OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

Fighting a battle up Hill's: Discovering new roles for observational healthcare data in causality assessment

Jesse Berlin (VP, Epidemiology, Janssen Research & Development), leaning heavily on
Patrick Ryan (on behalf of OMOP Research Team)

20 March 2013: LSHTM Seminar

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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 empirical methodological research to evaluate the performance of alternative methods with respect to 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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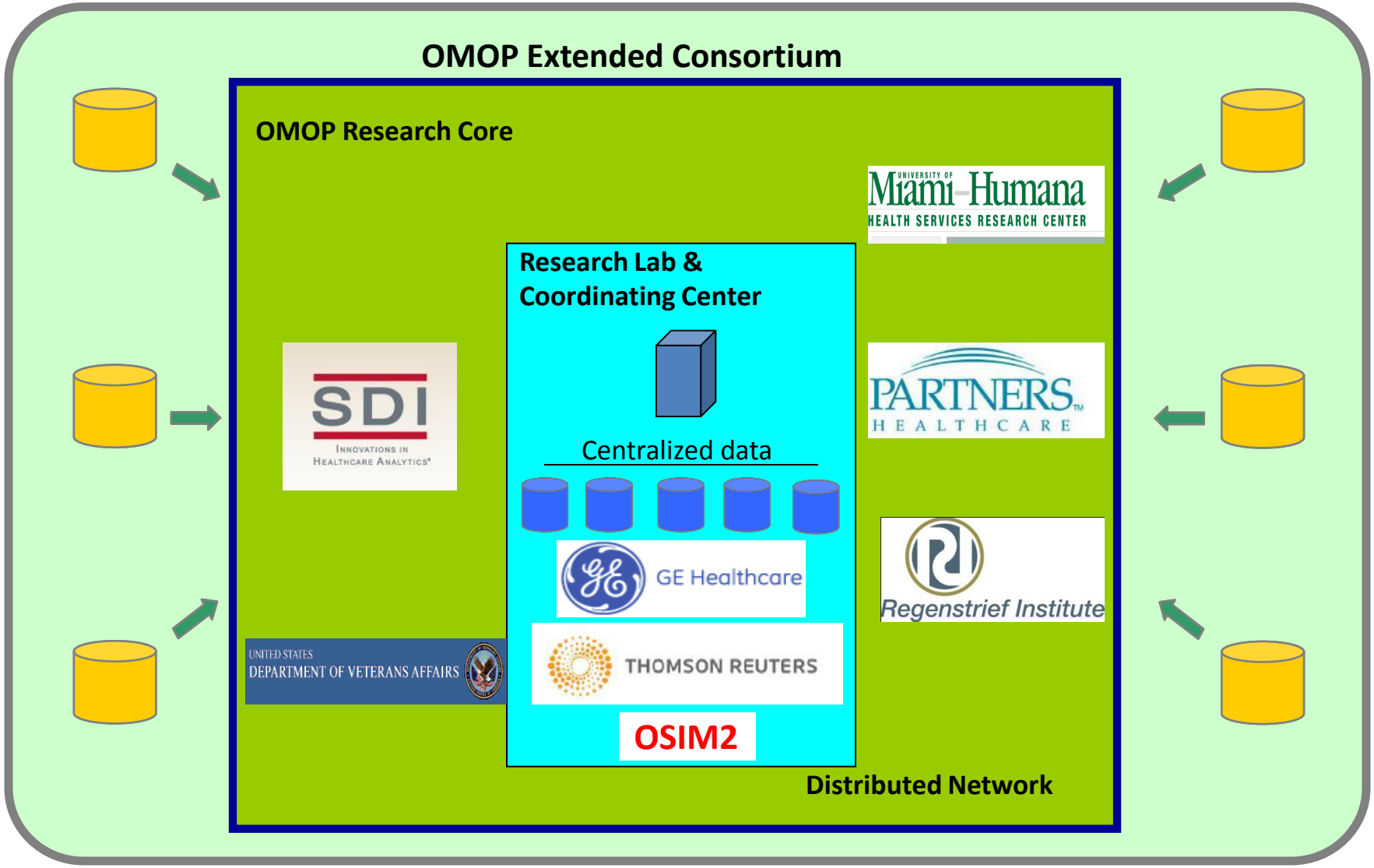
OMOP Data Community – First Two Years



178 million persons with patient-level data

5.4 billion drug exposures, 5.8 billion procedures, 2.3 billion clinical observations

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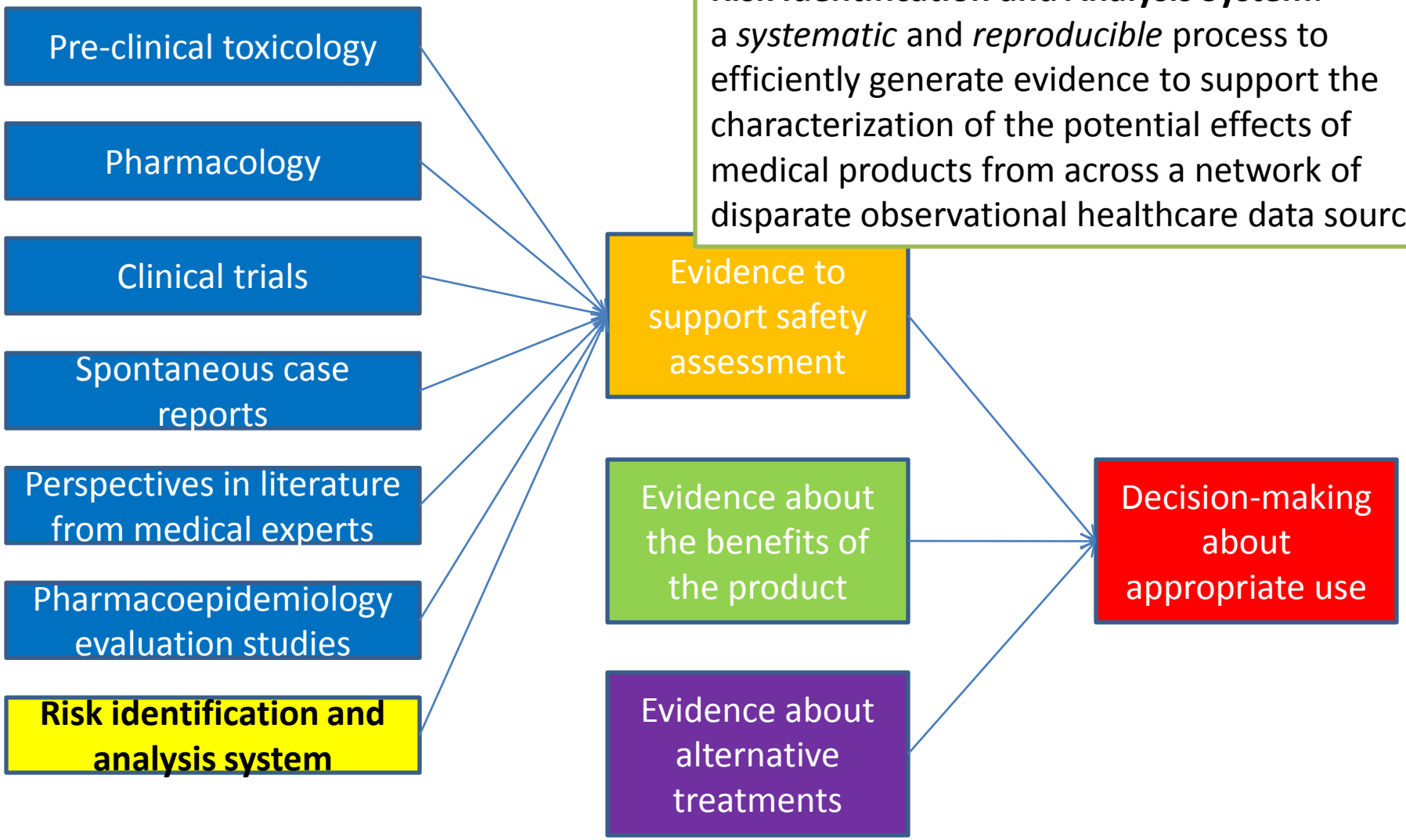
Risk identification and analysis system: One additional piece of evidence to inform medical decision-making

Risk Identification and Analysis System:
a *systematic* and *reproducible* process to efficiently generate evidence to support the characterization of the potential effects of medical products from across a network of disparate observational healthcare data sources



Is it "Evidence Synthesis?"

