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Lessons learned, Current Activities, and Anticipated Needs for Methods Research and Development: OMOP Perspective

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on behalf of OMOP Research Team
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FDA VISION FOR SENTINEL

FDA envisions that within three years, the system will be able to refine safety signals in near real-time. This will require approaches for:

- rapidly defining exposed cohorts;
- establishing algorithms to capture health outcomes of interest;
- using sophisticated modular programs capable of running evaluations with minimal input from epidemiologists and clinicians and limited or no ad hoc programming; and
- developing a framework to guide methodological approaches that include confounding adjustments to be available for safety surveillance evaluations.

They also expect that approaches for signal generation will be under development.

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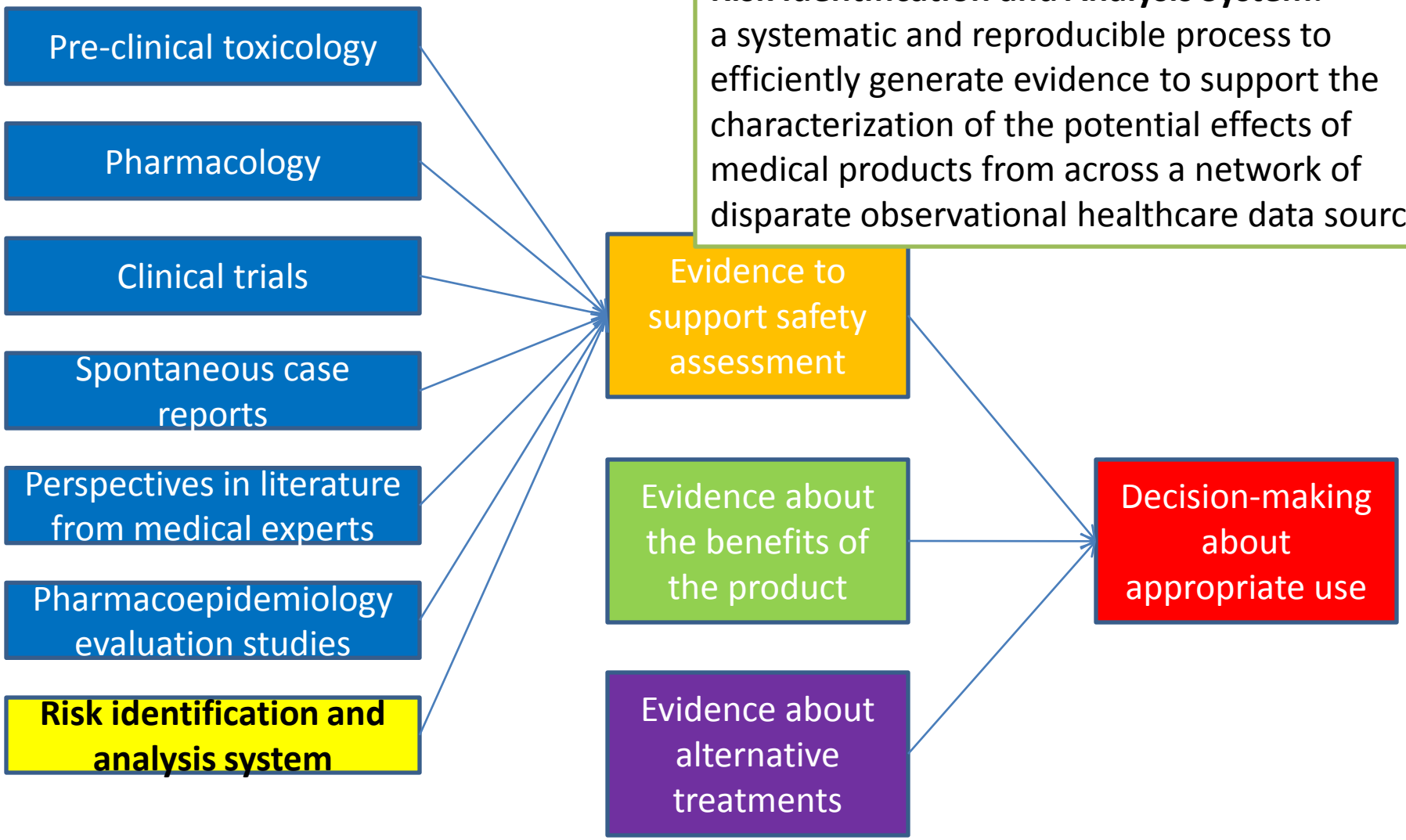
Risk identification and analysis system: One additional piece of evidence to inform medical decision-making

