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OMOP Method Evaluation

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on behalf of OMOP Research Team
August 9, 2010

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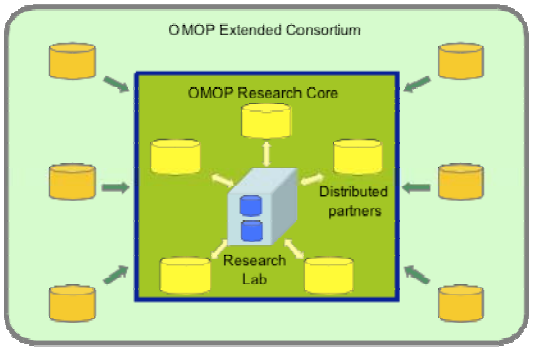
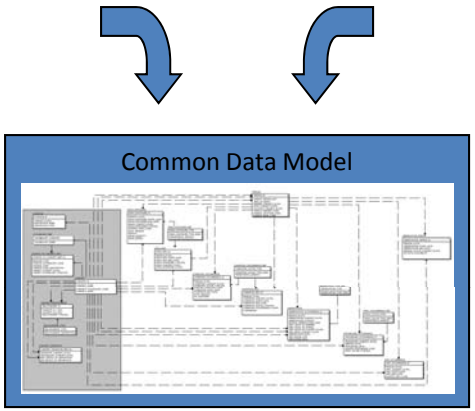
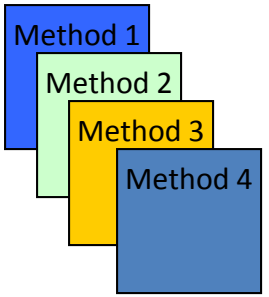
OMOP research experiment workflow





OMOP Methods Library



feasibility testing

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

Characterizing drug-outcome associations

- Active surveillance means different things to different people
  - Studying one drug-condition pair at a time
  - Broad-based screening across medical products and outcomes
- OMOP approach is to develop and test methods that may be appropriate anywhere on this continuum

Fundamental task: *Estimate* the strength of the drug-outcome relationship

Need for establishing 'ground truth' in methodological research

- Methodological research: goal is to measure performance of method in their ability to identify 'true' relationships and discern from false positive findings
- Research requires 'ground truth', as a 'gold standard' classification of test cases as true or false to be used to evaluate methods against
- Challenge with real data: 'truth' is unknown or ill-defined
  - Ideal: 'Truth' means knowledge of precise effect size
  - Actual: 'Truth' is dichotomized as 'is/is not related'
- Challenge with simulated data: data may not reflect complexities of real-world data

Analysis problems under study by OMOP

- **Monitoring of Health Outcomes of Interest (HOIs):**
  - **Estimate the strength of the association between drug exposure and specific events (e.g. acute liver failure, bleeding, MI)**
  - **Modest in number so can customize analytic approach**
  - **Ground truth based on expert assessment of drug-HOI causal associations based on literature search**
- **Identification of non-specified associations (NSA):**
  - **More exploratory in nature**
  - **Same goal: estimate the strength of the association between drug exposure and conditions**
  - **Necessarily more generic analyses (e.g., adjust for age and sex)**
  - **Ground truth causality assessment derived from the product labels**
- **Performance against simulated data**
  - **Complement 'real world' experiments**
  - **Ground truth explicitly defined**

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Parameter settings across the OMOP methods library

METHOD_NAME	HOI_PARAMETERS	NSA_PARAMETERS	Release date
Disproportionality analysis (DP)	112	112	15-Mar-10
Univariate self-controlled case series (USCCS)	64	64	2-Apr-10
Observational screening (OS)	162	162	8-Apr-10
Multi-set case control estimation (MSCCE)	32	16	16-Apr-10
Bayesian logistic regression (BLR)	24	24	21-Apr-10
Case-control surveillance (CCS)	48		2-May-10
IC Temporal Pattern Discovery (ICTPD)	84	84	23-May-10
Case-crossover (CCO)	48		1-Jun-10
HSIU cohort method (HSIU)	6	6	8-Jun-10
Maximized Sequential Probability Ratio Test (MSPRT)	144		25-Jul-10
High-dimensional propensity score (HDPS)			
Conditional sequential sampling procedure (CSSP)			
Statistical relational learning (SRL)			
Incident user design (HOI)			

http://omop.fnih.org/MethodsLibrary

Univariate self-controlled case series (USCCS) parameters

- Condition type (2): first occurrence or all occurrences of outcome
- Defining exposure time-at-risk:
  - Days from exposure start (2): should we include the drug start index date in the period at risk?
  - Surveillance window (4):
    - 30 d from exposure start
    - Duration of exposure (drug era start through drug era end)
    - Duration of exposure + 30 d
    - Duration of exposure + 60 d
- Precision of Normal prior (4): 0.5, 0.8, 1, 2
- Total parameters: 2x2x4x4 = 64 settings