- Medical (regulatory) decision-making involves:
  - Summarizing results from RCTs (possibly using meta-analytic techniques)
  - Evaluating multiple epidemiologic studies (possibly using meta-analytic techniques)
  - Evaluating spontaneous adverse event reports
  - "Weighing" the other streams of evidence (e.g., pharmacology, preclinical toxicology)
- Now add "risk identification and analysis system"
  - Is it "active surveillance?"
  - In the context of multiple data sources, is it (can it be, should it be) meta-analysis?

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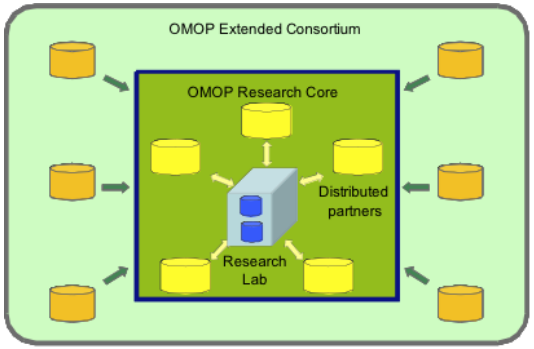
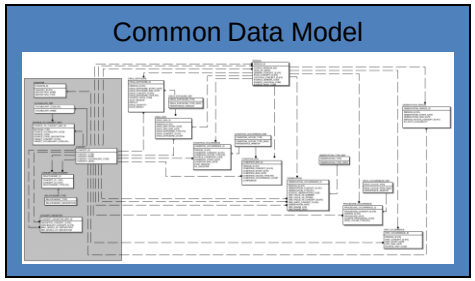
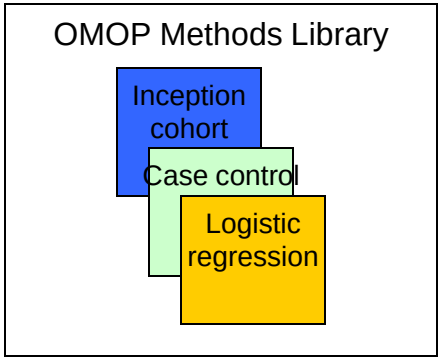
OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 170M+ lives
- Simulated data (OSIM)

- Open-source
- Standards-based
- Systematic data characterization and quality assurance





- 14 methods implemented as standardized procedures
- Full transparency with open-source code and documentation
- Epidemiology, statistical and machine learning designs

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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Ground truth for OMOP 2011/2012 experiments

isoniazid

fluticasone

indomethacin

clindamycin

	Positive controls	Negative controls	Total
Acute Liver Injury	81	37	118
Acute Myocardial Infarction	36	66	102
Acute Renal Failure	24	64	88
Upper Gastrointestinal Bleeding	24	67	91
Total	165	234	399

ibuprofen

loratadine

sertraline

pioglitazone

Criteria for positive controls:

- Event listed in Boxed Warning or Warnings/Precautions section of active FDA structured product label
- Drug listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Literature review identified no powered studies with refuting evidence of effect

Criteria for negative controls:

- Event not listed anywhere in any section of active FDA structured product label
- Drug not listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Literature review identified no powered studies with evidence of potential positive association

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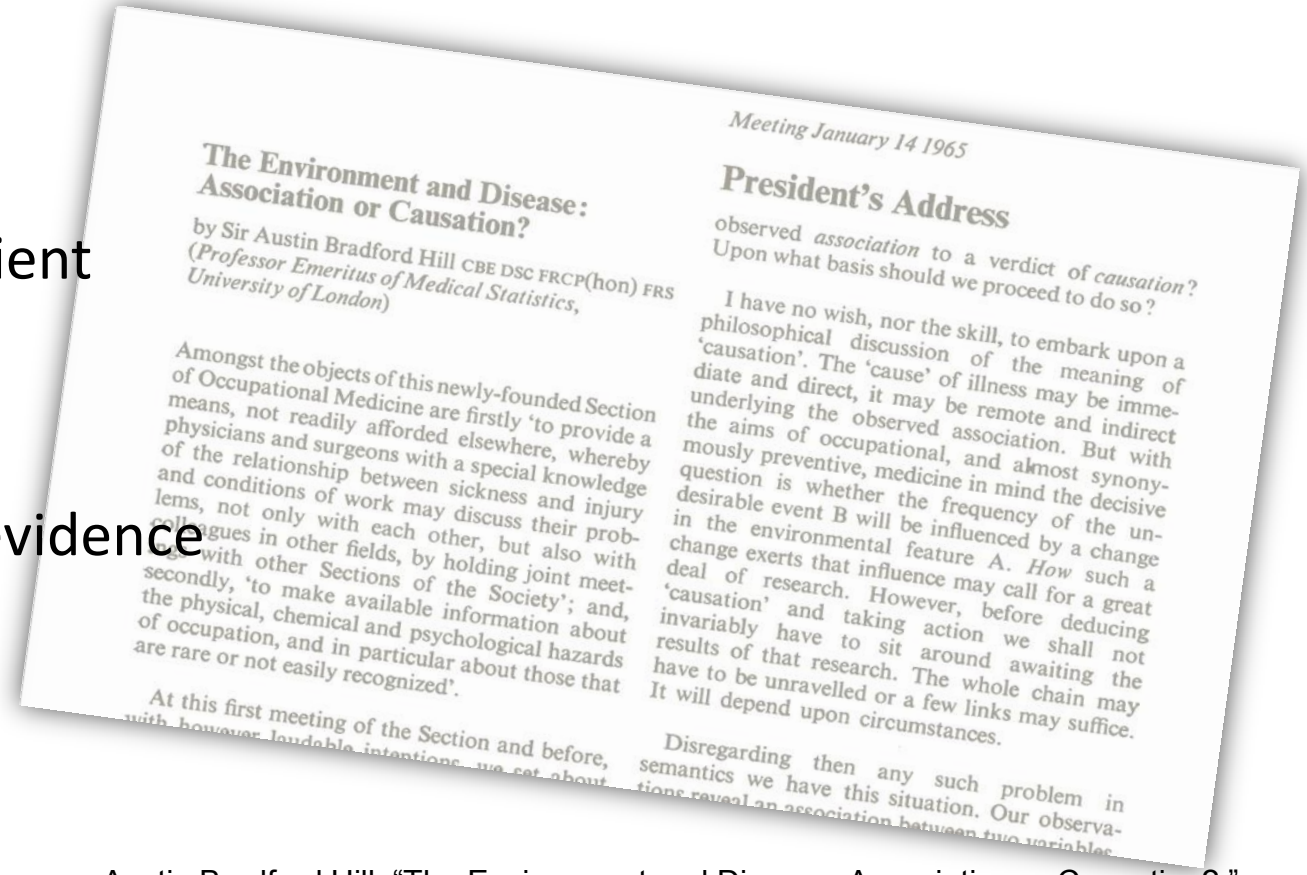
Hill's causality considerations

(OK – they are not criteria)

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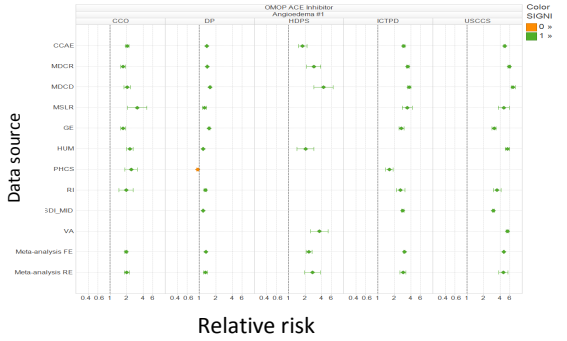
Vision for a risk identification and analysis system ‘causal dashboard’

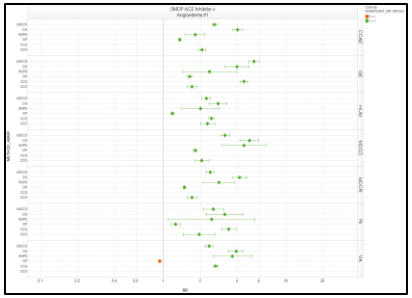
Drug ACE inhibitors ▼ **Outcome** Angioedema ▼

Strength of association

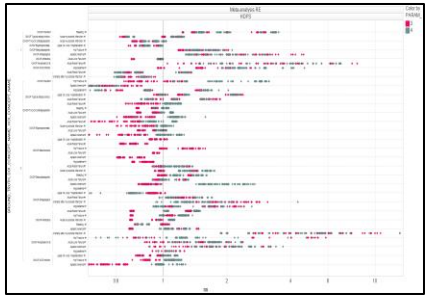


Consistency

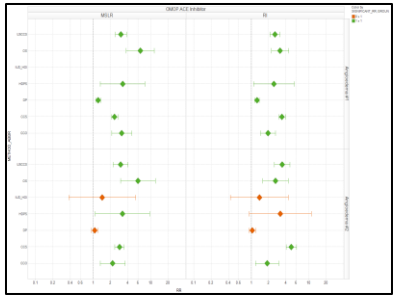
by data source



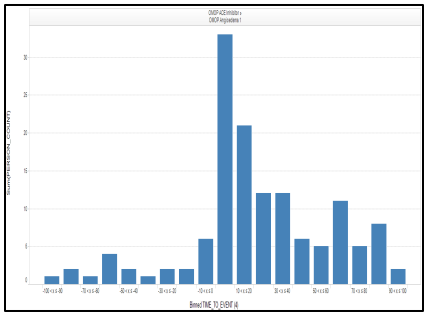
by method and parameters



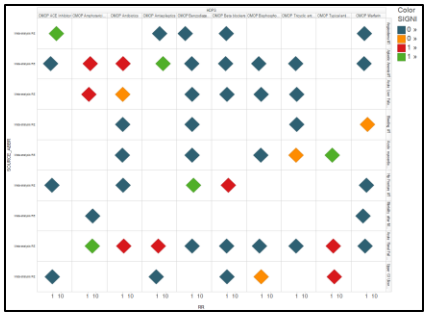
by outcome definition



Temporality

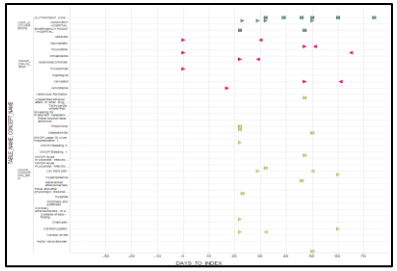


Specificity

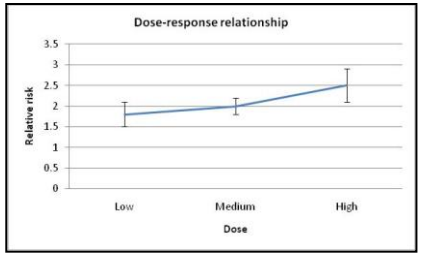


Plausibility

Interactive patient profiles



Biological gradient

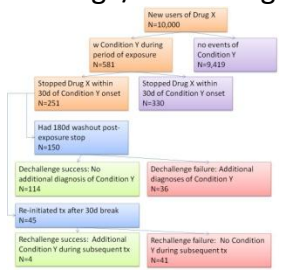


Analogy

Explore related conditions and treatments

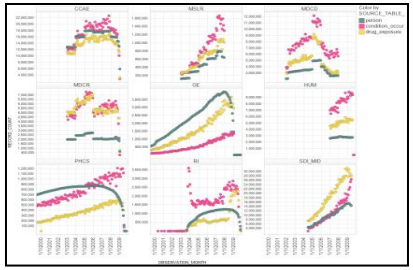
Experimental evidence

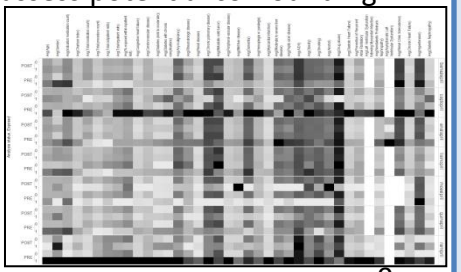
Dechallenge/Rechallenge



Coherence

Understand data and cohort to assess potential confounding





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Observational analyses to support each causal consideration

- **Strength of association**
  - Current focus: methods produce effect estimates (RR) of association between exposure and outcome
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy

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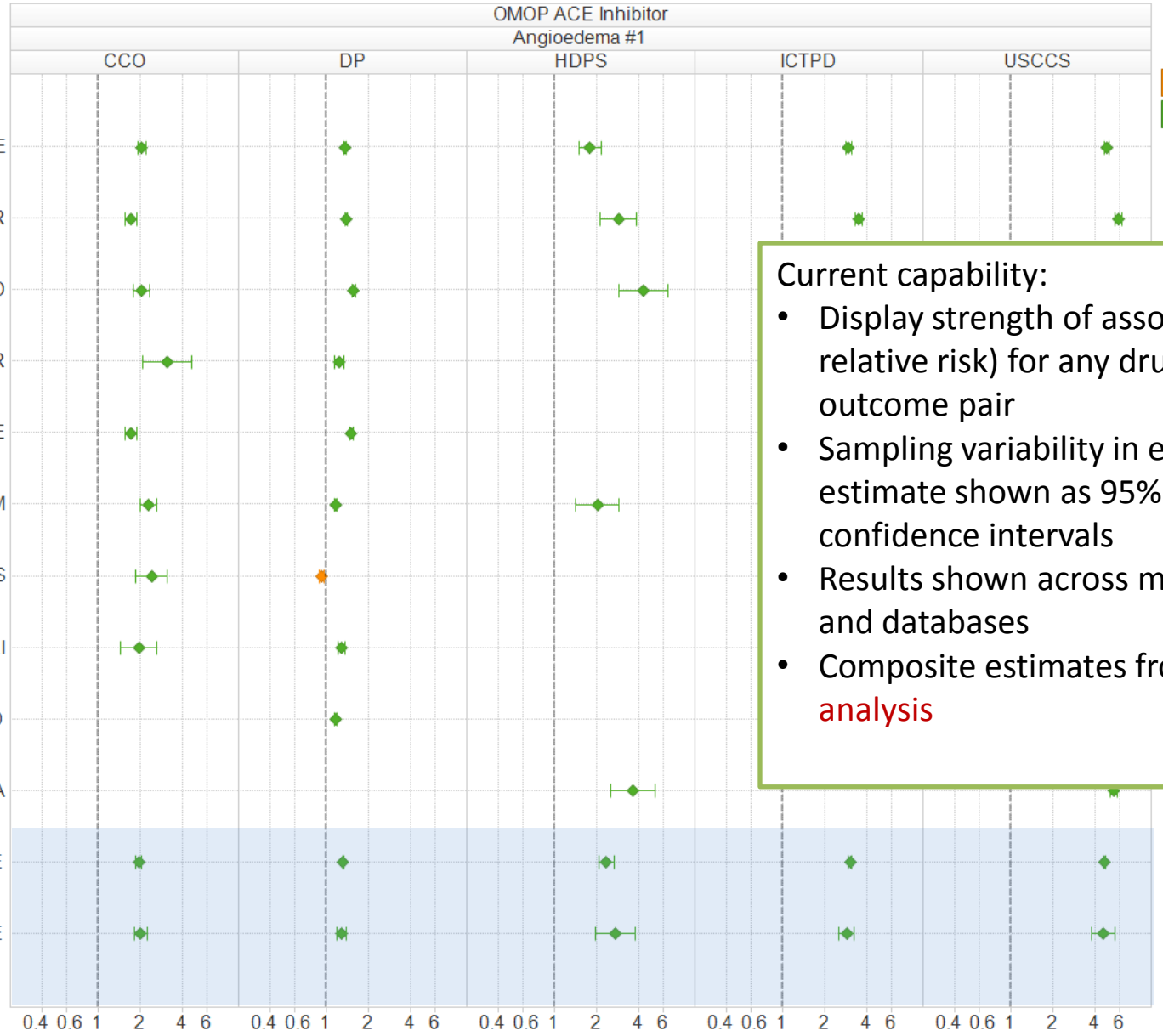
Exploring strength of association: Ex 1: ACE inhibitors - Angioedema



Current capability:

- Display strength of association (as relative risk) for any drug-outcome pair
- Sampling variability in effect estimate shown as 95% confidence intervals
- Results shown across methods and databases
- Composite estimates from meta-analysis

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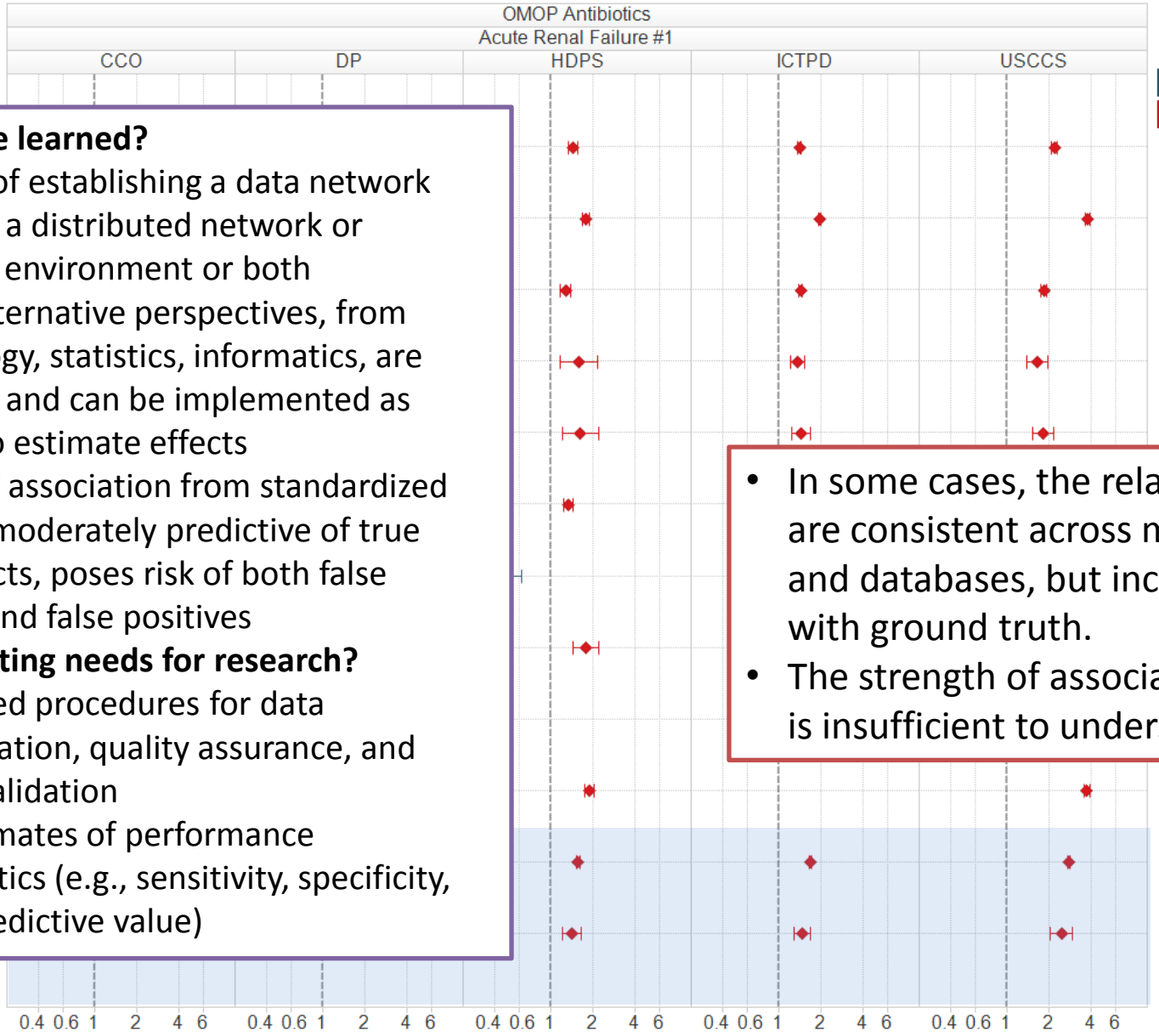
Strength of association:
Ex 2: Antibiotics – Acute Renal Failure



What have we learned?

- Feasibility of establishing a data network with either a distributed network or centralized environment or both
- Multiple alternative perspectives, from epidemiology, statistics, informatics, are considered and can be implemented as methods to estimate effects
- Strength of association from standardized analysis is moderately predictive of true causal effects, poses risk of both false negatives and false positives

What are existing needs for research?

- Standardized procedures for data characterization, quality assurance, and software validation
- Better estimates of performance characteristics (e.g., sensitivity, specificity, positive predictive value)

- In some cases, the relative risks are consistent across methods and databases, but inconsistent with ground truth.
- The strength of association alone is insufficient to understand why

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Observational analyses to support each causal consideration

- Strength of association
- **Consistency**
  - We currently consider four types of consistency:
  1. Consistency across different databases (including measures of heterogeneity)
  2. Consistency across different methods
  3. Consistency across parameters within method
  4. Consistency across different definitions of the health outcome of interest (HOI)
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy

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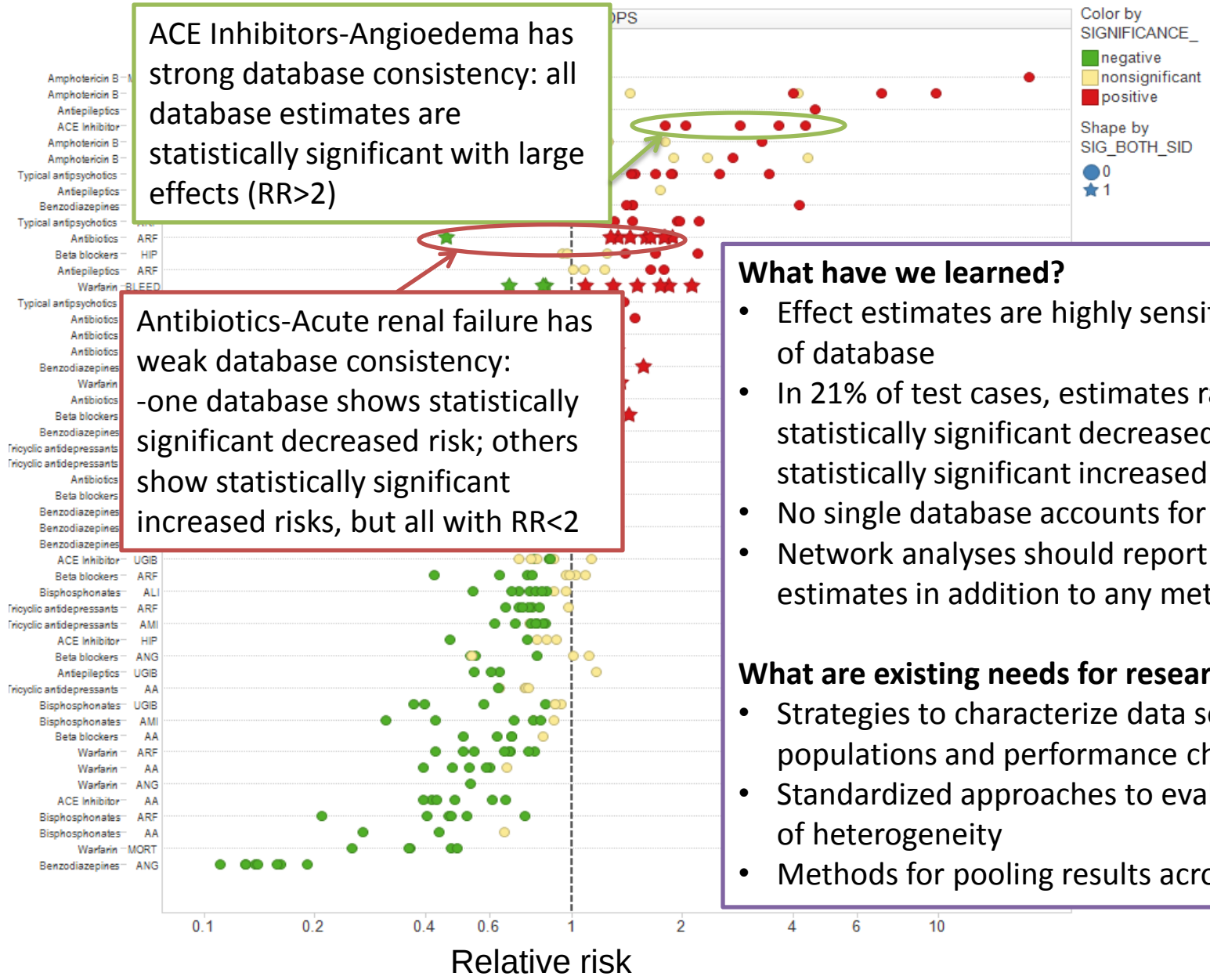
Range of estimates across databases when using high-dimensional propensity score inception cohort (HDPS)

ACE Inhibitors-Angioedema has strong database consistency: all database estimates are statistically significant with large effects (RR>2)

Antibiotics-Acute renal failure has weak database consistency:
-one database shows statistically significant decreased risk; others show statistically significant increased risks, but all with RR<2



What have we learned?

- Effect estimates are highly sensitive to choice of database
- In 21% of test cases, estimates ranged from statistically significant decreased risk to statistically significant increased risk
- No single database accounts for heterogeneity
- Network analyses should report source-specific estimates in addition to any meta-analyses

What are existing needs for research?

- Strategies to characterize data source populations and performance characteristics
- Standardized approaches to evaluate sources of heterogeneity
- Methods for pooling results across sources

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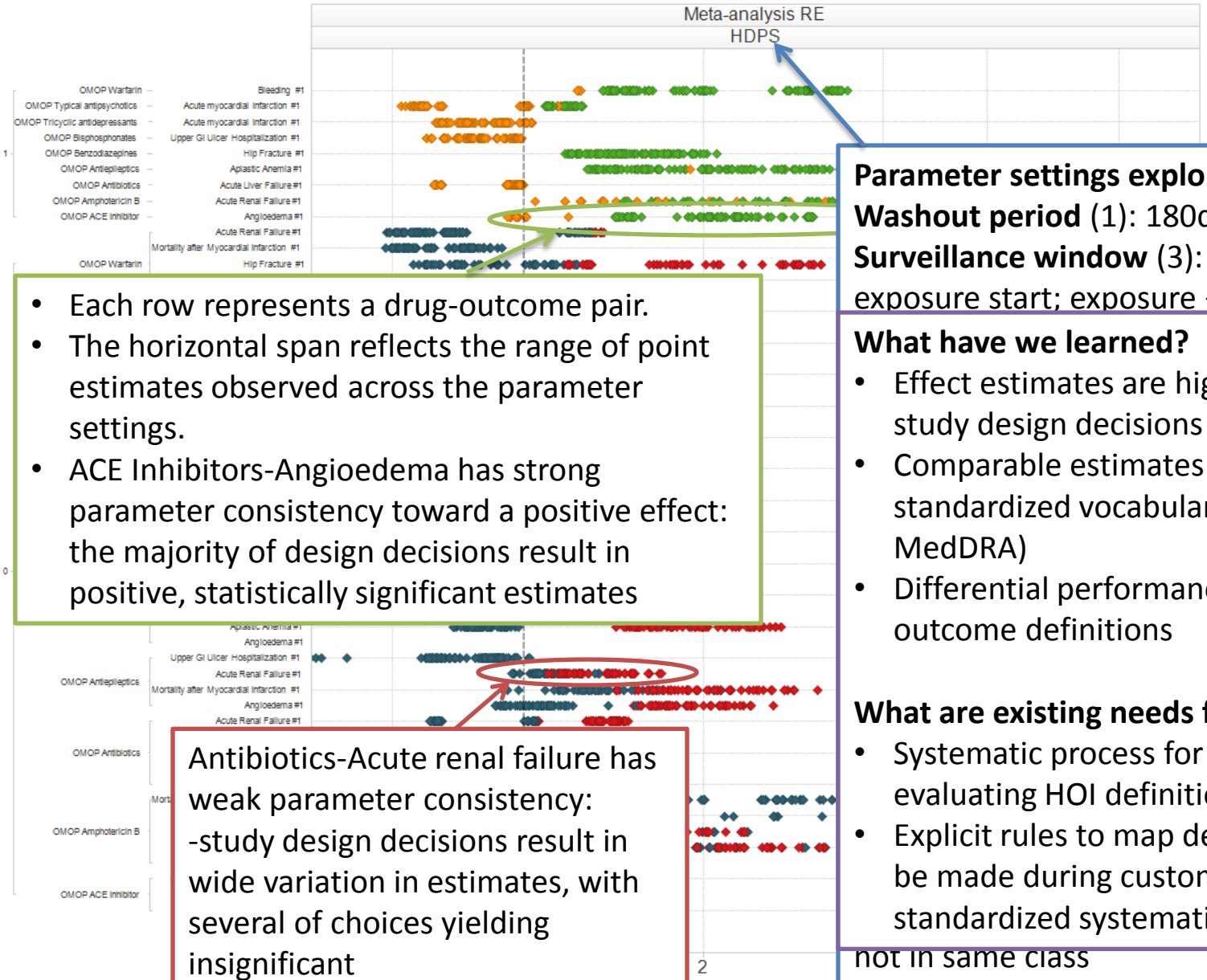
Range of estimates across high-dimensional propensity score inception cohort (HDPS) parameter settings



- Each row represents a drug-outcome pair.
- The horizontal span reflects the range of point estimates observed across the parameter settings.
- ACE Inhibitors-Angioedema has strong parameter consistency toward a positive effect: the majority of design decisions result in positive, statistically significant estimates

Antibiotics-Acute renal failure has weak parameter consistency:
-study design decisions result in wide variation in estimates, with several of choices yielding insignificant

Parameter settings explored in OMOP:
Washout period (1): 180d
Surveillance window (3): 30 days from exposure start; exposure + 30d ; all time

not in same class

What have we learned?

- Effect estimates are highly sensitive to study design decisions
- Comparable estimates across alternative standardized vocabularies (ICD9, SNOMED, MedDRA)
- Differential performance by alternative outcome definitions

What are existing needs for research?

- Systematic process for defining and evaluating HOI definitions
- Explicit rules to map decisions that would be made during custom evaluations into standardized systematic process

Important Message

- Show the results by data source
- Show the sensitivity analyses (or at least report them)
- Showing ONLY a combined result is not enough (and may be misleading)

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Observational analyses to support each causal consideration

- Strength of association
- Consistency
- Specificity
- **Temporality**
  - Evaluate time-to-event relationship between exposure and outcome
  - High incidence of events prior to exposure may suggest co-occurrence correlation without causal relationship
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy

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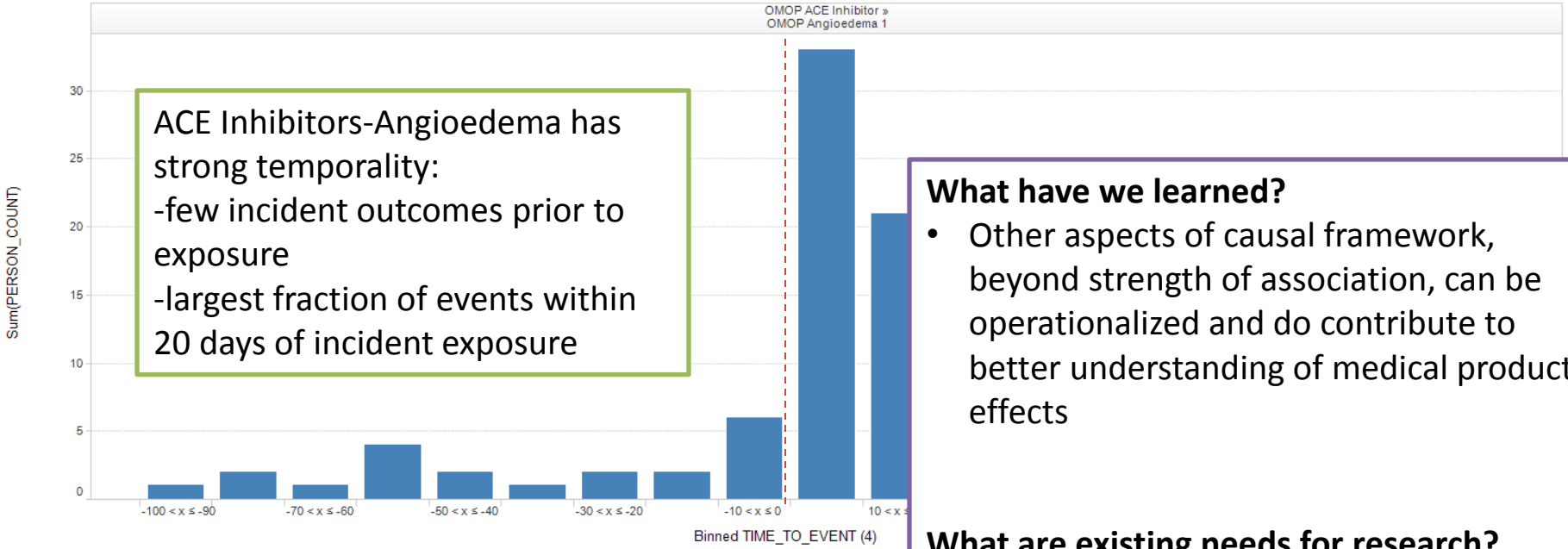
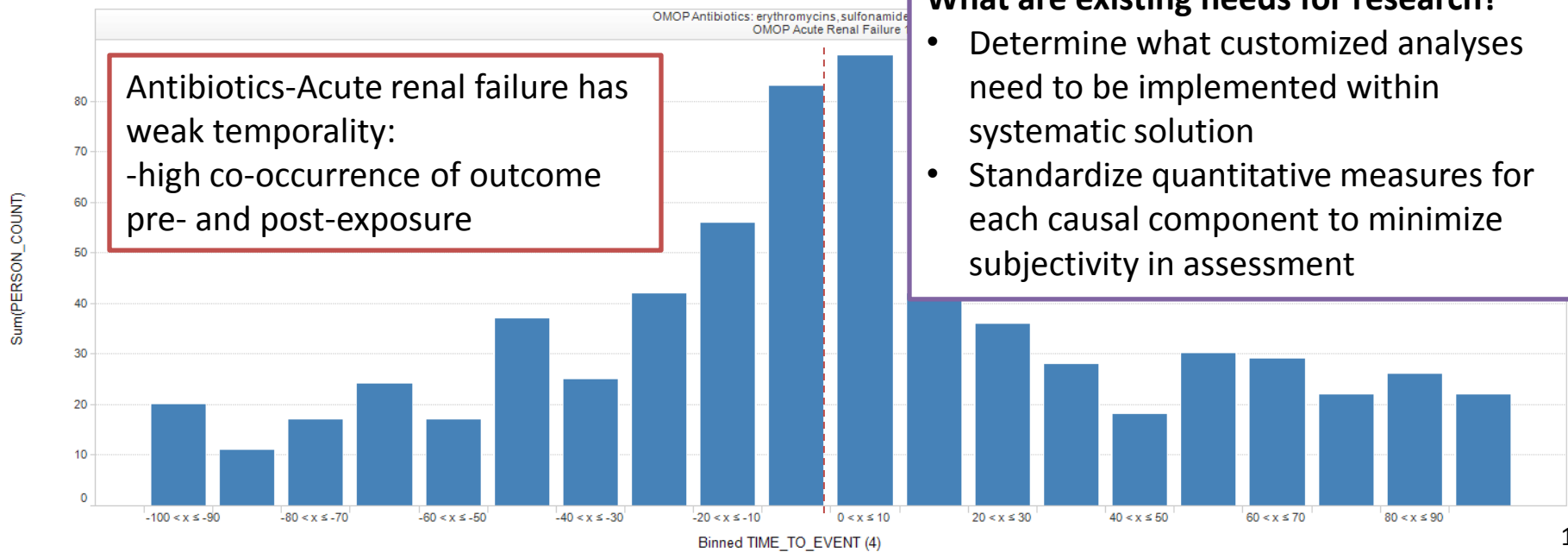
Temporality



ACE Inhibitors-Angioedema has strong temporality:
-few incident outcomes prior to exposure
-largest fraction of events within 20 days of incident exposure



Antibiotics-Acute renal failure has weak temporality:
-high co-occurrence of outcome pre- and post-exposure

What have we learned?

- Other aspects of causal framework, beyond strength of association, can be operationalized and do contribute to better understanding of medical product effects

What are existing needs for research?

- Determine what customized analyses need to be implemented within systematic solution
- Standardize quantitative measures for each causal component to minimize subjectivity in assessment

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Observational analyses to support each causal consideration

- Strength of association
- Consistency
- Specificity
- Temporality
- Biological gradient
- Coherence
- **Plausibility**
  - Explore interactive patient profiles to identify clinically relevant patterns or alternative explanations
  - Extend beyond population-level treatment effects to study patient-centered outcomes
- **Experimental evidence**
  - Use observational data to approximate natural experiments at the patient level
  - Summarizing dechallenge/rechallenge attempts, successes, and failures can provide supplemental evidence about provider suspicions and patient events
- Analogy

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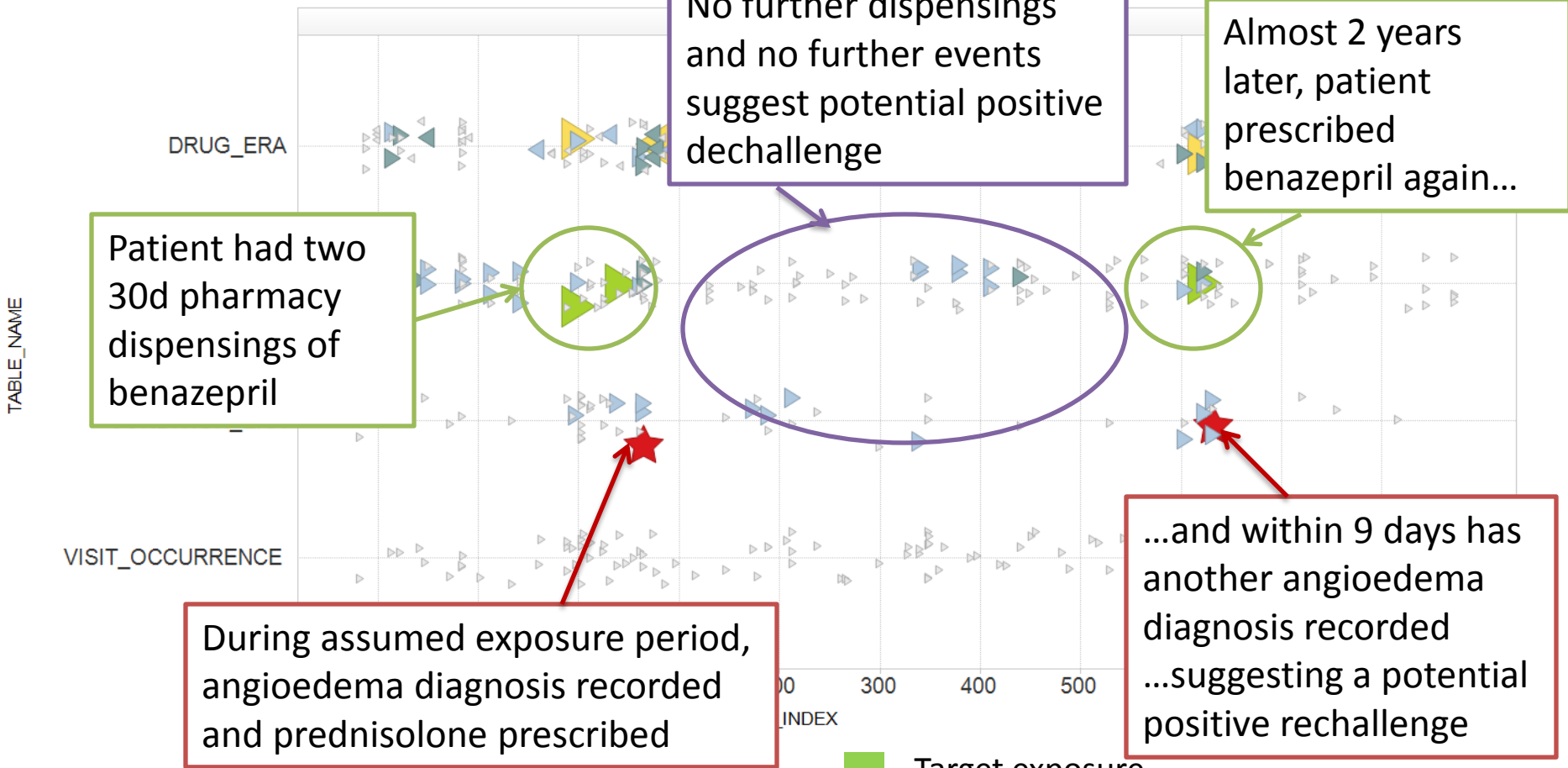
Patient profiles to explore plausibility and experimental evidence

PERSON_ID	AGE_AT_INDEX	GENDER	COHORT_NAME
20015229241	44	MALE	ACE inhibitor-A



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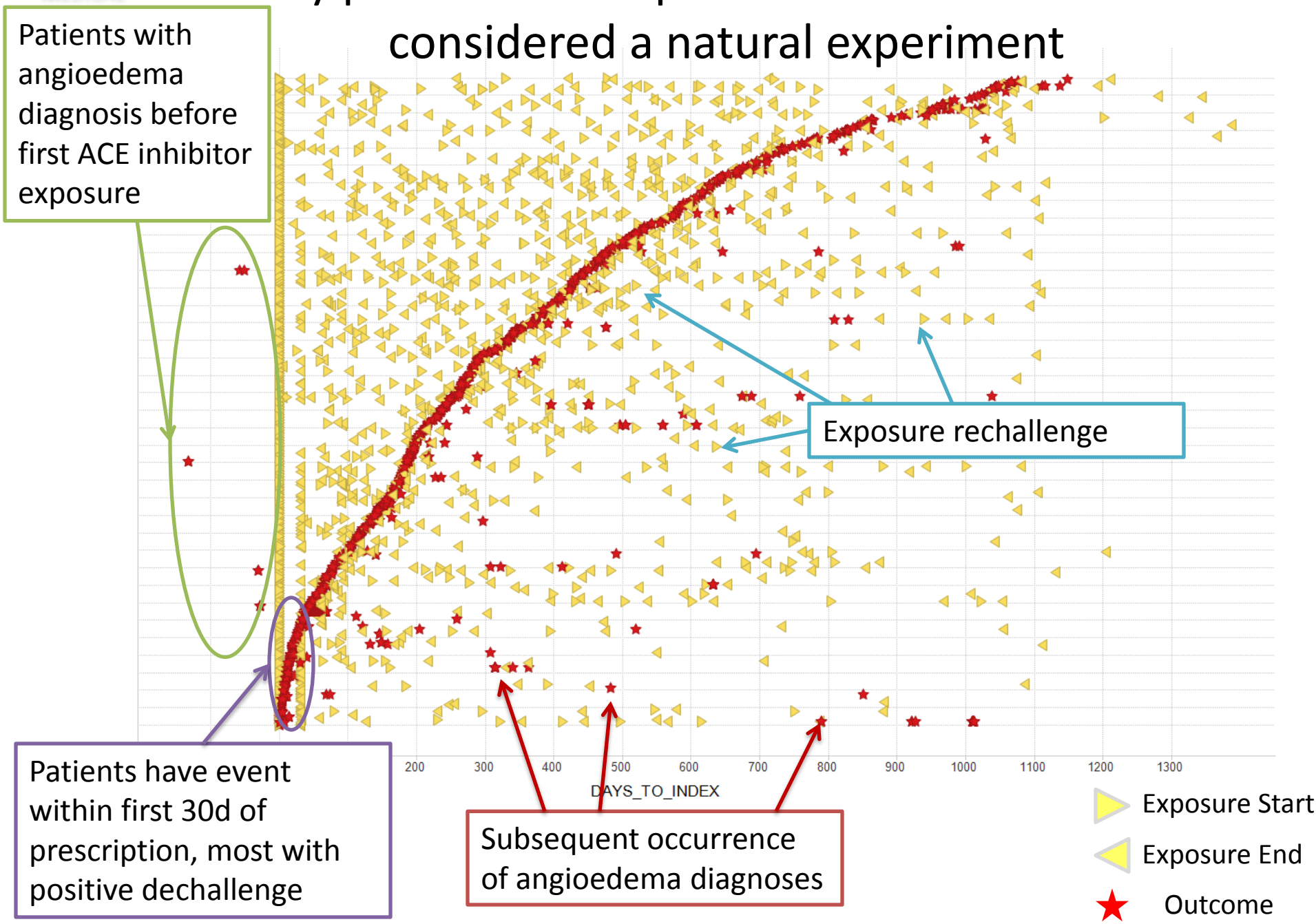
Every patient with exposure and outcome can be considered a natural experiment



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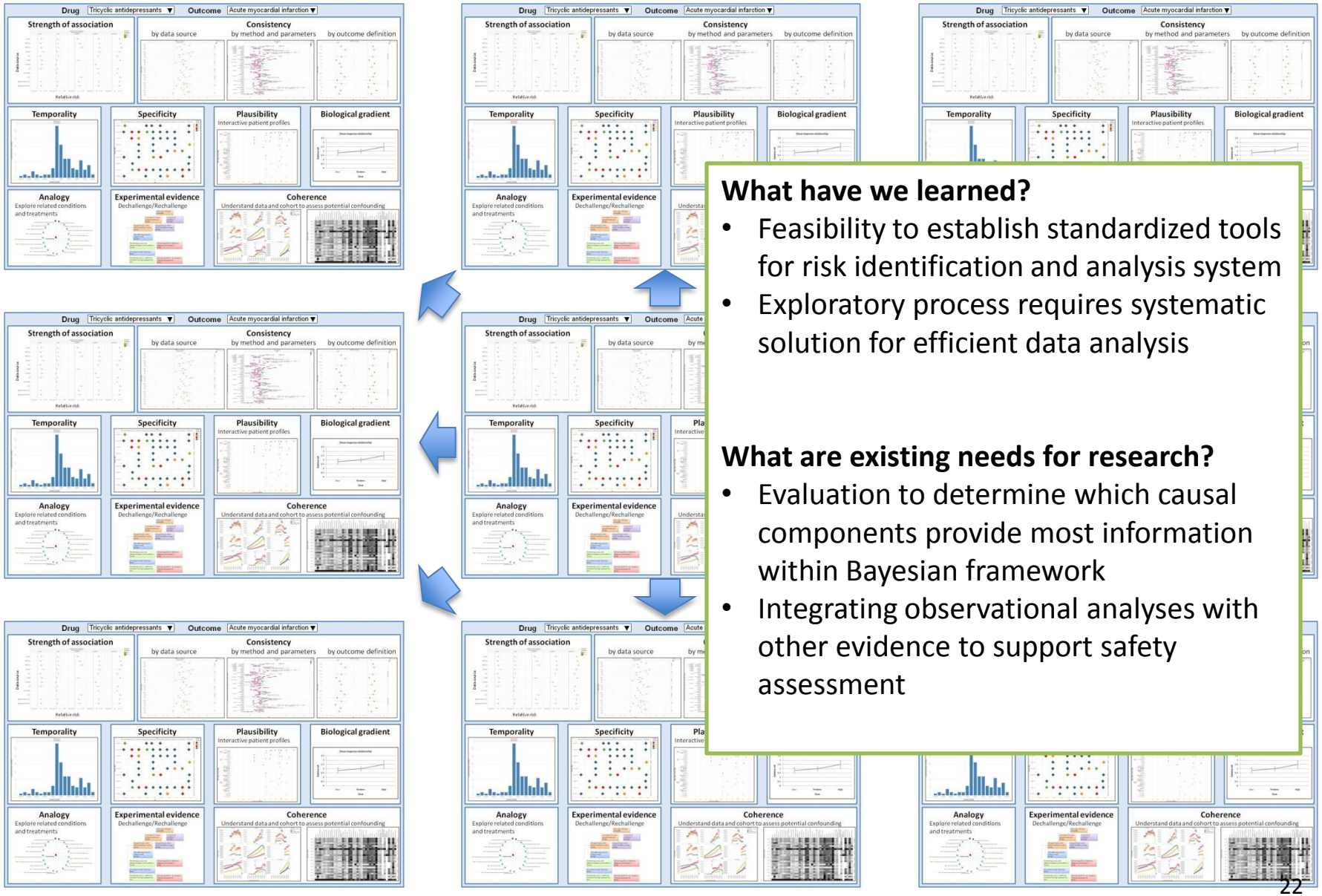
Exploratory framework for studying effects

Urticaria | Angioedema | Anaphylactic reactions

lisinopril

ACE inhibitors

ARBs



What have we learned?

- Feasibility to establish standardized tools for risk identification and analysis system
- Exploratory process requires systematic solution for efficient data analysis

What are existing needs for research?

- Evaluation to determine which causal components provide most information within Bayesian framework
- Integrating observational analyses with other evidence to support safety assessment

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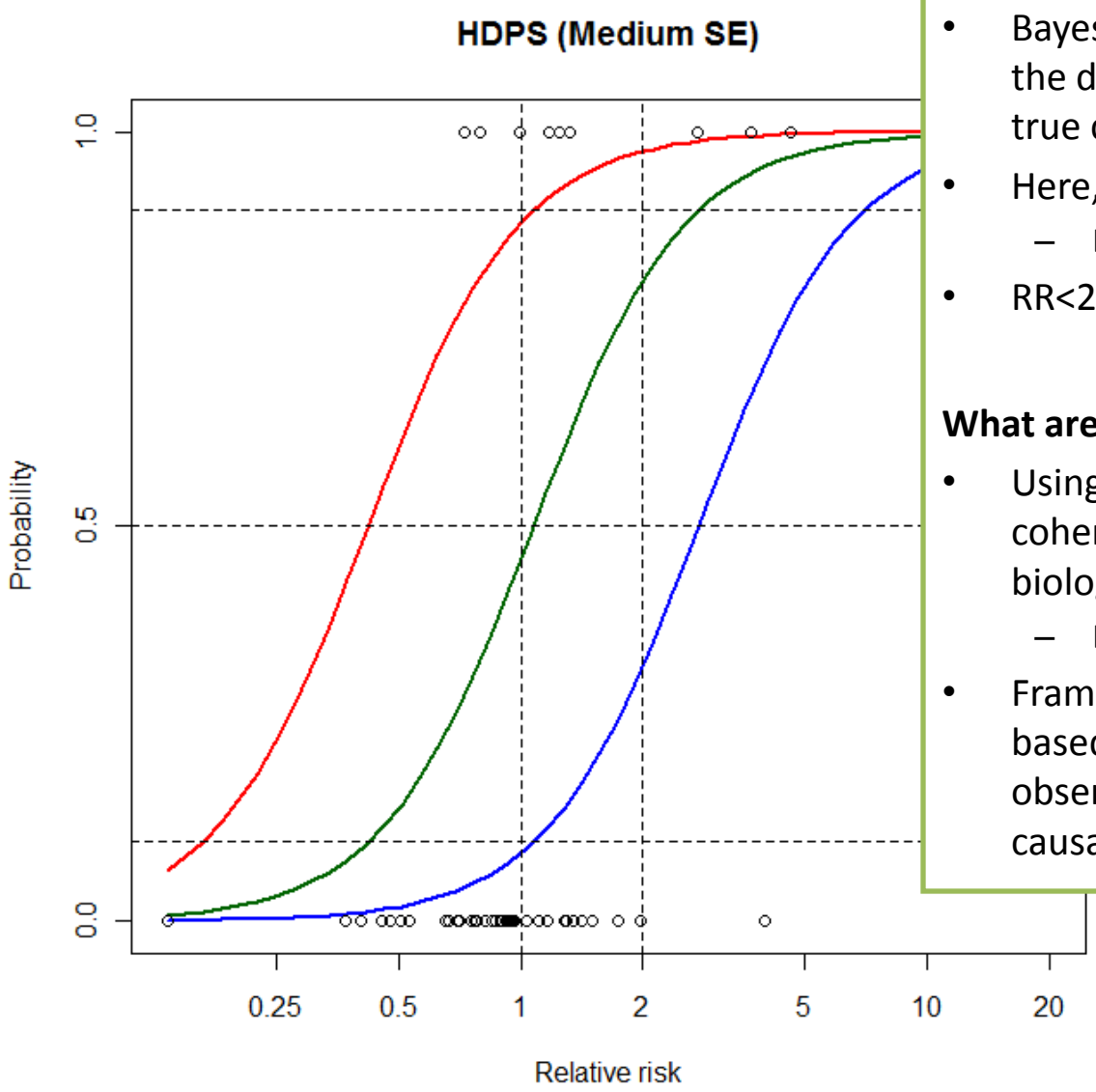
Quantitative framework for studying effects



What has been learned?

- Bayesian framework can answer: 'in light of the data, what is our revised belief of a true causal effect?'
- Here, p(true | RR, SE)
  - Logistic regression with 2 predictors
- RR<2 are largely uninformative

What are existing needs for research?

- Using Hill: p(true | RR, SE, temporality, coherence, consistency, plausibility, biological gradient, specificity, etc.)
  - Logistic regression with many predictors
- Framework rests on confidence in model, based on empirical evidence of how observational analyses correspond to true causal status

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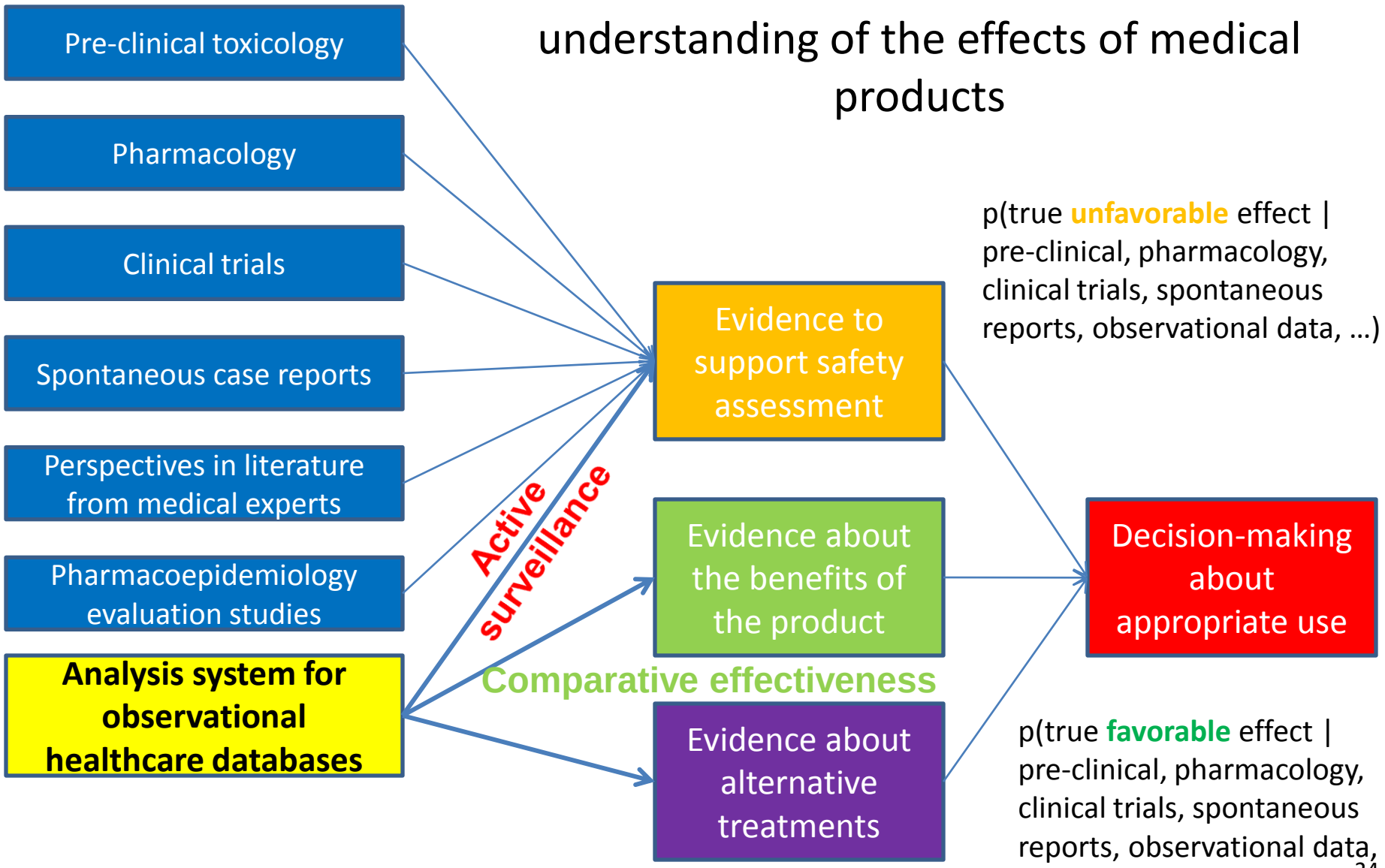
Opportunities for a coordinated system that leverages a network of observational healthcare databases to enhance our understanding of the effects of medical products



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Concluding thoughts

- A standards-based common clinical information model is feasible and can accommodate disparate data sources
- Multiple analytical use cases can be satisfied within one framework, but scope of data needs may vary
- Standardized analytics enable efficient exploration of a large set of research/public health questions in a consistent, transparent, and reproducible process
- Large-scale analytics and interactive visualization can maximize value of EHR data resources by generating clinically meaningful knowledge for all stakeholders

Concluding thoughts from Sir Bradford Hill

"Yet too often I suspect we waste a deal of time, we grasp the shadow and lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no statistical difference'. Like fire, the χ^2 test is an excellent servant and a bad master."

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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For more information

- **http://omop.fnih.org**

- Everything is there