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



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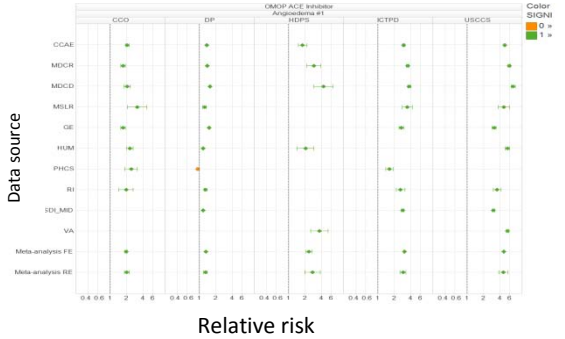
Vision for a risk identification and analysis system ‘causal dashboard’

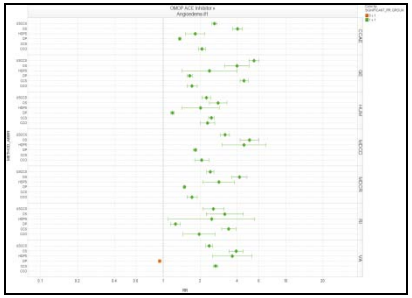
Drug Tricyclic antidepressants ▼ **Outcome** Acute myocardial infarction ▼

Strength of association

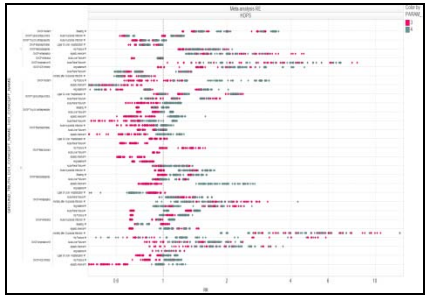


Consistency

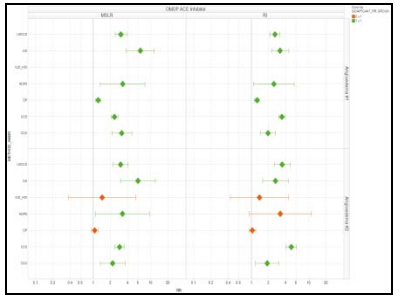
by data source



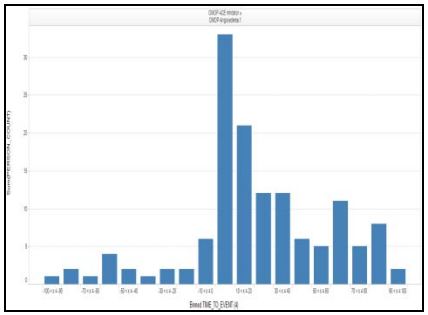
by method and parameters



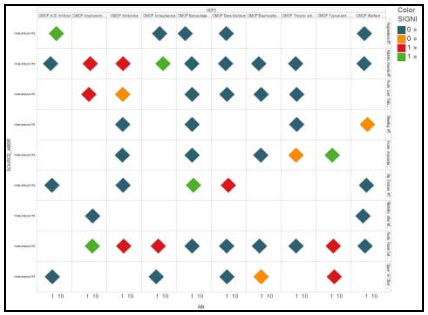
by outcome definition



Temporality

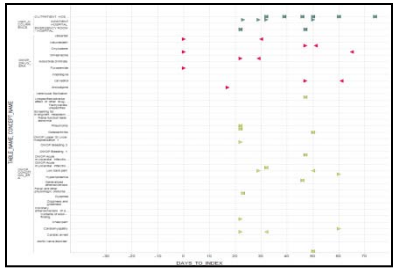


Specificity

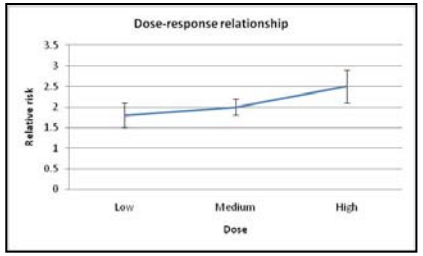


Plausibility

Interactive patient profiles



Biological gradient

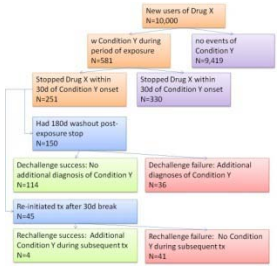


Analogy

Explore related conditions and treatments

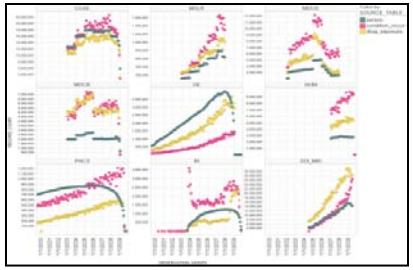
Experimental evidence

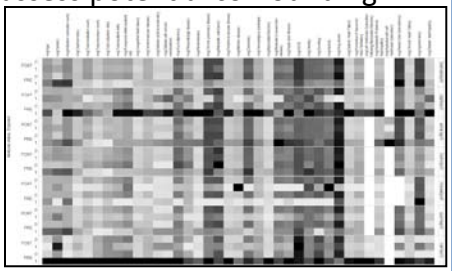
Dechallenge/Rechallenge



Coherence

Understand data and cohort to assess potential confounding





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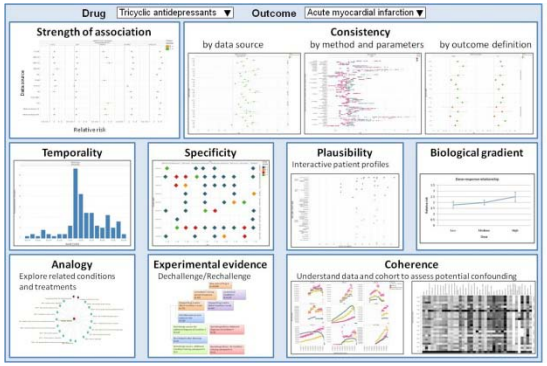
Complementary paths toward evidence generation

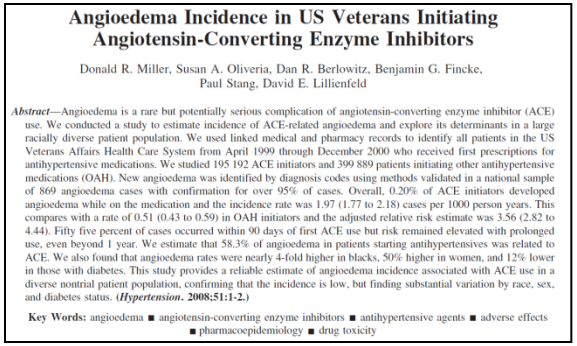
Risk identification and analysis system



- Exploratory framework scalable to study large sets of drug-outcome pairs
- Immediate access to standardized information, but limited flexibility
- Defined performance characteristics

- System may generate question that warrants custom evaluation
- Evaluation may trigger questions that require rapid response from system

Custom evaluation studies



Angioedema Incidence in US Veterans Initiating Angiotensin-Converting Enzyme Inhibitors

Donald R. Miller, Susan A. Oliveria, Dan R. Berlowitz, Benjamin G. Fincke, Paul Stang, David E. Lillienfeld