- An example configuration applied to Thomson Reuters MarketScan Lab Supplemental database MSLR (ANALYSIS_ID=503005)
  - Condition type = all occurrences
  - Days from exposure start = 1
  - Surveillance window = 30d from exposure start
  - Precision of prior = 0.8

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‘Ground truth’ for Monitoring Health Outcomes of Interest

Test cases to be used for evaluating method performance for 'Monitoring of Health Outcomes of Interest'

	Drug									
Outcome	ACE Inhibitors	Amphotericin B	Antibiotics	Antiepileptics	Benzodiazepines	Beta blockers	Bisphosphonates	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema	R	N		N	N	N				N
Aplastic Anemia	N	N	N	R	N	N	N	N		N
Acute Liver Injury		N	R		N	N	N	N		
Bleeding			N		N			N		R
GI Ulcer Hospitalization	N			N		N	R		N	
Hip Fracture	N	N	N		R	N				N
Hospitalization	B									
Myocardial Infarction			N		N		N	R	R	
Mortality after MI		N		N		B				N
Renal Failure		R	N	N	N	N	N	N	N	N

Legend	Total
B- 'True positive' benefit	2
R- 'True positive' risk	9
N- 'Negative control'	44
Avoid selection due to labeling	
Not selected due to correlation with HOI	

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Each outcome has multiple definitions under study

Full set of test cases to be used for evaluating method performance for 'Monitoring of Health Outcomes of Interest' safety outcomes

		Drug									
Outcome	Definition	ACE Inhibitors	Amphotericin B	Antibiotics	Antiepileptics	Benzodiazepines	Beta blockers	Bisphosphonates	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema	1 D1	R	N		N	N	N				N
	2 D1P	R	N		N	N	N				N
Aplastic Anemia	1 D1	N	N	N	R	N	N	N	N		N
	2 D1P	N	N	N	R	N	N	N	N		N
	3 D2P	N	N	N	R	N	N	N	N		N
	4 L	N	N	N	R	N	N	N	N		N
	5 D2PL	N	N	N	R	N	N	N	N		N
Acute Liver Injury	1 D1		N	R		N	N	N	N		
	2 D2		N	R		N	N	N	N		
	3 D2P		N	R		N	N	N	N		
	4 D2PL		N	R		N	N	N	N		
	5 L1		N	R		N	N	N	N		
	6 L2		N	R		N	N	N	N		
	7 D3		N	R		N	N	N	N		
Acute Renal Failure	1 D1		R	N	N	N	N	N	N	N	N
	2 D1P		R	N	N	N	N	N	N	N	N
	3 L		R	N	N	N	N	N	N	N	N
	4 D2		R	N	N	N	N	N	N	N	N
Bleeding	1 D1			N		N			N		R
	2 D1V			N		N			N		R
	3 D2P			N		N			N		R
GI Ulcer Hospitalization	1 D	N			N		N	R		N	
	2 DP	N			N		N	R		N	
Hip Fracture	1 D	N	N	N		R	N				N
	2 DP1	N	N	N		R	N				N
	3 DP1L	N	N	N		R	N				N
	4 DP2	N	N	N		R	N				N
Myocardial Infarction	1 D1			N		N		N	R	R	
	2 D2			N		N		N	R	R	
	3 D2P			N		N		N	R	R	
	4 PL			N		N		N	R	R	
Mortality after MI	1 D1		N		N						N
	2 D2		N		N						N
	3 D2P		N		N						N
	4 PL		N		N						N

Legend	Total	213
R- 'True positive' risk		35
N- 'Negative control'		178
Not used for HOI safety assessment		

Studying method performance for 'signal refinement'

- Apply method with a specific set of parameter settings to a database for a particular drug-outcome pair that has a prior suspicion of being potentially related
- Example: Run USCCS 503005 on MSLR for ACE inhibitors – Angioedema
  - USCCS outputs point estimates of the effect size as a score on log odds scale

- Challenges:
  - How to put the resulting score in context?
  - If we had applied the same method to other drug-outcome pairs, what types of scores would we expect?
    - How many other true positives would get a score >= 1.05?
    - How many false positives would be identified with a threshold of 1.05?
  - What if we modified one of the methods parameters?
  - What if we applied the method to a different database?

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Studying method performance for 'signal refinement'

- Repeatedly apply the method to a single database for a particular drug-outcome pair, but do it for ALL drugs of interest and ALL health outcomes of interest
- Repeat that process for all parameter settings within the method, then repeat for all methods, then repeat for all databases

	Drug									
Outcome	ACE Inhibitors	Amphotericin B	Antibiotics	Antiepileptics	Benzodiazepines	Beta blockers	Bisphosphonates	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema #1	1.05			-0.50	0.35	0.35				-0.25
Angioedema #2	1.01			-0.05	0.36	0.35				-0.05
Aplastic Anemia #1	0.33	-0.69	0.52	0.70	0.24	0.12	-0.04	-0.21		0.59
Aplastic Anemia #2	0.10	-0.45	0.88	0.32	0.47	0.10	-0.57	-0.32		0.26
Aplastic Anemia #3	0.10	-0.45	0.88	0.32	0.47	0.10	-0.57	-0.32		0.26
Aplastic Anemia #4	-0.46		-0.40	0.87	0.55	-0.02	0.19	0.01		0.32
Aplastic Anemia #5	-0.14	-0.45	0.67	0.79	0.51	0.12	-0.25	-0.22		0.37
Acute Liver Failure #1		-0.20	0.16		0.06	0.00	-0.01	0.00		
Acute Liver Failure #2		0.07	0.10		0.01	-0.08	-0.01	-0.03		
Acute Liver Failure #3		-0.31	-0.07		0.25	-0.15	-0.19	0.27		
Acute Liver Failure #4			-0.09		-0.12	-0.12	-0.07			
Acute Liver Failure #5			1.56		0.59	0.01	0.37	-0.55		
Acute Liver Failure #6			1.99		1.04	0.54	0.69	-0.26		
Acute Liver Failure #7		0.58	0.17		0.02	0.00	0.09	0.02		
Acute Renal Failure #1		-0.38	0.64	0.29	0.09	0.10	-0.40	0.06	0.56	0.05
Acute Renal Failure #2		-0.02	0.03	0.50	-0.12	0.02	0.06	0.59	-0.11	0.05
Acute Renal Failure #3		0.72	0.71	-0.43	0.38	-0.07	-0.51	-0.19	0.80	0.09
Acute Renal Failure #4		-0.38	0.65	0.29	0.10	0.10	-0.38	0.04	0.56	0.06
Bleeding #1			0.25		0.10			0.00		0.46
Bleeding #2			0.32		0.19			0.05		0.49
Bleeding #3			0.26		0.09			0.01		0.22
Hip Fracture #1	-0.27		-0.04		-0.08	-0.02				0.25
Hip Fracture #2	-0.12		-0.04		-0.01	0.04				0.30
Hip Fracture #3	-0.29		-0.19		0.27	-0.24				0.08
Hip Fracture #4	-0.29		-0.19		0.27	-0.24				0.08
Acute myocardial Infarction #1			0.07		0.14		0.01	0.05	0.41	
Acute myocardial Infarction #2			0.19		0.07		-0.21	-0.07	0.29	
Acute myocardial Infarction #3			0.19		0.10		-0.19	-0.09	0.38	
Acute myocardial Infarction #4										
Mortality after Myocardial Infarction #1				-0.45						-0.31
Mortality after Myocardial Infarction #2				-0.27						-0.61
Mortality after Myocardial Infarction #3				-0.27						-0.57
Mortality after Myocardial Infarction #4										
Upper GI Ulcer Hospitalization #1	0.13			-0.12		0.11	0.07		0.47	
Upper GI Ulcer Hospitalization #2	0.23			-0.08		0.15	-0.06		0.50	

Rank-order scores to see which pairs are 'found first'

Sort the scores in descending order
(bigger scores mean more confidence in true association)

Test cases with tied scores are sorted in ascending order by ground truth, drug_id, and condition_id

Drug-outcome pairs that are unscored are treated as if they produced minimum score

Perfect predictive model would have all red rows at the top and all the blue rows at the bottom

Drug	Outcome	Score	Score Rank	Ground Truth
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1
OMOP Antibiotics	Aplastic Anemia #3	0.88	6	0
OMOP Antibiotics	Aplastic Anemia #2	0.88	7	0
OMOP Antiepileptics	Aplastic Anemia #4	0.87	8	1
OMOP Typical antipsychotics	Acute Renal Failure #3	0.80	9	0
OMOP Antiepileptics	Aplastic Anemia #5	0.79	10	1
OMOP Amphotericin B	Acute Renal Failure #3	0.72	11	1
OMOP Antibiotics	Acute Renal Failure #3	0.71	12	0
OMOP Antiepileptics	Aplastic Anemia #1	0.70	13	1
OMOP Bisphosphonates	Acute Liver Failure #6	0.69	14	0
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0
OMOP Antibiotics	Acute Renal Failure #4	0.65	16	0
OMOP Antibiotics	Acute Renal Failure #1	0.64	17	0
OMOP Tricyclic antidepressants	Acute Renal Failure #2	0.59	18	0
OMOP Benzodiazepines	Acute Liver Failure #5	0.59	19	0
OMOP Warfarin	Aplastic Anemia #1	0.59	20	0
OMOP Amphotericin B	Acute Liver Failure #7	0.58	21	0
OMOP Typical antipsychotics	Acute Renal Failure #4	0.56	22	0
OMOP Typical antipsychotics	Acute Renal Failure #1	0.56	23	0
OMOP Benzodiazepines	Aplastic Anemia #4	0.55	24	0
OMOP Beta blockers	Acute Liver Failure #6	0.54	25	0
OMOP Antibiotics	Aplastic Anemia #1	0.52	26	0
OMOP Benzodiazepines	Aplastic Anemia #5	0.51	27	0
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #2	0.50	28	0
OMOP Antiepileptics	Acute Renal Failure #2	0.50	29	0
OMOP Warfarin	Bleeding #2	0.49	30	1
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #1	0.47	31	0
OMOP Benzodiazepines	Aplastic Anemia #3	0.47	32	0
OMOP Benzodiazepines	Aplastic Anemia #2	0.47	33	0
OMOP Warfarin	Bleeding #1	0.46	34	1
OMOP Typical antipsychotics	Acute myocardial Infarction #1	0.41	35	1
OMOP Benzodiazepines	Acute Renal Failure #3	0.38	36	0
OMOP Typical antipsychotics	Acute myocardial Infarction #3	0.38	37	1

…list ranked for scores of all 213 drug-outcome pairs

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

Positive predictive value = precision = TP/ (TP+FP)

Negative predictive value = TN / (FN+TN)

Sensitivity = Recall = TP/ (TP+FN)

Specificity = TN/ (FP+TN)

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Calculate performance using specific thresholds chosen as the score for each pair

Drug	Outcome	Score	Score Rank	Ground Truth	precision	false positive rate	sensitivity
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1	1.00	0.00	0.03
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1	1.00	0.00	0.06
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1	1.00	0.00	0.09
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0	0.75	0.01	0.09
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1	0.80	0.01	0.11
OMOP Antibiotics			6	0	0.67	0.01	0.11
OMOP Antibiotics			7	0	0.57	0.02	0.11
OMOP Antiepileptics			8	1	0.63	0.02	0.14
OMOP Typical antipsychotics			9	0	0.56	0.02	0.14
OMOP Antiepileptics			10	1	0.60	0.02	0.17
OMOP Amphotericin B			11	1	0.64	0.02	0.20
OMOP Antibiotics			12	0	0.58	0.03	0.20
OMOP Antiepileptics			13	1	0.62	0.03	0.23
OMOP Bisphosphonates			14	0	0.57	0.03	0.23
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0	0.53	0.04	0.23
OMOP Antibiotics	Acute Renal Failure #4	0.65	16	0	0.50	0.04	0.23
OMOP Antibiotics	Acute Renal Failure #1	0.64	17	0	0.47	0.05	0.23
OMOP Tricyclic antidepressants	Acute Renal Failure #2	0.59	18	0	0.44	0.06	0.23
OMOP Benzodiazepines	Acute Liver Failure #5	0.59	19	0	0.42	0.06	0.23
OMOP Warfarin	Aplastic Anemia #1	0.59	20	0	0.40	0.07	0.23
OMOP Amphotericin B	Acute Liver Failure #7	0.58	21	0	0.38	0.07	0.23
OMOP Typical antipsychotics	Acute Renal Failure #4	0.56	22	0	0.36	0.08	0.23
OMOP Typical antipsychotics	Acute Renal Failure #1	0.56	23	0	0.35	0.08	0.23
OMOP Benzodiazepines	Aplastic Anemia #4	0.55	24	0	0.33	0.09	0.23
OMOP Beta blockers	Acute Liver Failure #6	0.54	25	0	0.32	0.10	0.23
OMOP Antibiotics	Aplastic Anemia #1	0.52	26	0	0.31	0.10	0.23
OMOP Benzodiazepines	Aplastic Anemia #5	0.51	27	0	0.30	0.11	0.23
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #2	0.50	28	0	0.29	0.11	0.23
OMOP Antiepileptics	Acute Renal Failure #2	0.50	29	0	0.28	0.12	0.23
OMOP Warfarin	Bleeding #2	0.49	30	1	0.30	0.12	0.26

'Precision' describes what proportion of pairs at or above this score are true relationships

For ACE inhibitor-Angioedema #2, score = 1.01.

