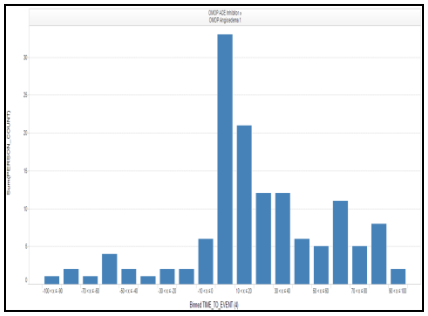
by method and parameters



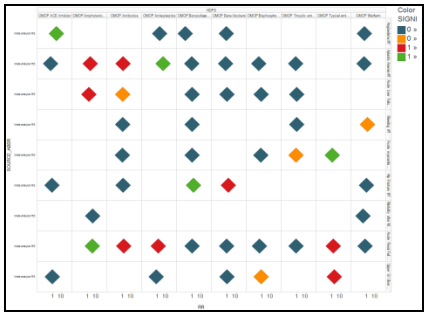
by outcome definition



Temporality

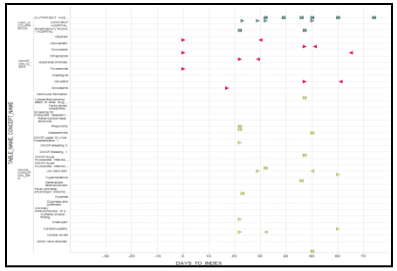


Specificity

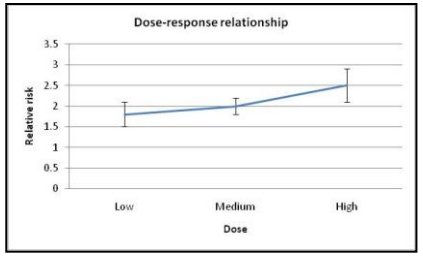


Plausibility

Interactive patient profiles



Biological gradient

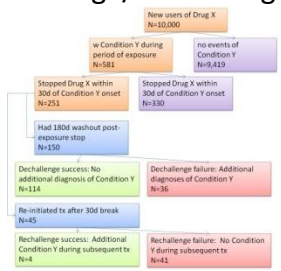


Analogy

Explore related conditions and treatments

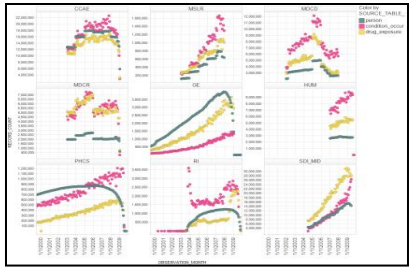
Experimental evidence

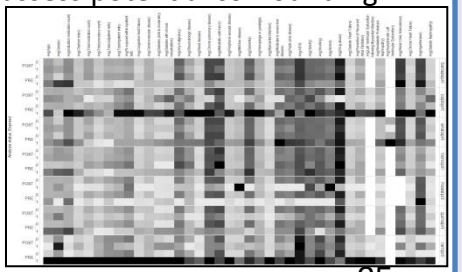
Dechallenge/Rechallenge



Coherence

Understand data and cohort to assess potential confounding





Brief Summary

- Empiric investigation should help provide insight into the optimal method, data, and definitions to be used for risk identification
  - We investigated a number of methods, parameter settings, and datasets in a small number of test cases using a few techniques for evaluating method performance
- Thusfar, no one clear 'best' method has yet to emerge, as it depends on tolerance for false positives vs. false negatives
- In our initial efforts, 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

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ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Institution's Convening Activities

Joshua Benner, Fellow, Economic Studies

Managing Director, Engelberg Center for Health Care Reform

The Brookings Institution

Engelberg Center's Convening Activities

Activity	Description	Participants
Roundtable Webinars	Webinars cover a diverse range of initiatives that are relevant to active surveillance and Sentinel's development	All interested stakeholders
Expert Workshops	Workshops focus on specific policy and technical topics that inform Sentinel's development	Subject matter experts relevant to specific meeting
Brookings Active Surveillance Implementation Council Meetings	Small workshops consider issues related to implementation of the Sentinel System, considering far-term issues that may arise	Senior leaders from stakeholder groups
Public Stakeholder Workshops	Large, annual meetings provide a forum to engage the public in dialogue about the direction of Sentinel's activities	All interested stakeholders

Meeting Topics

Past meetings have covered a variety of topics including:

Technical Issues	Policy
• Distributed data networks • Signal refinement methods • Statistical issues • Setting methods research and development priorities	• Legal issues • Communication policies • Role of data and analytic partners, and industry in Sentinel

Common theme: ensuring sustainability of the Sentinel System

- Building a public private partnership
- Developing a model for long-term stakeholder participation
- Synergies with related initiatives

Opportunities for Additional Involvement

Participate in Brookings convened meetings:

- **Active Surveillance Roundtable Webinars:** held every 1 to 2 months
- **Sentinel Annual Public Workshop:** January 18, 2012 at the Marriot at Metro Center in Washington DC

Provide feedback and comments:

- **Suggest meeting topics** for workshops or future webinars
  E-mail:
  Sally Cluchey: Scluchey@brookings.edu
  Michelle Wong: Mwong@brookings.edu

Follow our work:

- **Brookings website** for Brookings convened meeting summaries
  http://www.brookings.edu/health/Projects/surveillance.aspx
- **FDA website** to sign up for Sentinel updates:
  http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:
http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx