OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

Active surveillance on medical observational databases

Ivan Zorych, Columbia University
Patrick Ryan, Janssen Research
Martijn Schuemie, Erasmus Medical Center
David Madigan, Columbia University

August 2
JSM 2012, San Diego

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

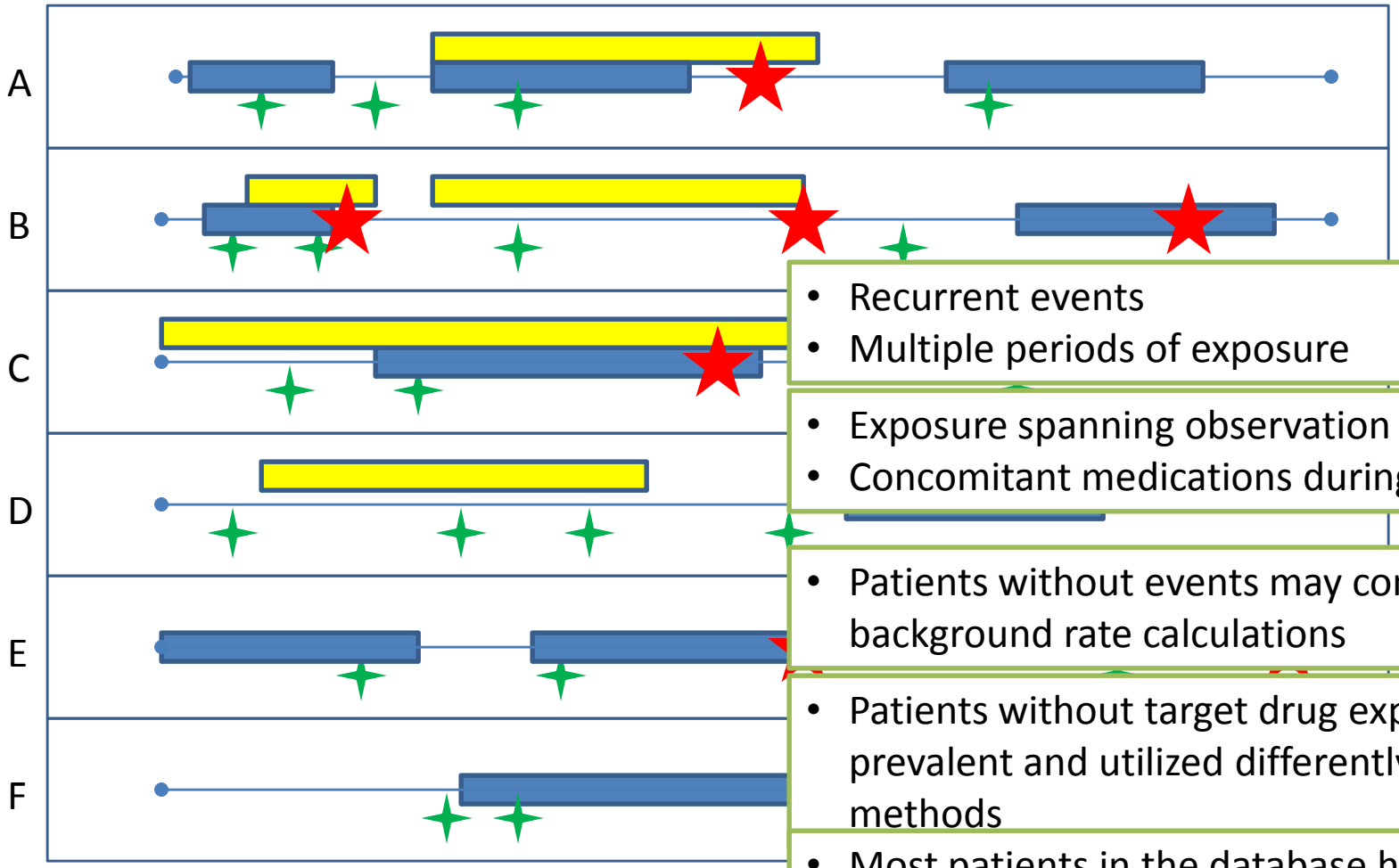
Introduction

- "In the fall of 2007, Congress passed the FDA Amendments Act (FDAAA), mandating FDA to establish an active surveillance system for monitoring drugs, using electronic data from healthcare information holders. The Sentinel Initiative is FDA's response to that mandate. Its goal is to build and implement a new active surveillance system that will eventually be used to monitor all FDA-regulated products." (http://www.fda.gov)

- One of the goals of the Observational Medical Outcomes Partnership (OMOP) is to define methods that can assess the feasibility and utility of using observational data to identify and evaluate associations between drugs and health-related conditions.

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Patient profiles in observational data



- Recurrent events
- Multiple periods of exposure

- Exposure spanning observation period
- Concomitant medications during events

- Patients without events may contribute to background rate calculations

- Patients without target drug exposure are prevalent and utilized differently across all methods

- Most patients in the database have neither the target drug nor the target outcome

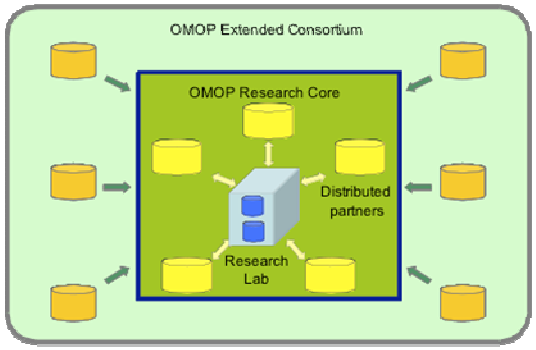
Target condition

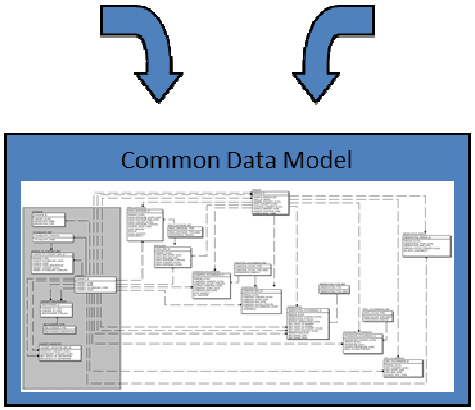
Other conditions

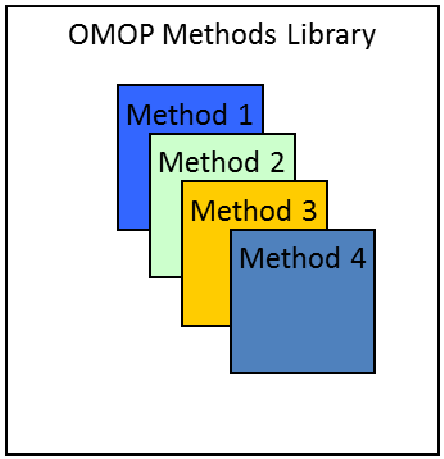
Other drugs

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Experiment Overview: OMOP 2010/2011 Research Experiment







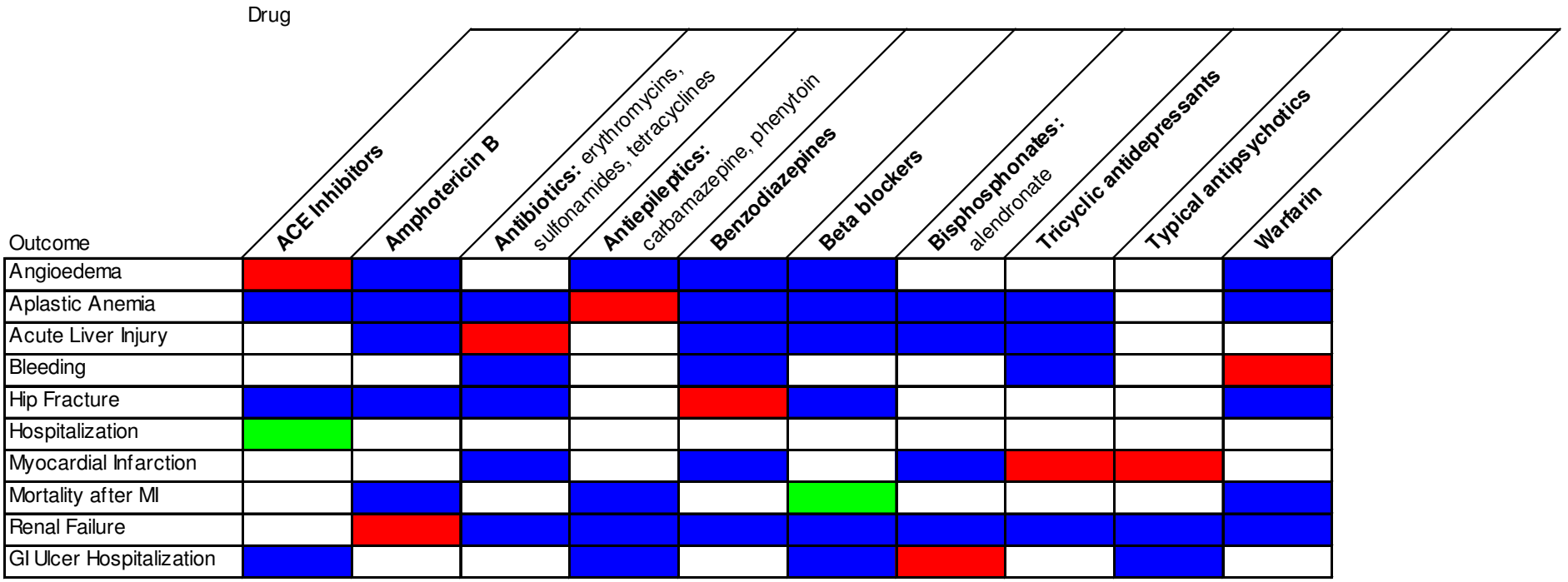
Health Outcomes of Interest
- Angioedema
- Aplastic Anemia
- Acute Liver Injury
- Bleeding
- GI Ulcer Hospitalization
- Hip Fracture
- Hospitalization
- Myocardial Infarction
- Mortality after MI
- Renal Failure

Drugs
- ACE Inhibitors
- Amphotericin B
- Antibiotics
- Antiepileptics
- Benzodiazepines
- Beta blockers
- Bisphosphonates
- Tricyclic antidepressants
- Typical antipsychotics
- Warfarin

Non-specified conditions
-All outcomes in condition terminology
-'Labeled events' as reference
  -Warning
  -Precautions
  -Adverse Reactions
  -Postmarketing Experience

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

‘Ground truth’ assumed for Monitoring Health Outcomes of Interest, 2010/2011



Legend	Total
True positive' benefit	2
True positive' risk	9
Negative control'	44

http://omop.fnih.org/OMOPWhitePapers

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

‘Ground truth’ OMOP 2011/2012 Research Experiment

	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

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Real data used in OMOP experiments

Name	General Database Description	Pop Size (M)
GE Centricity Electronic Health Record (GE)	Derived from data pooled by providers using GE Centricity Office (an ambulatory electronic health record) into a data warehouse in a HIPAA-compliant manner.	11.2
MarketScan® Research Databases from Thomson Reuters	*MarketScan Lab Database (MSLR)*- Represents privately insured population, with administrative claims from inpatient, outpatient, and pharmacy services supplemented by laboratory results.	1.5
	MarketScan Medicaid Multi-State Database (MDCD)- Contains administrative claims data for Medicaid enrollees from multiple states.	11.1
	MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)- Captures administrative claims for retirees with Medicare supplemental insurance paid by employers, including services provided under Medicare-covered payment, employer-paid portion, and any out-of-pocket expenses.	4.4
	MarketScan Commercial Claims and Encounters (CCAE)- Represents privately insured population and captures administrative claims with patient-level de-identified data from inpatient and outpatient visits and pharmacy claims of multiple insurance plans.	58

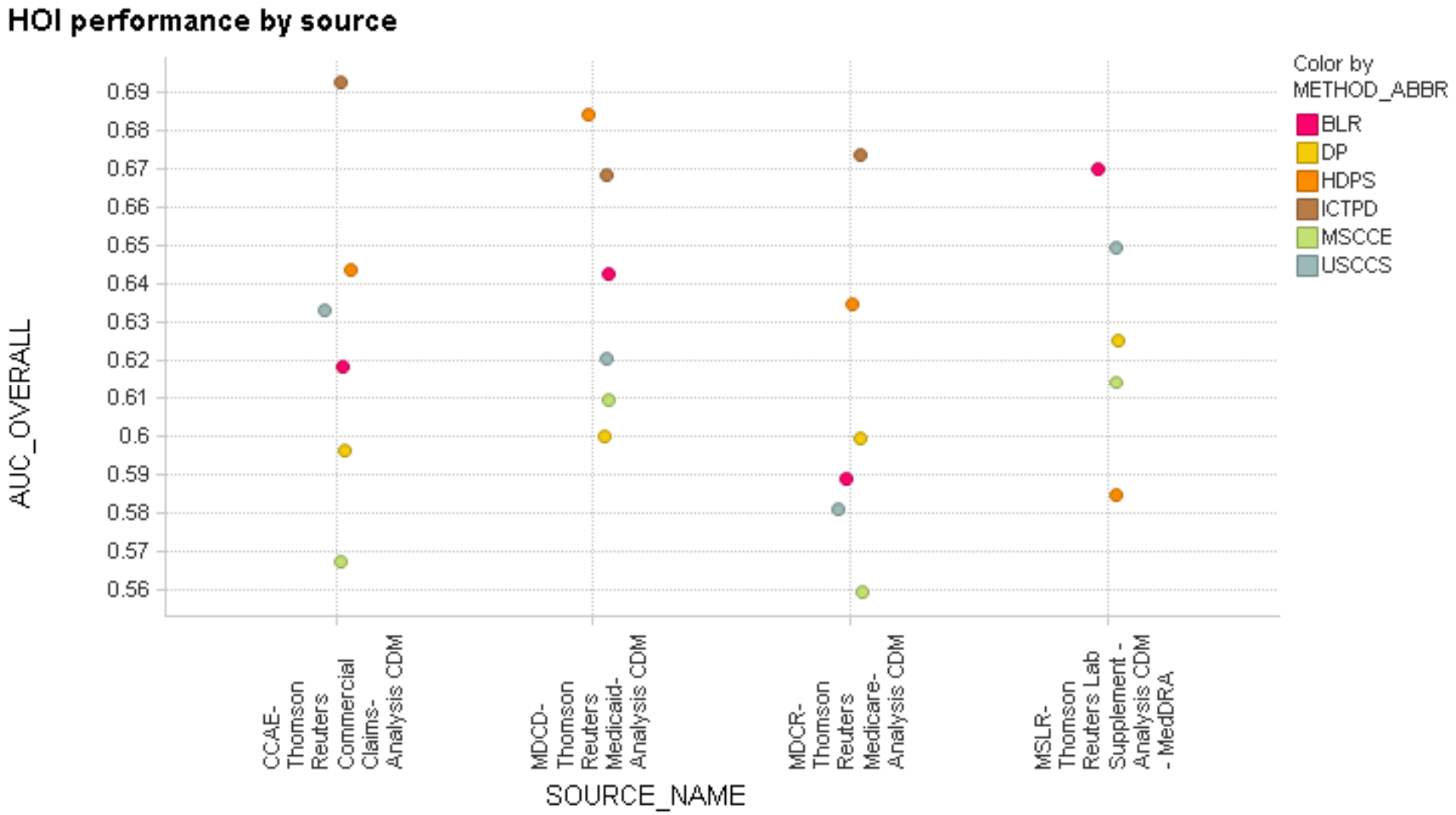
OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Summary of methods tested in OMOP 2011/2012 experiment

Method	Abbreviation	Parameter combinations	Contributor
Cohort	CM	126	Columbia U./OMOP Team
Case-control	CC	384	Columbia U./OMOP Team
Self-controlled case series	SCCS	560	Columbia U./OMOP Team
Observational screening	OS	54	UBC/ProSanos, GlaxoSmithKline
Temporal pattern discovery	ICTPD	42	Uppsala Monitoring Centre
Disproportionality analysis	DP	48	Columbia U./OMOP Team
Longitudinal Gamma Poisson Shrinker	LGPS	32	Erasmus MC

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Methods by database (AUC), 2010/2011



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Disproportionality analysis (DP)*

- three different approaches to constructing the two-by-two table for drug A and condition X: Distinct Patients, SRS, and Modified-SRS
- incident and prevalent conditions. The incident case only considers the first occurrence of each event, whereas the prevalent case considers all occurrences.
- DP metrics: proportional reporting ratio, reporting odds ratio, BCPNN, EBGM, signed chi square, PRR05; ROR05; BCPNN05; EB05
- Two versions of the method available from http://omop.fnih.org/MethodsLibrary

**Zorych, Madigan, Ryan, Bate (2011) "Disproportionality methods for pharmacovigilance in longitudinal observational databases"*
"

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Case-Control*

- The case-control design has been commonly applied in retrospective studies
- Cases defined as 'incident events', i.e. we consider the first occurrence of each condition and denote the date of such occurrence as the *index date;*
- All patients with a given condition create a set of cases
- To be selected to the case group, a patient has to be observed for at least M days prior to the index date
- Controls: all patients in the database who did not experience the condition and were enrolled/observed for at least M days are potential controls. To create a set of controls for a given case set, we divide all cases into sub-groups by sex and age.

**available for download from http://omop.fnih.org/MethodsLibrary, (two versions)*

Case-control (cont.)

- For each case group we create an index-pool that contains index-dates of all the patients in the case group. Each index-date from this index-pool is associated with a sex-age group of corresponding case patients.
- For each index-date we select, using randomization, controls from the pool of potential controls of the same sex and age who were observed on this *index date* and were enrolled into the medical plan for at least days prior to the *index date.*
- If control is selected, it is assigned this index-date as a "control index-date."
- We stop looking for controls for the particular index-date if some fixed number of controls is reached.

CC: additional features

The newest version of the method includes a number of new features such as selecting controls by matching on visit dates, restricting analysis to the first occurrence of each drug, nesting within an indication, and using an option for either conditional logistic regression or Bayesian logistic regression. When the regression is used for analysis, a number of additional covariates may be included into the model: number of drugs that the person has taken, number of person's conditions, number of visits, Charlson comorbidity index

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Cohort Method (CM*)

- This cohort approach to medical claims data includes selection of new-user cohorts

- There are three ways to select covariates and calculate propensity score in our implementation:
  - one is based on high-dimensional propensity adjustment approach (Schneeweiss et al. 2009);
  - the second way to calculate propensity is to use Bayesian regression that includes all variables from up to three dimensions as covariates.
  - The third way is based on calculating propensity utilizing the most prevalent covariates from all selected data dimensions (by Alan Brookhart, Incident User Design (IUD-HOI) Method, OMOP method library)

CM (cont.)

- Method calculate several estimates adjusted for propensity: stratified (by propensity groups) odds ratio using the Mantel-Haenszel method, adjusted odds ratio using multivariate logistic regression to model outcome as a function of exposure and indicator variables for groups of propensity score, and adjusted odds ratio from the similar multivariate logistic regression model where propensity participates as a continuous variable.
- Other available features include nesting within indication when only patients that had an indication are included into each, target or comparator, cohort. A number of additional covariates may be included into the model that estimates propensity: number of drugs that the person has taken, number of person's conditions, number of visits, Charlson comorbidity index.

Self-controlled designs

- Self-controlled case series (SCCS)*
- Observational screening (OS)
- IC Temporal Pattern Discovery (ICTPD)

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Smith et al. 2011 study design and results

- Data source: Administrative claims from health insurance board of Quebec
- Study design: Cohort
- Exposure: all patients dispensed >=30d of therapy, 180d washout
- Unexposed cohort: 2 patients per exposed, matched by age, gender, and region, with no tuberculosis therapy
- Time-at-risk: Length of exposure + 60 days
- Events: Incident hospital admission for noninfectious or toxic hepatitis
- "Event ratio" estimated with conditional logistic regression
- Covariates: prior hospitalization, Charlson score, comorbidities

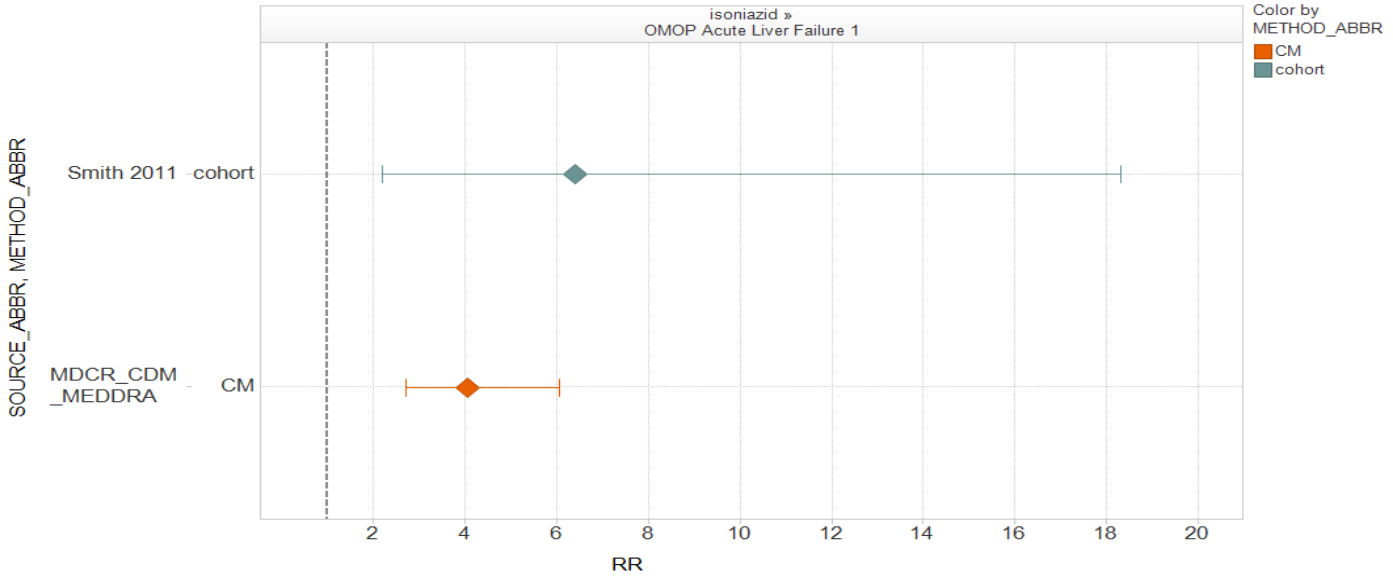
Table 2: Event rates and odds ratios for outcomes of interest, by cohort

	Crude event rate, events/total (rate per 100 patients)		Event ratio, cohort treated for LTBI v. untreated cohort (95% CI)		
Outcome; age, yr	LTBI therapy cohort	Untreated cohort*	Crude OR†	Adjusted OR‡	Adjusted OR§
Hospital admission for hepatic event of interest§					
Total	45/9145 (0.5)	15/18 290 (0.1)	6.5 (3.8–11.1)	3.7 (2.0–6.9)	2.7 (1.3–5.6)
≤ 35	5/4523 (0.1)	1/9046 (0.0)	10.0 (1.2–85.6)	NC	NC
36–50	8/2533 (0.3)	7/5066 (0.1)	2.6 (1.0–6.9)	2.0 (0.6–6.9)	1.5 (0.4–5.6)
51–65	10/1232 (0.8)	4/2464 (0.2)	7.0 (2.3–21.3)	2.9 (0.7–13.0)	2.6 (0.4–16.0)
> 65	22/857 (2.6)	3/1714 (0.2)	10.8 (4.2–28.0)	6.4 (2.2–18.3)	3.2 (0.9–11.7)

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

OMOP replication: isoniazid – acute liver injury

- Data source: MarketScan Medicare Beneficiaries (MDCR)
- Study design: Cohort
- Exposure: all patients dispensed new use of isoniazid, 180d washout
- Unexposed cohort: Patient with indicated diagnosis (e.g. pulmonary tuberculosis) but no exposure to isoniazid; negative control drug referents
- Time-at-risk: Length of exposure + 30 days, censored at incident events
- Covariates: age, sex, index year, Charlson score, number of prior visits, all prior medications, all comorbidities, all priority procedures
- “Odds ratio” estimated through propensity score stratification (20 strata)



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Opatrny et al. 2008 study design and results

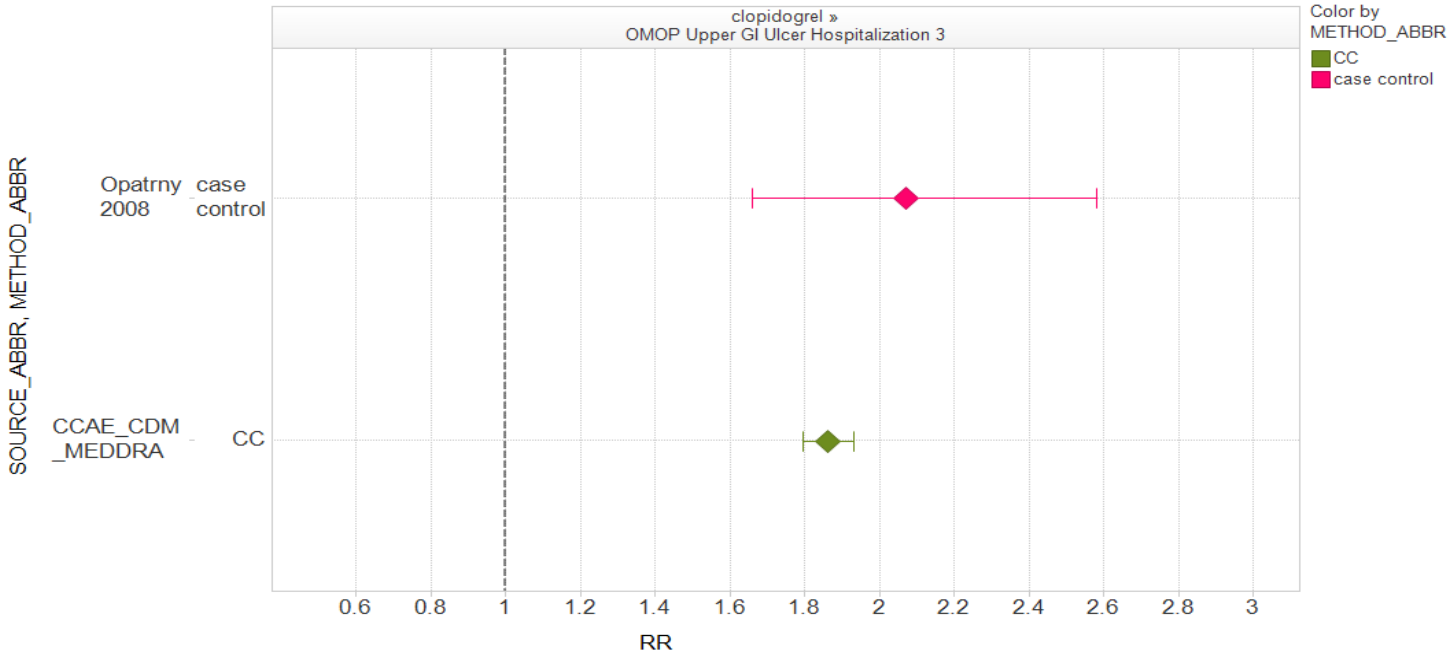
- Data source: General Practice Research Database
- Study design: Case-control
- Case definition: First episode of upper GI hemorrhage
- 10 controls per case, matched on index date, age, and practice
- Exposure definition: Prescription issues in 90 days before index date
- Exclusion criteria: < 3 years of observation
- "RR" estimated with conditional logistic regression
- Covariates: sex, BMI, BP, smoking, comorbidities, concomitant medications

Agent	Cases ($n = 4028$)	Controls ($n = 40\ 171$)	Crude rate ratio	Adjusted rate ratio*	95% confidence interval
Antidepressants					
SSRI	335 (8.3%)	1780 (4.4%)	1.97	1.33	1.09, 1.62
TCA	262 (6.5%)	1764 (4.4%)	1.52	1.04	0.83, 1.30
Venlafaxine	56 (1.4%)	229 (0.6%)	2.48	1.85	1.34, 2.55
Anticoagulant					
Warfarin	281 (7.0%)	1130 (2.8%)	2.64	2.17	1.82, 2.59
Clopidogrel	160 (4.0%)	532 (1.3%)	3.16	2.07	1.66, 2.58

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

OMOP replication: clopidogrel – upper GI bleeding

- Data source: MarketScan Commercial Claims and Encounters (CCAE)
- Study design: Case-control
- Nesting within indication (unstable angina)
- Case definition: First episode of upper GI hemorrhage
- 10 controls per case, matched on age, gender, and index date
- Exposure definition: Length of exposure + 30d
- Exclusion criteria: <180d of observation before case



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Fischer et al. 2005 study design and results

- Data source: General Practice Research Database
- Study design: Case-control
- Case definition: First-time acute myocardial infarction
- 4 controls per cases, matched on age, sex, practice, index year
- Exposure definition: Current users = drug started before and supply ended after index date
- Exclusion criteria: < 3 years of observation
- "RR" estimated with conditional logistic regression
- Covariates: BMI, smoking, comorbidities

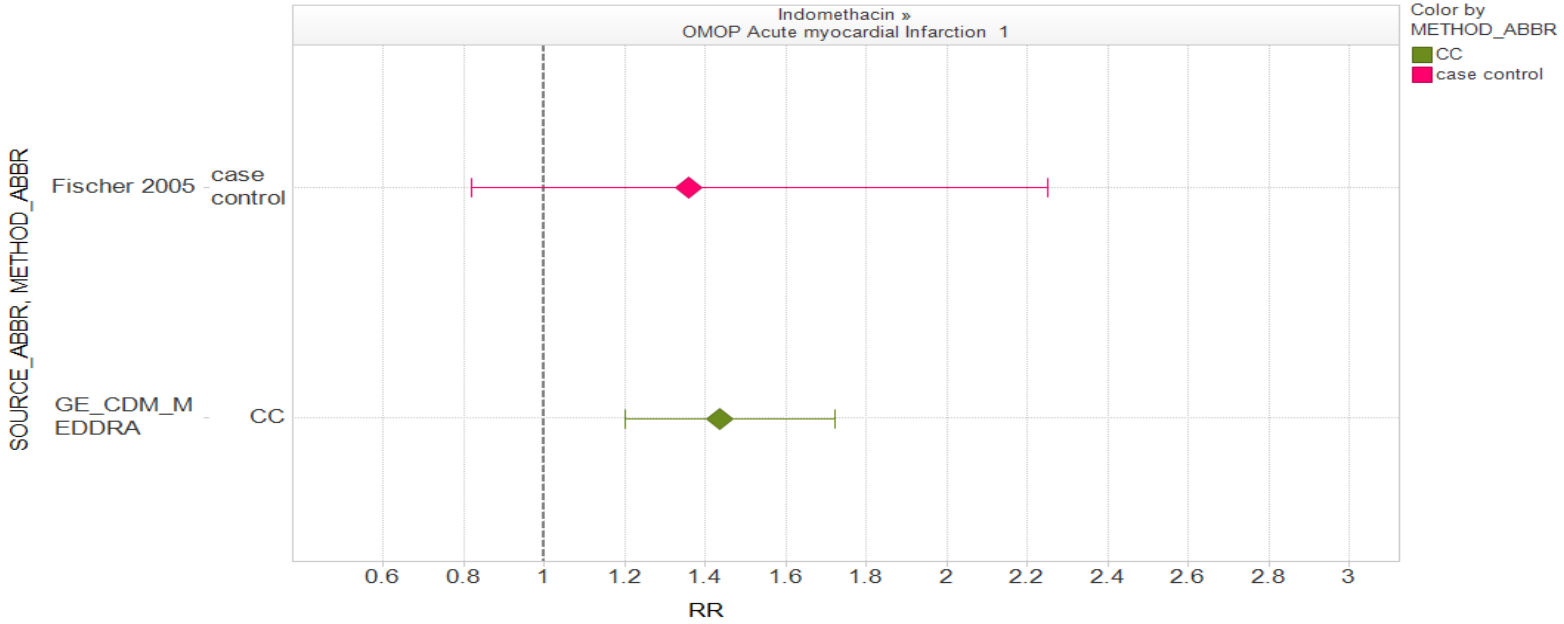
Table 2. Risk of First-Time Acute Myocardial Infarction in Those Currently Taking NSAIDs, Stratified by Individual Agents

Exposure	No. of Cases (n=8688)	No. of Controls (n=33,923)	Adjusted OR[a] (95% CI)
No NSAID use	3203	13,551	1.00 (ref)
Current NSAID use at index date	650	2339	1.07 (0.96–1.19)
Diclofenac[b]	260	834	1.23 (1.00–1.51)
Ibuprofen[b]	176	656	1.16 (0.92–1.46)
Naproxen[b]	63	251	0.96 (0.66–1.38)
Indomethacin[b]	36	124	1.36 (0.82–2.25)
Piroxicam[b]	30	114	0.95 (0.53–1.69)
Ketoprofen[b]	18	109	0.86 (0.44–1.70)

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

OMOP replication: indomethacin – acute myocardial infarction

- Data source: GE Centricity
- Study design: Case-control
- Case definition: First-time acute myocardial infarction
- 10 controls per cases, matched on age, sex, index year
- Exposure definition: Current users = drug started before and supply ended after index date
- Exclusion criteria: < 180d of observation
- “OR” estimated with Mantel-Haenszel stratification on age and sex



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Griffin et al. 2000 study design and results

- Data source: Tennessee Medicaid
- Study design: Case-control
- Case definition: First-time admission for acute renal failure
- 10,000 controls
- Exposure definition: Current users = drug started before and supply ended after index date
- Exclusion criteria: < 1 years of observation
- “RR” estimated with logistic regression
- Covariates: age, gender, ethnicity, hospitalization, prior drug use

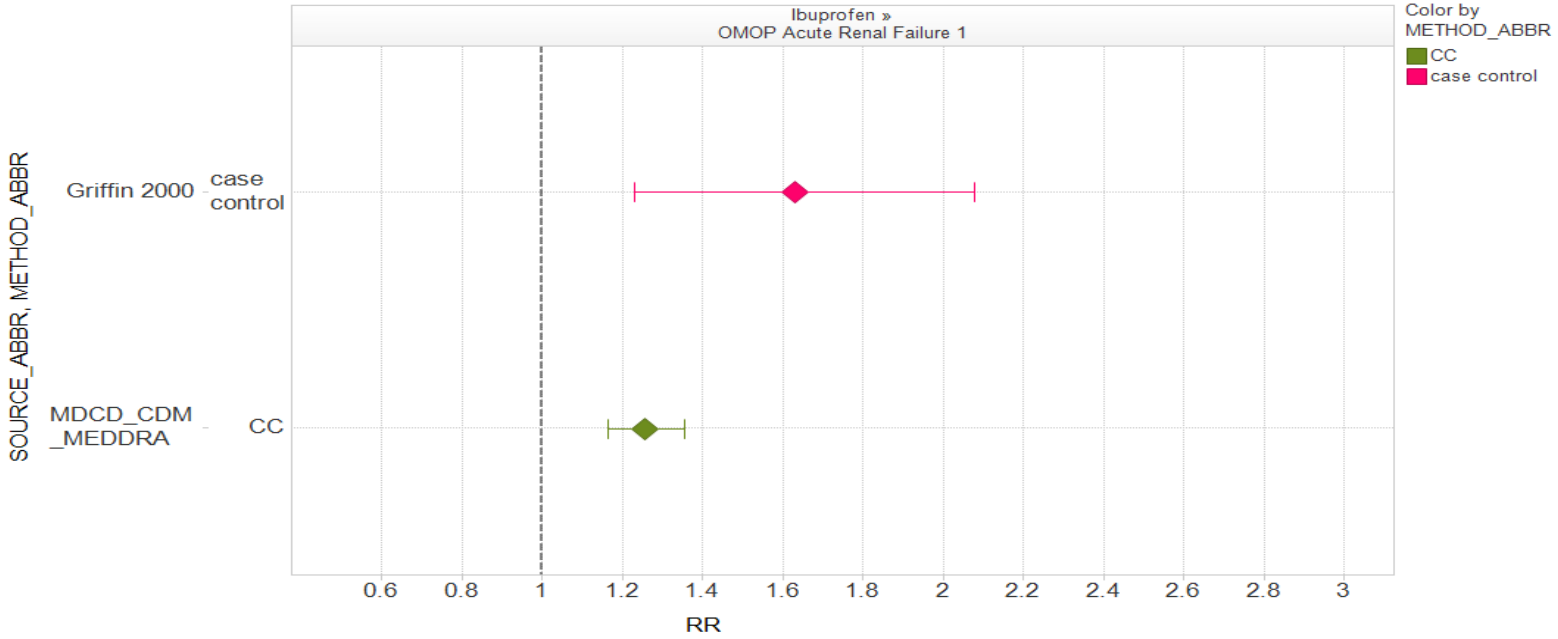
TABLE 4. Associations between use of individual NSAIDs* and hospitalization for acute renal failure among Tennessee Medicaid enrollees aged ≥65 years, 1987–1991

NSAID	Current use (%)		Odds ratio†	95% confidence interval
	Cases	Controls		
Ibuprofen	6.34	3.97	1.63	1.23, 2.08
Naproxen	1.95	1.78	[illegible]	[illegible]
Piroxicam	2.22	1.32	1.95	1.23, 2.93
Nonaspirin salicylates	0.83	0.83	0.90	0.48, 1.68
Fenoprofen	1.61	0.81	1.75	1.05, 2.92
Indomethacin	1.78	0.64	2.40	1.44, 4.00

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

OMOP replication: ibuprofen – acute renal failure

- Data source: MarketScan Multi-state Medicaid (MDCD)
- Study design: Case-control
- Case definition: First-time acute renal failure
- 10 controls per cases, matched on age, sex, index year
- Exposure definition: Current users = drug started before and supply ended after index date
- Exclusion criteria: < 180d of observation
- “OR” estimated with Mantel-Haenszel stratification on age and sex



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Tata et al. 2005 study design and results

- Data source: THIN
- Study design: Self-controlled case series
- Case definition: First diagnosis of upper GI bleed
- Exposure definition: Length of exposure of SSRI
- Exclusion criteria: < 180d of observation
- "IRR" estimated with conditional Poisson regression

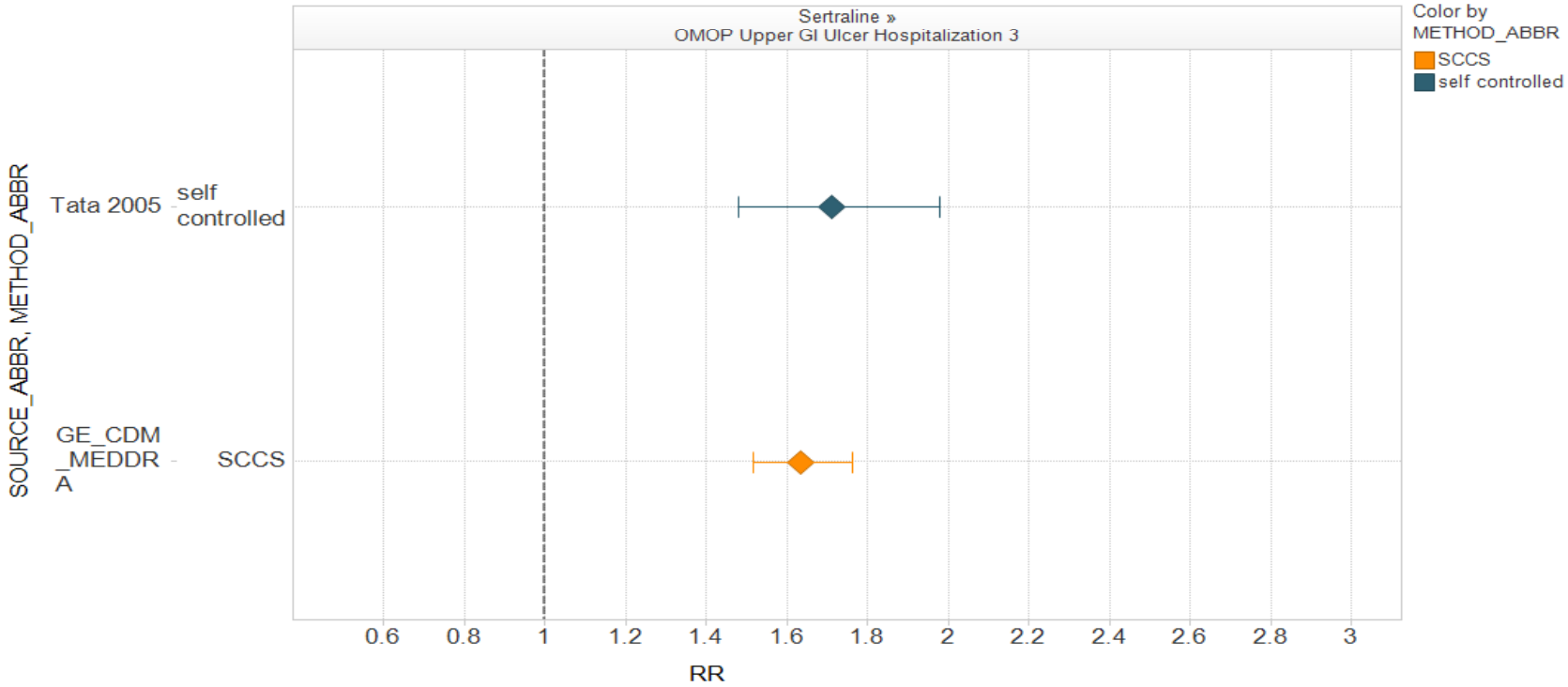
In our self-controlled analysis, we identified 8130 cases with at least one exposure to an anti-depressant or an NSAID. The incidence rate ratios (IRR) for gastro-intestinal bleeding occurring during drug exposure were 1.71 (95% CI 1.48–1.98) for SSRIs, 1.23 (95% CI 1.06–1.42) for TCAs, and 2.71 (95% CI 2.51–2.91) for NSAIDs. With concurrent prescription, the IRRs were

Aliment Pharmacol Ther **22**, 175–181

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

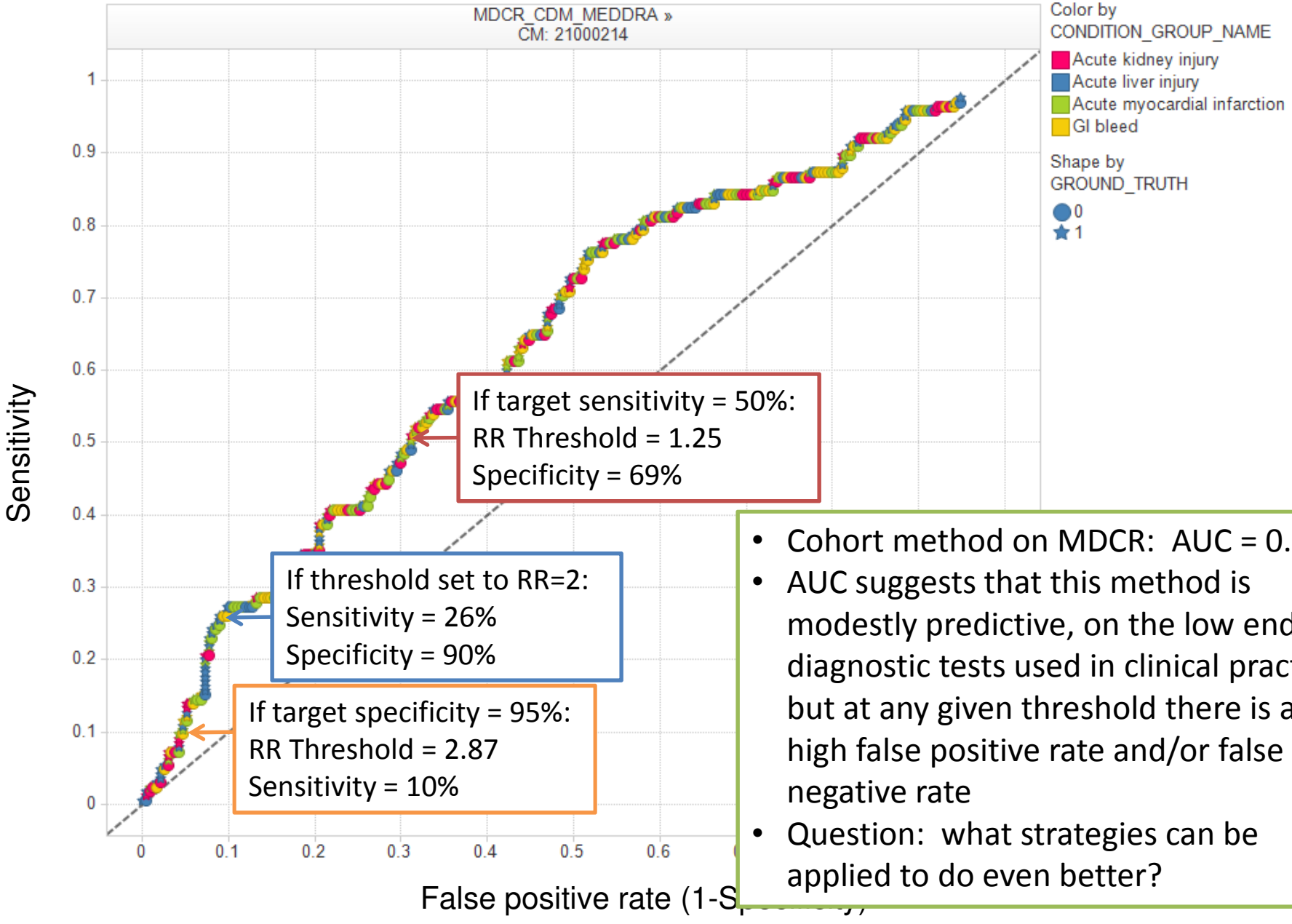
OMOP replication : sertraline – upper gastrointestinal bleeding

- Data source: GE Centricity
- Study design: Self-controlled case series
- Case definition: First diagnosis of upper GI bleed
- Exposure definition: Length of exposure of sertraline
- Exclusion criteria: < 180d of observation
- “IRR” estimated with conditional Poisson regression



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

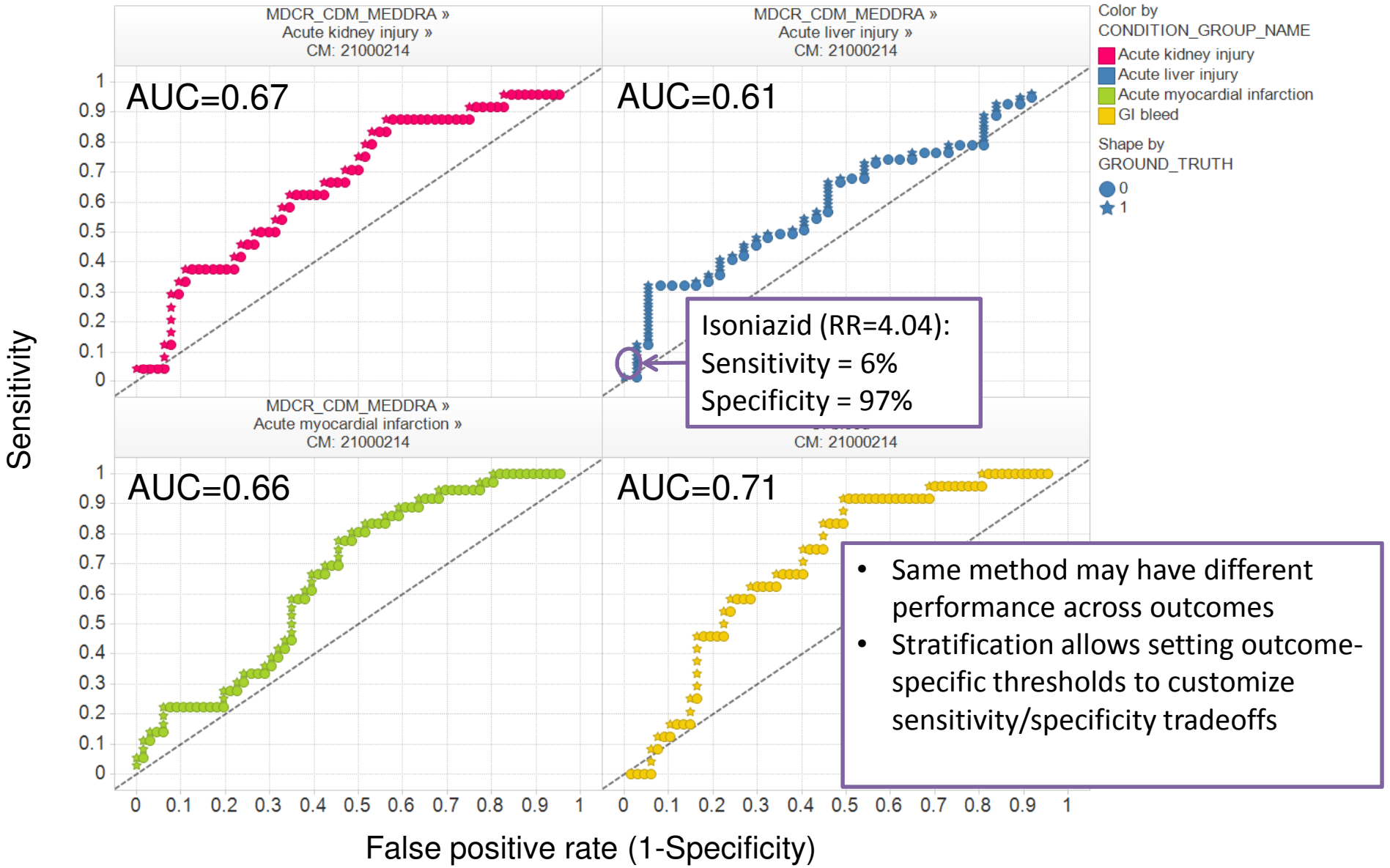
Setting thresholds from an ROC curve



- Cohort method on MDCR: AUC = 0.64
- AUC suggests that this method is modestly predictive, on the low end of diagnostic tests used in clinical practice, but at any given threshold there is a high false positive rate and/or false negative rate
- Question: what strategies can be applied to do even better?

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

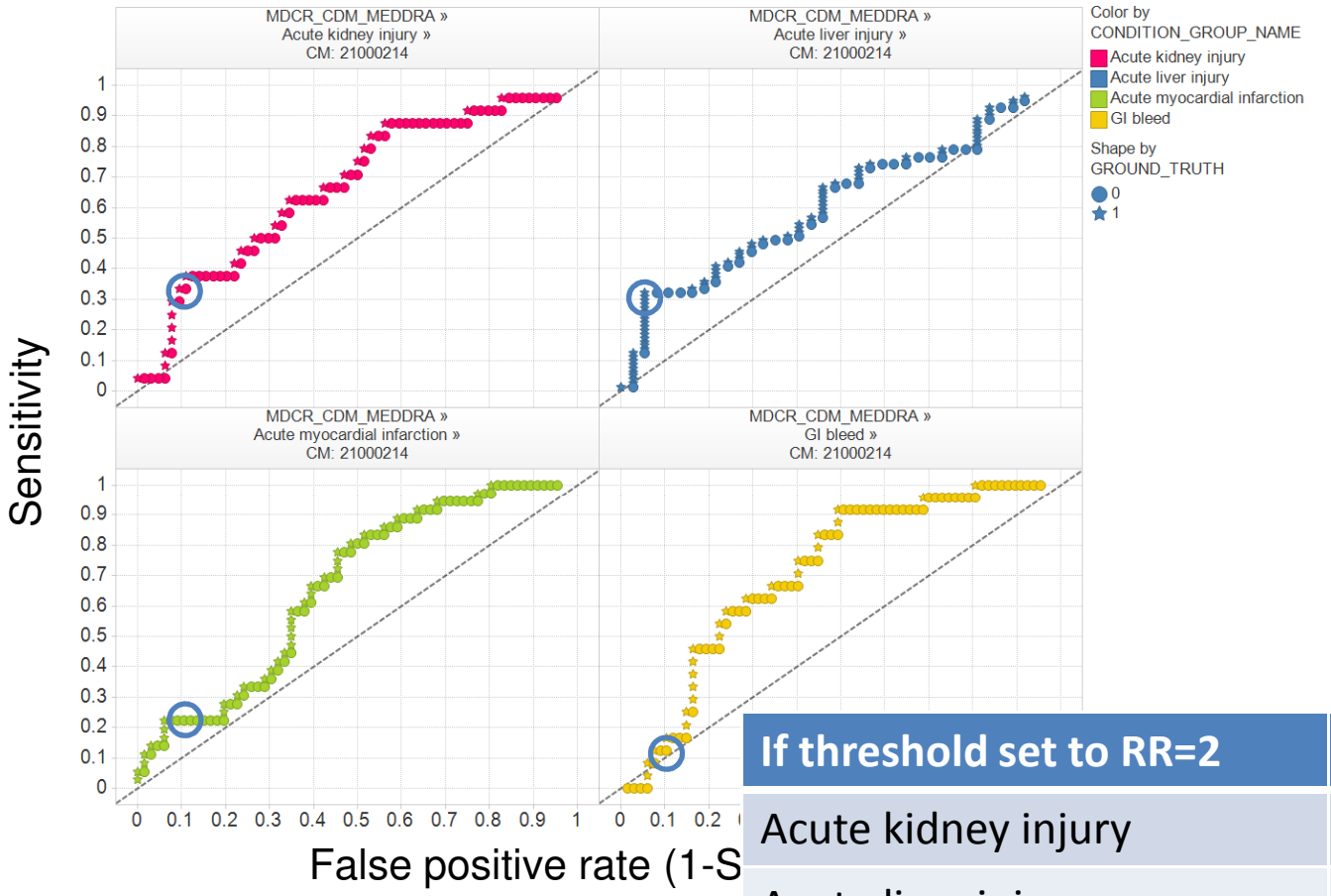
Partition by outcome



- Same method may have different performance across outcomes
- Stratification allows setting outcome-specific thresholds to customize sensitivity/specificity tradeoffs

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

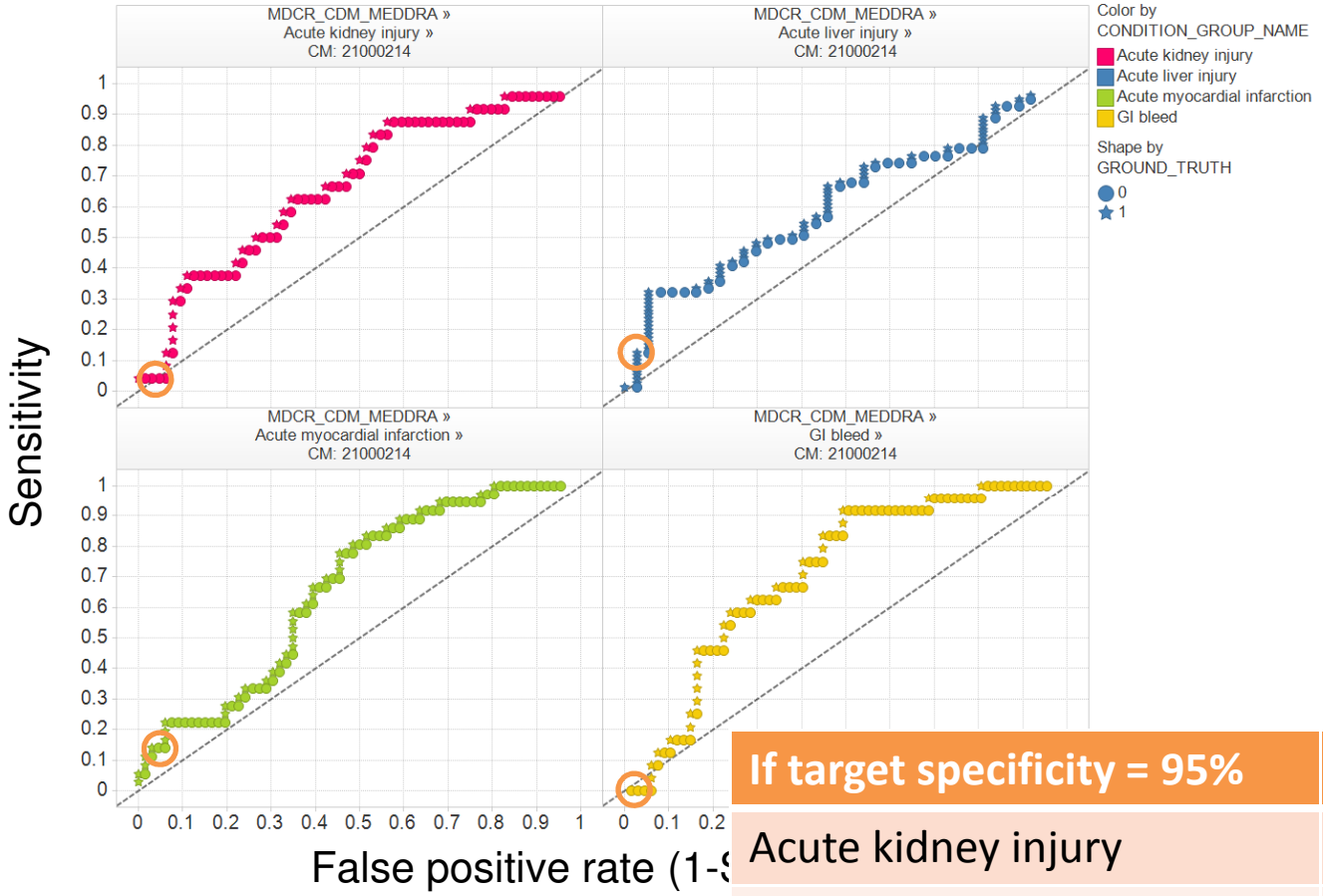
Partition by outcome: setting decision thresholds



If threshold set to RR=2	Sensitivity	Specificity
Acute kidney injury	33%	89%
Acute liver injury	30%	95%
Acute myocardial infarction	22%	89%
GI bleed	13%	90%

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

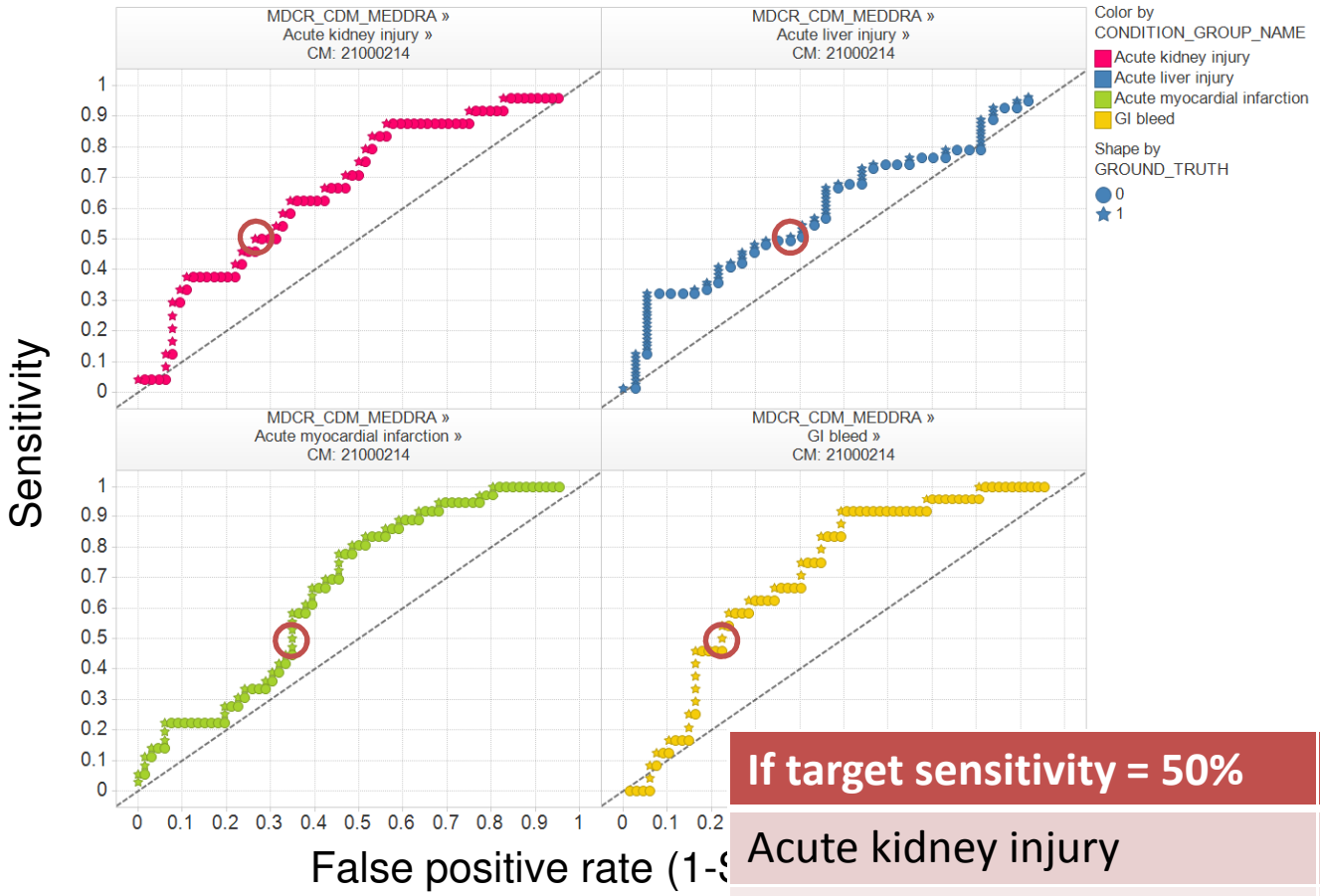
Partition by outcome: setting decision thresholds



If target specificity = 95%	Threshold	Sensitivity
Acute kidney injury	4.97	4%
Acute liver injury	2.32	12%
Acute myocardial infarction	2.42	14%
GI bleed	3.18	0%

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

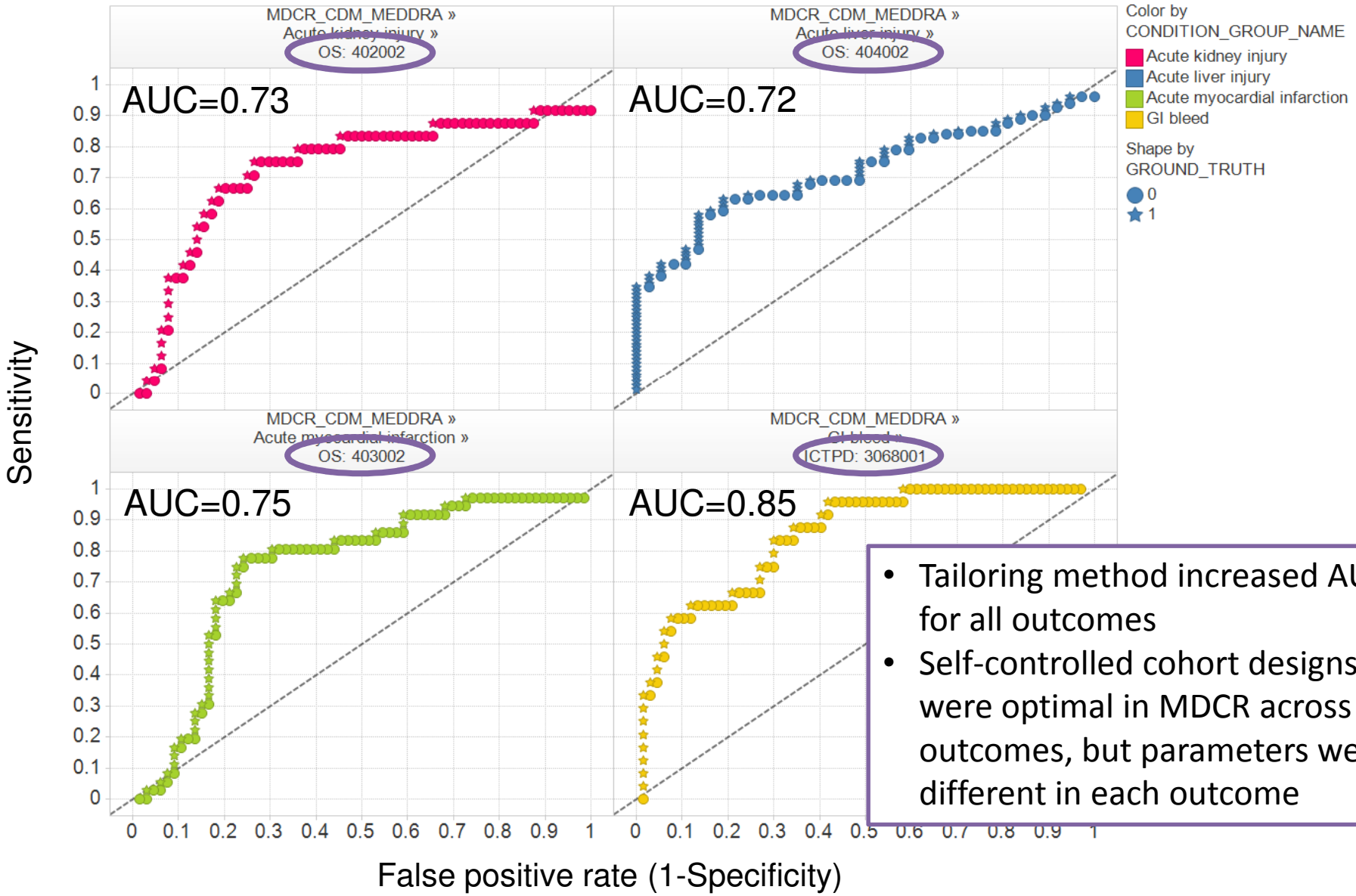
Partition by outcome: setting decision thresholds



If target sensitivity = 50%	Threshold	Specificity
Acute kidney injury	1.36	73%
Acute liver injury	1.18	68%
Acute myocardial infarction	1.25	65%
GI bleed	1.38	78%

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Idea: Tailor analyses to the outcome



- Tailoring method increased AUC for all outcomes
- Self-controlled cohort designs were optimal in MDCR across all outcomes, but parameters were different in each outcome

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

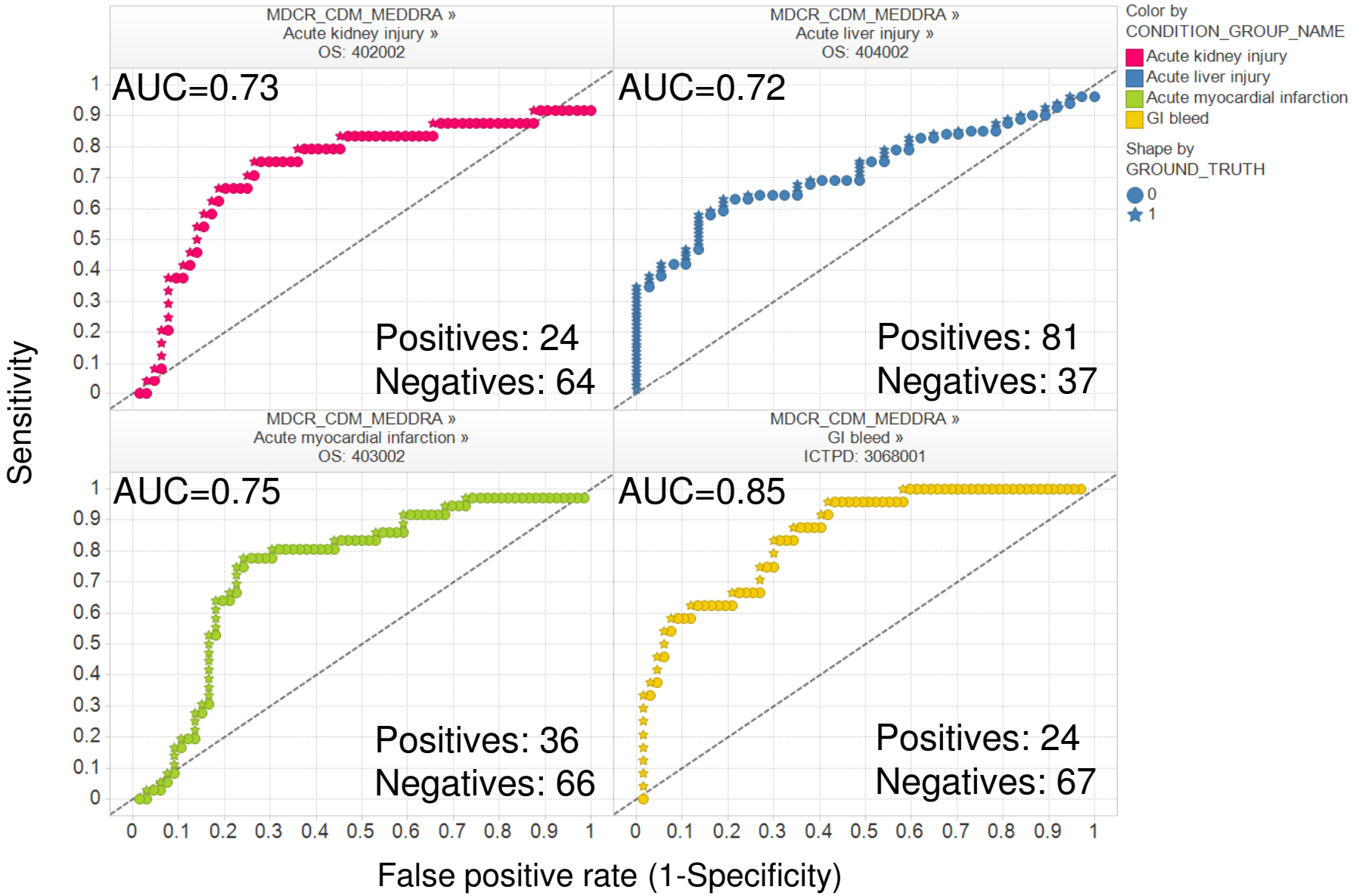
Determining sufficient sample

- Estimate prevalence of all drugs and all outcomes, stratified by gender and age decile
- Calculate the expected number of patients with drug and outcome, assuming independence (E)
- Minimum detectable relative risk (MDRR) is the effect size that can be expected to be observed with sufficient power given the sample
- A cohort study estimator[1] was consistently applied to all test cases
  - $MDRR = \{1 + (z_{\alpha} - z_{1-\beta})/2*\sqrt{(E)}\}^2$
    - where $\alpha=0.05$, $\beta=0.80$

[1]Armstrong AJE 1987

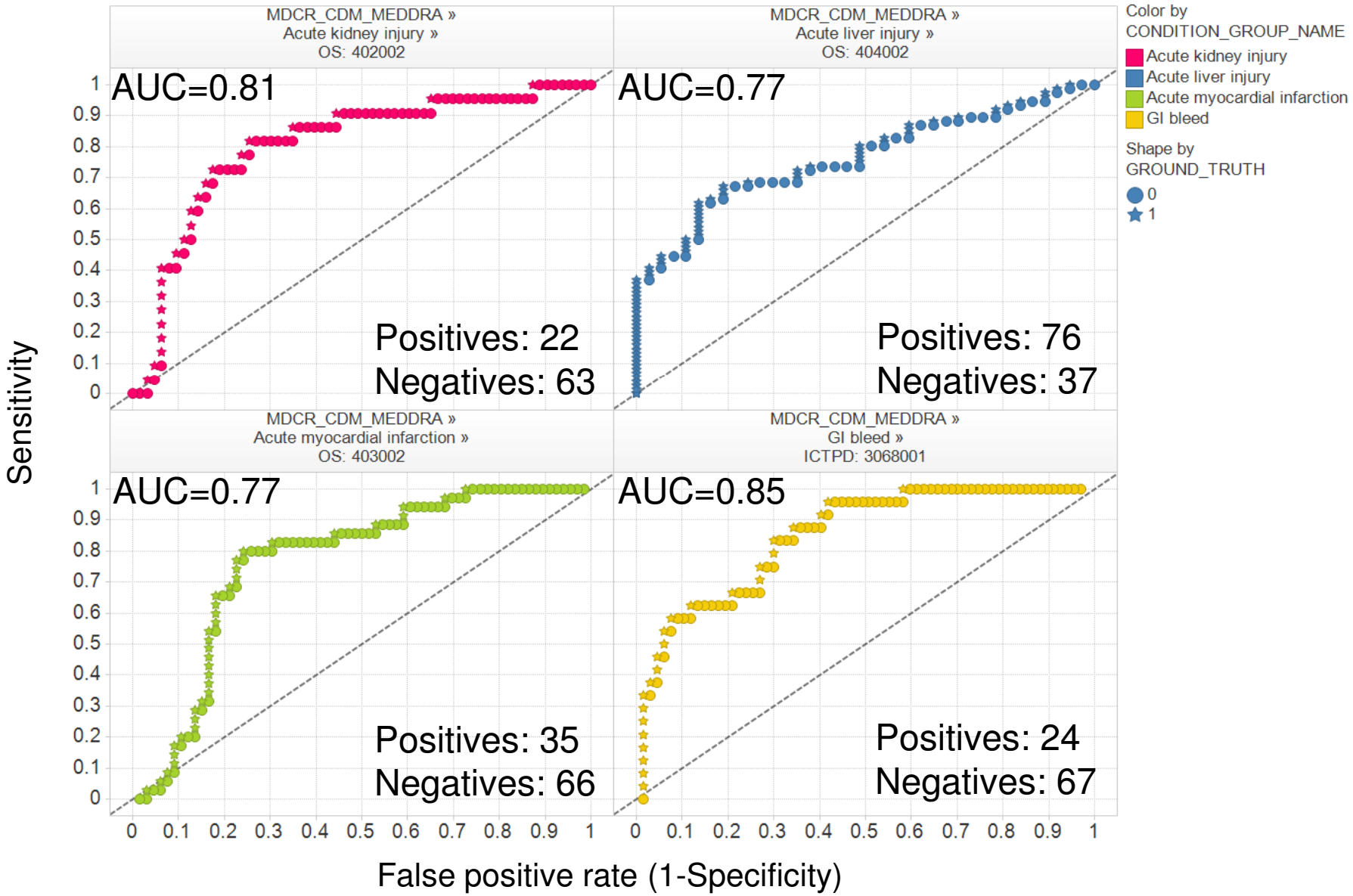
OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Idea: Restrict analyses to pairs with sufficient sample: All test cases



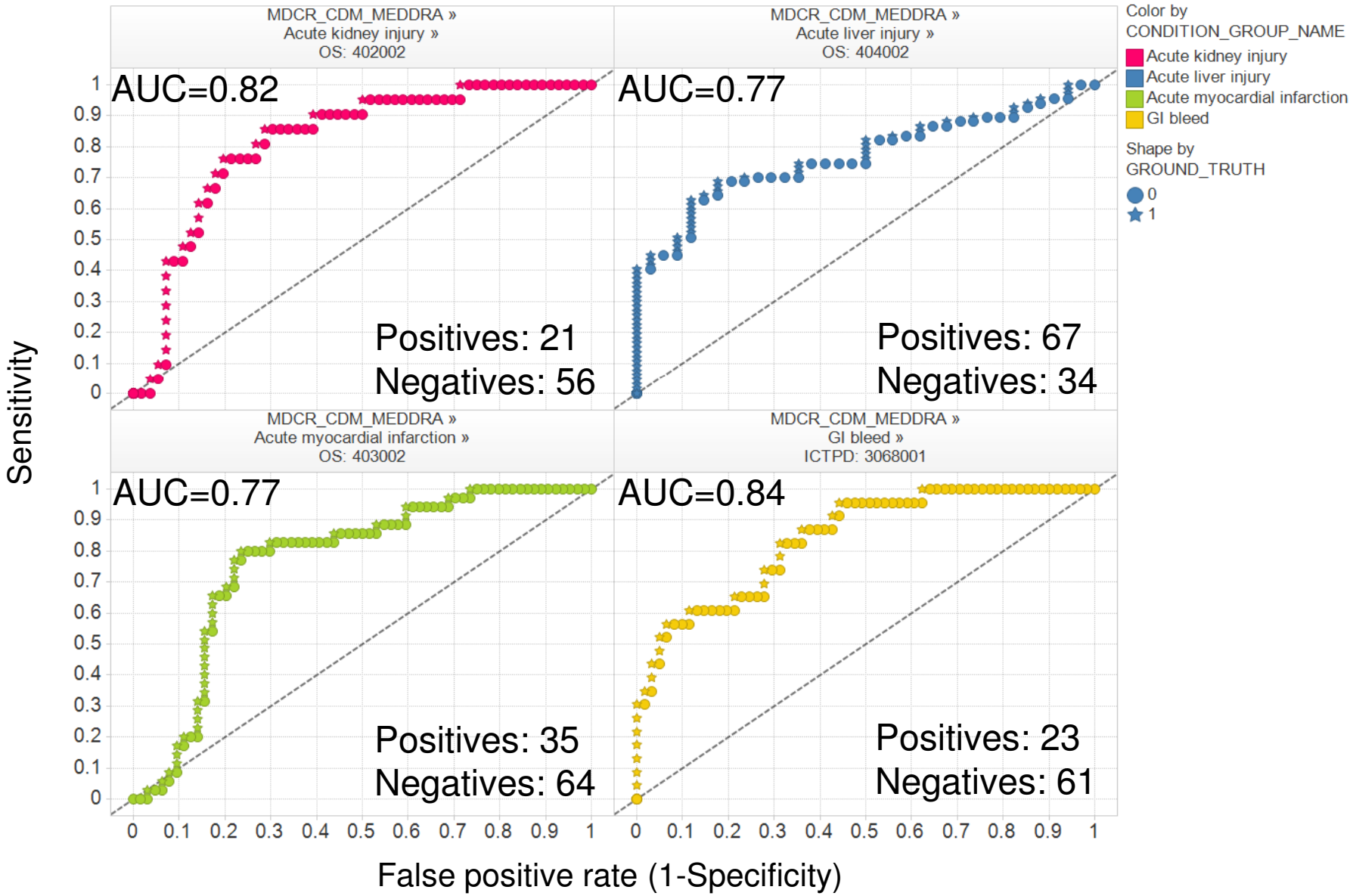
OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Idea: Restrict analyses to pairs with sufficient sample: Test cases with minimum detectable RR = **4.0**



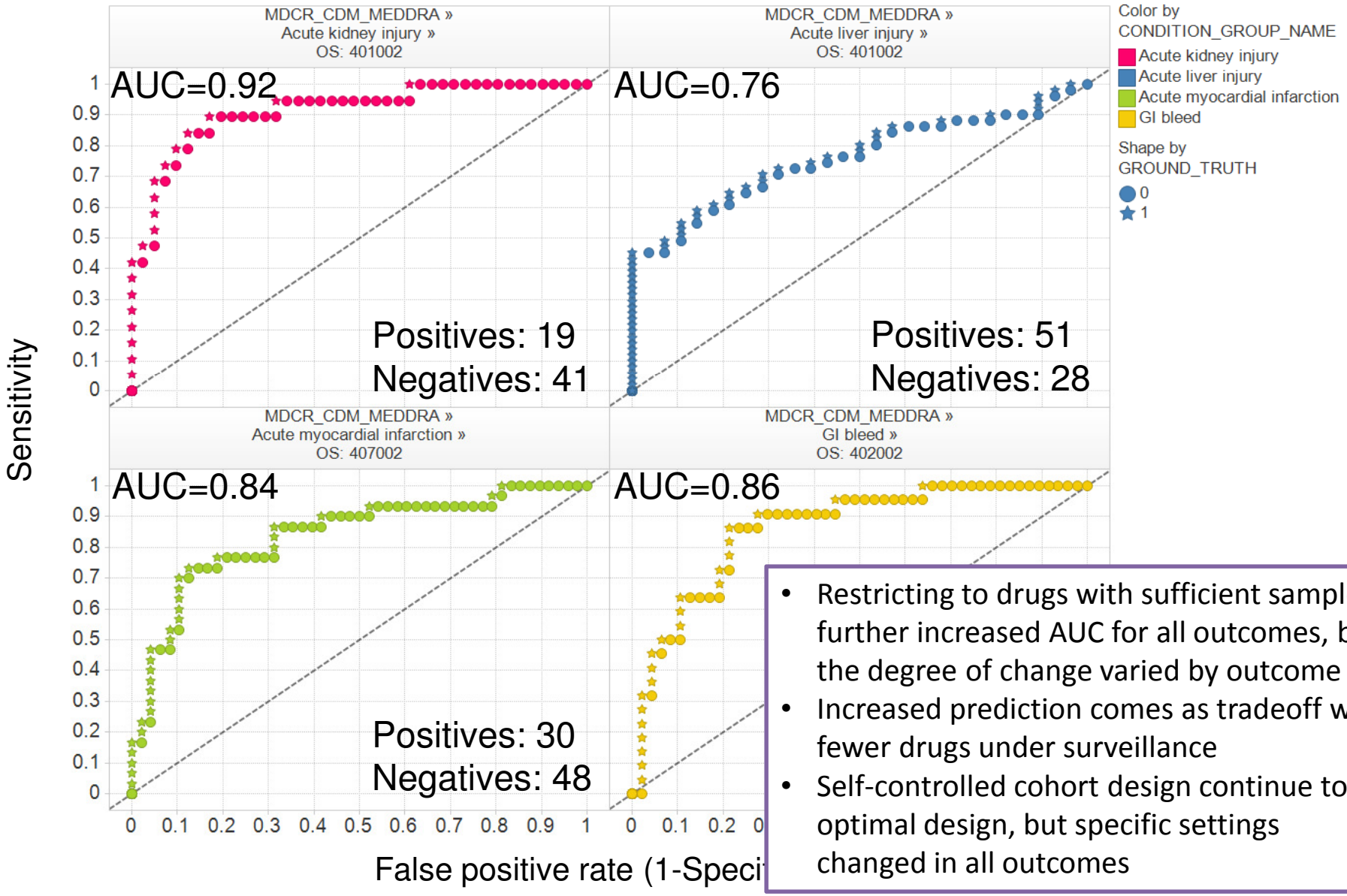
OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Idea: Restrict analyses to pairs with sufficient sample: Test cases with minimum detectable RR = **2.0**



OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

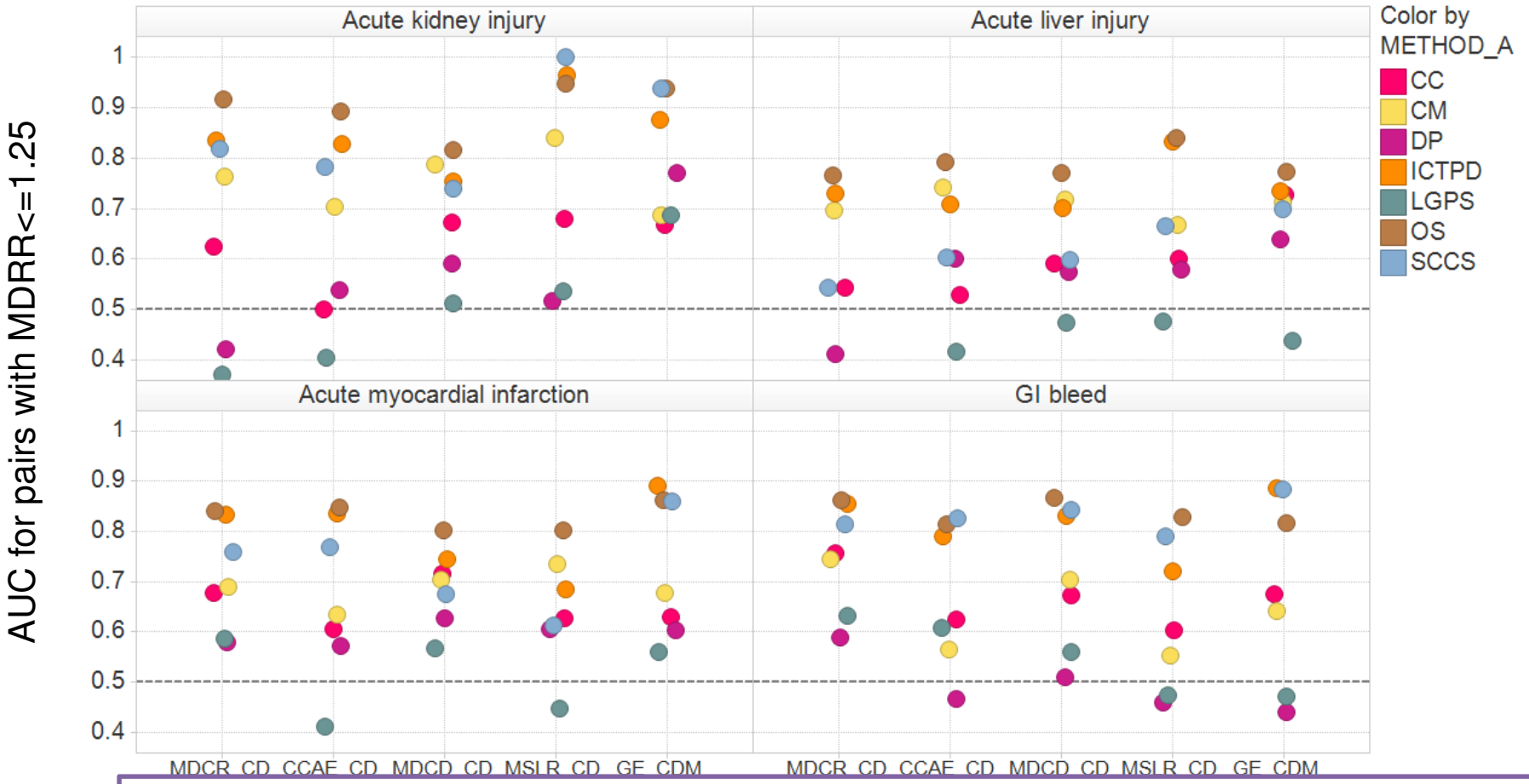
Idea: Restrict analyses to pairs with sufficient sample: Test cases with minimum detectable RR = **1.25**



- Restricting to drugs with sufficient sample further increased AUC for all outcomes, but the degree of change varied by outcome
- Increased prediction comes as tradeoff with fewer drugs under surveillance
- Self-controlled cohort design continue to be optimal design, but specific settings changed in all outcomes

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

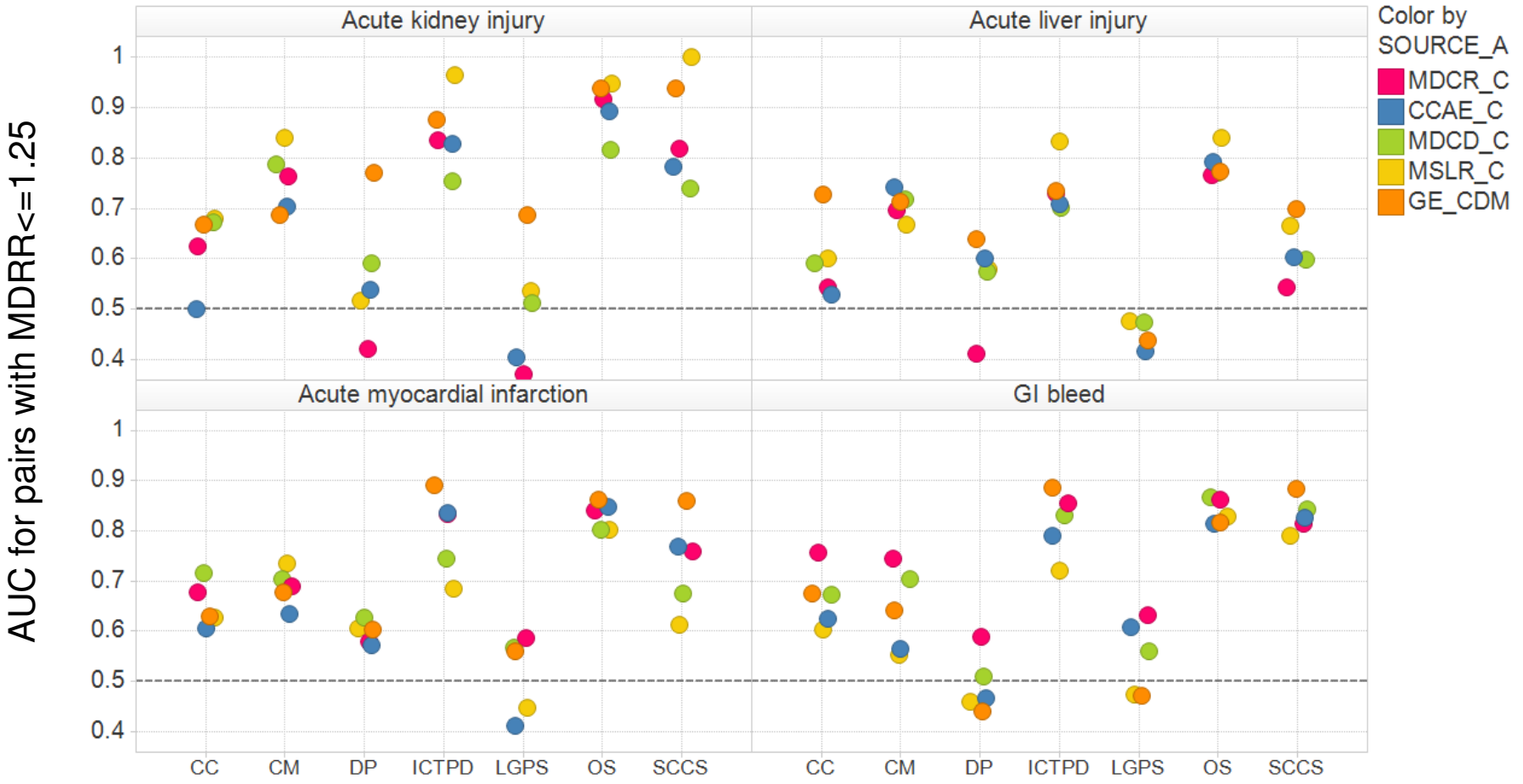
Performance across methods, by database



- All self-controlled designs (OS, ICTPD, SCCS) are consistently at or near the top of performance across all outcomes and sources
- Cohort and case-control designs have comparable performance, consistently lower than all self-controlled designs
- Substantial variability in performance across the optimal settings of each method

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Performance across databases, by method



- Less variability in performance across databases as compared to across methods
- Methods with AUC at or below 0.5 are uninformative in discriminating effects
- Crude unadjusted metrics (DP, LGPS) consistently underperform other methods and should be discouraged from use in decision-making

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Lessons for building a risk identification system

- Strategies to improve performance:
  - Partition results by outcome
  - Tailor analysis to outcome
  - Restrict to sufficient sample size
  - Optimize analysis to the data source
- OMOP's experimental evidence suggests that following these strategies may yield predictive accuracy at or better than most clinical screening tools used in standard practice

OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP

Acknowledgments

Christian Reich

Mark Khayter

Marc Suchard

OMOP FNIH for financial and technical support