5 pairs have scores >=1.01

4 of those pairs are true

Precision = 4/5 = 0.80

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Calculate performance using specific thresholds chosen as the score for each pair

Drug	Outcome	Score	Score Rank	Ground Truth	precision	false positive rate	sensitivity
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1	1.00	0.00	0.03
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1	1.00	0.00	0.06
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1	1.00	0.00	0.09
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0	0.75	0.01	0.09
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1	0.80	0.01	0.11
OMOP Antibiotics	Aplastic Anemia #3	0.88	6	0	0.67	0.01	0.11
OMOP Antibiotics	Aplastic Anemia #2	0.88	7	0	0.57	0.02	0.11
OMOP Antiepileptics	Aplastic Anemia #4	0.87	8	1	0.63	0.02	0.14
OMOP Typical antipsychotics	Acute Renal Failure #3	0.80	9	0	0.56	0.02	0.14
OMOP Antiepileptics	Aplastic Anemia #5	0.79	10	1	0.60	0.02	0.17
OMOP Amphotericin B	Acute Renal Failure #3	0.72	11	1	0.64	0.02	0.20
OMOP Antibiotics	Acute Renal Failure #3	0.71	12	0	0.58	0.03	0.20
OMOP Antiepileptics	Aplastic Anemia #1	0.70	13	1	0.62	0.03	0.23
OMOP Bisphosphonates	Acute Liver Failure #6	0.69	14	0	0.57	0.03	0.23
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0	0.53	0.04	0.23
OMOP Antibiotics					0.50	0.04	0.23
OMOP Antibiotics					0.47	0.05	0.23
OMOP Tricyclic antidepr					0.44	0.06	0.23
OMOP Benzodiazepines					0.42	0.06	0.23
OMOP Warfarin					0.40	0.07	0.23
OMOP Amphotericin B					0.38	0.07	0.23
OMOP Typical antipsycl					0.36	0.08	0.23
OMOP Typical antipsychotics					0.35	0.08	0.23
OMOP Benzodiazepines	Aplastic Anemia #4	0.55	24	0	0.33	0.09	0.23
OMOP Beta blockers	Acute Liver Failure #6	0.54	25	0	0.32	0.10	0.23
OMOP Antibiotics	Aplastic Anemia #1	0.52	26	0	0.31	0.10	0.23
OMOP Benzodiazepines	Aplastic Anemia #5	0.51	27	0	0.30	0.11	0.23
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #2	0.50	28	0	0.29	0.11	0.23
OMOP Antiepileptics	Acute Renal Failure #2	0.50	29	0	0.28	0.12	0.23
OMOP Warfarin	Bleeding #2	0.49	30	1	0.30	0.12	0.26

'False positive rate' details the fraction of the negative controls that are identified with scores above the given threshold

For Antibiotics-Aplastic Anemia #5, score = 0.67.
8 negative control pairs have scores >=0.67
False positive rate = 8/178 = 0.04

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Calculate performance using specific thresholds chosen as the score for each pair

Drug	Outcome	Score	Score Rank	Ground Truth	precision	false positive rate	sensitivity
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1	1.00	0.00	0.03
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1	1.00	0.00	0.06
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1	1.00	0.00	0.09
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0	0.75	0.01	0.09
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1	0.80	0.01	0.11
OMOP Antibiotics	Aplastic Anemia #3	0.88	6	0	0.67	0.01	0.11
OMOP Antibiotics	Aplastic Anemia #2	0.88	7	0	0.57	0.02	0.11
OMOP Antiepileptics	Aplastic Anemia #4	0.87	8	1	0.63	0.02	0.14
OMOP Typical antipsychotics	Acute Renal Failure #3	0.80	9	0	0.56	0.02	0.14
OMOP Antiepileptics	Aplastic Anemia #5	0.79	10	1	0.60	0.02	0.17
OMOP Amphotericin B	Acute Renal Failure #3	0.72	11	1	0.64	0.02	0.20
OMOP Antibiotics	Acute Renal Failure #3	0.71	12	0	0.58	0.03	0.20
OMOP Antiepileptics	Aplastic Anemia #1	0.70	13	1	0.62	0.03	0.23
OMOP Bisphosphonates	Acute Liver Failure #6	0.69	14	0	0.57	0.03	0.23
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0	0.53	0.04	0.23
OMOP Antibiotics	Acute Renal Failure #4	0.65	16	0	0.50	0.04	0.23
OMOP Antibiotics	Acute Renal Failure #1	0.64	17	0	0.47	0.05	0.23
OMOP Tricyclic antidepressants	Acute Renal Failure #2	0.59	18	0	0.44	0.06	0.23
OMOP Benzodiazepines	Acute Liver Failure #5	0.59	19	0	0.42	0.06	0.23
OMOP Warfarin	Aplastic Anemia #1	0.59	20	0	0.40	0.07	0.23
OMOP Amphotericin B	Acute Liver Failure #7	0.58	21	0	0.38	0.07	0.23
OMOP Typical antipsychotics	Acute Renal Failure #4	0.56	22	0	0.36	0.08	0.23
OMOP Typical antipsychotics	Acute Renal Failure #1	0.56	23	0	0.35	0.08	0.23
OMOP Benzodiaz					0.33	0.09	0.23
OMOP Beta bloc					0.32	0.10	0.23
OMOP Antibiotics					0.31	0.10	0.23
OMOP Benzodiaz					0.30	0.11	0.23
OMOP Typical ar					0.29	0.11	0.23
OMOP Antiepilep					0.28	0.12	0.23
OMOP Warfarin	Bleeding #2	0.49	30	1	0.30	0.12	0.26

'Sensitivity', or 'recall', details the fraction of the true positives that are identified with scores above the given threshold

For Warfarin-Bleeding #2, score = 0.49.

9 'true positive' pairs have scores >=0.49; Sensitivity = 9/35 = 0.26

Accuracy measures from different perspectives

- **Area under ROC curve (AUC)** – what is the composite tradeoff between sensitivity and specificity at all possible threshold values?
- **Mean average precision (MAP)** – on average, what proportion of predictions are true at different thresholds?
- **p@k** - among the top k (e.g. 100) scores, what percentage are true?
- **recall@FPR** - if we can tolerate a particular false positive rate (e.g. 5%), what fraction of the true positives will we identify?
- **Average false positive rate** – what is the average false positive rate observed for each of the true positives?

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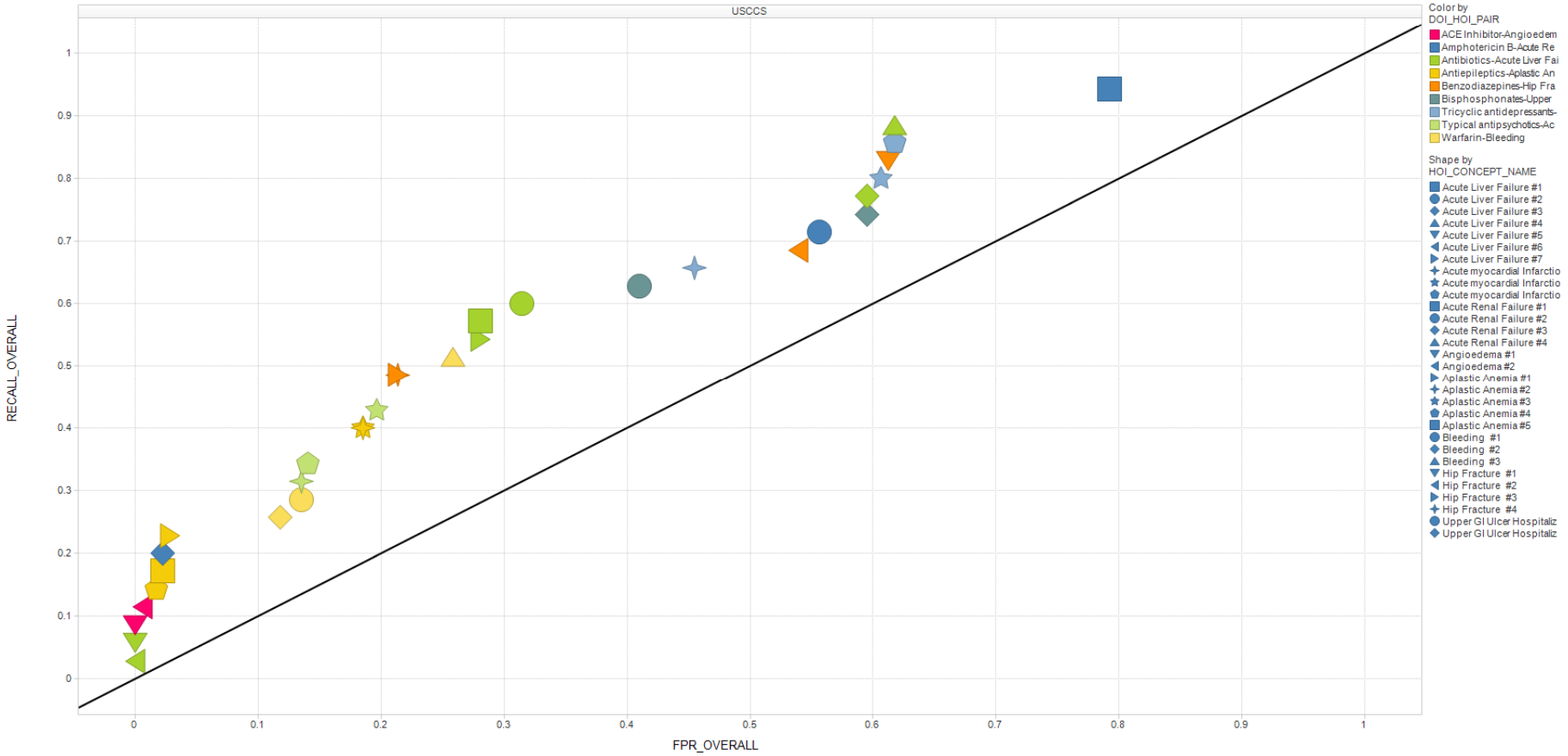
Receiver Operating Characteristic (ROC) curve



- 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)

USCCS in MSLR: AUC = 0.659

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Calculating MAP

Drug	Outcome	Score	Score Rank	Ground Truth	precision	MAP element
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1	1.00	1.00
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1	1.00	1.00
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1	1.00	1.00
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0	0.75	
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1	0.80	0.80
OMOP Antibiotics	Aplastic Anemia #3	0.88	6	0	0.67	
OMOP Antibiotics	Aplastic Anemia #2	0.88	7	0	0.57	
OMOP Antiepileptics	Aplastic Anemia #4	0.87	8	1	0.63	0.63
OMOP Typical antipsychotics	Acute Renal Failure #3	0.80	9	0	0.56	
OMOP Antiepileptics	Aplastic Anemia #5	0.79	10	1	0.60	0.60
OMOP Amphotericin B	Acute Renal Failure #3	0.72	11	1	0.64	0.64
OMOP Antibiotics	Acute Renal Failure #3	0.71	12	0	0.58	
OMOP Antiepileptics	Aplastic Anemia #1	0.70	13	1	0.62	0.62
OMOP Bisphosphonates	Acute Liver Failure #6	0.69	14	0	0.57	
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0	0.53	
OMOP Antibiotics	Acute Renal Failure #4	0.65	16	0	0.50	
OMOP Antibiotics	Acute Renal Failure #1	0.64	17	0	0.47	
OMOP Tricyclic antidepressants	Acute Renal Failure #2	0.59	18	0	0.44	
OMOP Benzodiazepines	Acute Liver Failure #5	0.59	19	0	0.42	
OMOP Warfarin	Aplastic Anemia #1	0.59	20	0	0.40	
OMOP Amphotericin B	Acute Liver Failure #7	0.58	21	0	0.38	
OMOP Typical antipsychotics	Acute Renal Failure #4	0.56	22	0	0.36	
OMOP Typical antipsychotics	Acute Renal Failure #1	0.56	23	0	0.35	
OMOP Benzodiazepines	Aplastic Anemia #4	0.55	24	0	0.33	
OMOP Beta blockers	Acute Liver Failure #6	0.54	25	0	0.32	
OMOP Antibiotics	Aplastic Anemia #1	0.52	26	0	0.31	
OMOP Benzodiazepines	Aplastic Anemia #5	0.51	27	0	0.30	
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #2	0.50	28	0	0.29	
OMOP Antiepileptics	Acute Renal Failure #2	0.50	29	0	0.28	
OMOP Warfarin	Bleeding #2	0.49	30	1	0.30	0.30