Abstract—Angioedema is a rare but potentially serious complication of angiotensin-converting enzyme inhibitor (ACE) use. We conducted a study to estimate incidence of ACE-related angioedema and explore its determinants in a large racially diverse patient population. We used linked medical and pharmacy records to identify all patients in the US Veterans Affairs Health Care System from April 1999 through December 2000 who received first prescriptions for antihypertensive medications. We studied 195 192 ACE initiators and 399 889 patients initiating other antihypertensive medications (OAH). New angioedema was identified by diagnosis codes using methods validated in a national sample of 869 angioedema cases with confirmation for over 95% of cases. Overall, 0.20% of ACE initiators developed angioedema while on the medication and the incidence rate was 1.97 (1.77 to 2.18) cases per 1000 person years. This compares with a rate of 0.51 (0.43 to 0.59) in OAH initiators and the adjusted relative risk estimate was 3.56 (2.82 to 4.44). Fifty five percent of cases occurred within 90 days of first ACE use but risk remained elevated with prolonged use, even beyond 1 year. We estimate that 58.3% of angioedema in patients starting antihypertensives was related to ACE. We also found that angioedema rates were nearly 4-fold higher in blacks, 50% higher in women, and 12% lower in those with diabetes. This study provides a reliable estimate of angioedema incidence associated with ACE use in a diverse nontrial patient population, confirming that the incidence is low, but finding substantial variation by race, sex, and diabetes status. (*Hypertension*. 2008;51:1-2.)

Key Words: angioedema ■ angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ adverse effects ■ pharmacoepidemiology ■ drug toxicity

- Specific study of one drug/one outcome designed with clinical judgment and subject matter expertise
- Resource- and time-intensive to draft protocol and execute analysis de novo
- Unknown performance

How to use a Risk Identification and Analysis System?

- It's a policy decision, not a scientific one
  - System can be used to study one drug-outcome pair (e.g. refinement/evaluation) or to proactively monitor multiple drugs and outcomes (e.g. generation)
- Access to system is also a policy, not scientific, issue
  - All stakeholders (regulators, manufacturers, payers, health care systems, clinicians, patients) have vested interest in understanding the effects of medical products
  - Full transparency throughout process
    - Active participation throughout design, execution, and interpretation
    - Open access to documents, source code, data/software validation procedures PRIOR to analysis
    - Immediate access to full results as soon as available

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Developing an Agenda to Advance Methods Research and Development

- **The most pressing issues**
  - Clear agreement on what we mean by 'surveillance' and the lexicon in general
  - What changes could be made to the existing OMOP methods performance studies that would substantively impact their value?
  - What is the value of these analyses and what is its 'utility' in the evidence base? Exploratory, confirmatory, contributory?
  - Research funding and research infrastructure (e.g., people, access to data, training)
  - Governance that allows transparent, open, collaborative model
- **What are the collaborative projects needed to address the gaps?**
  - Aside from the simulated data, what current examples of 'ground truth' can be identified?
  - Further empiric study design amendments
- **Who are the relevant stakeholders and ultimate consumers and what could they also gain from this effort?**
  - Regulators, clinicians, patients, payers?

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Objectives of future research

- Create a shared central resource to enable collaborative methodological research and development across all stakeholders and establish common practices for data analysis validation and evaluation.
- Develop and evaluate alternative strategies for synthesizing effect estimates across an observational data network, including quantifying and adjusting for heterogeneity across sources and parameter sensitivity within methods.
- Determine appropriate heuristics to guide study design decisions for specific drug-outcome scenarios, and establish practices for comprehensive sensitivity analyses.
- Establish a quantitative framework for integrating disparate information, including formalizing causal framework within observational data and synthesizing observational evidence with other sources (pre-clinical toxicology, clinical trials, spontaneous reporting) as part of holistic safety assessment.
- Research and develop new methods for patient segmentation, including predictive modeling for prognosis of which patients have higher risk of outcomes and how alternative treatment decisions may impact the risks.
- Establish a standardized procedure for creating and evaluating health outcome of interest definitions.
- Embed ability to monitor impact of Regulatory interventions on risk and utilization.