- Identify precision for all 'true' pairs
- For unscored 'true' pairs, assign minimum precision
- Average all precisions across 35 true pairs

sum (MAP elements) / 35

USCCS in MSLR: MAP = 0.369

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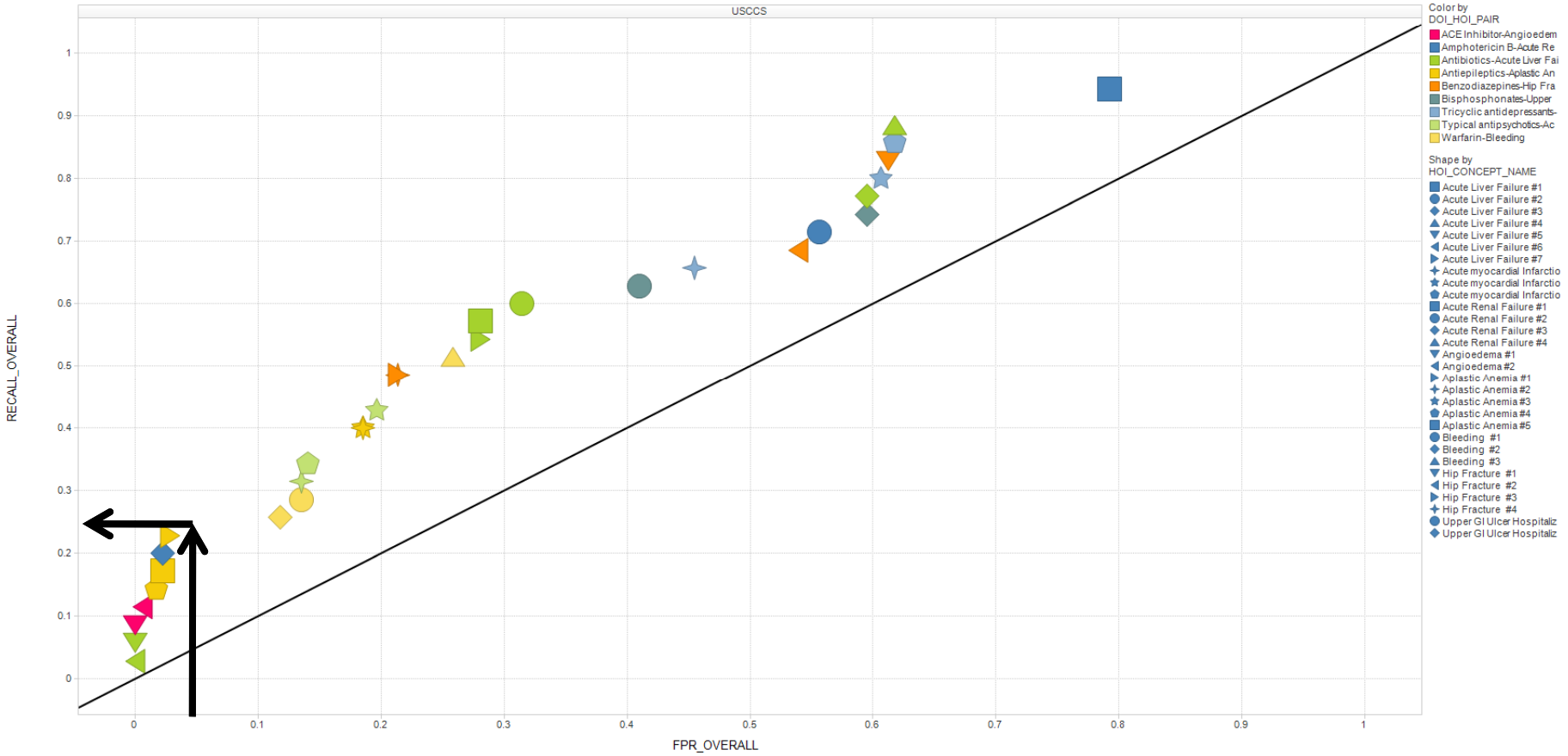
Precision-at-k

Drug	Outcome	Score	Score Rank	Ground Truth
OMOP Antibiotics	Acute Liver Failure #6	1.99	1	1
OMOP Antibiotics	Acute Liver Failure #5	1.56	2	1
OMOP ACE Inhibitor	Angioedema #1	1.05	3	1
OMOP Benzodiazepines	Acute Liver Failure #6	1.04	4	0
OMOP ACE Inhibitor	Angioedema #2	1.01	5	1
OMOP Antibiotics	Aplastic Anemia #3	0.88	6	0
OMOP Antibiotics	Aplastic Anemia #2	0.88	7	0
OMOP Antiepileptics	Aplastic Anemia #4	0.87	8	1
OMOP Typical antipsychotics	Acute Renal Failure #3	0.80	9	0
OMOP Antiepileptics	Aplastic Anemia #5	0.79	10	1
OMOP Amphotericin B	Acute Renal Failure #3	0.72	11	1
OMOP Antibiotics	Acute Renal Failure #3	0.71	12	0
OMOP Antiepileptics	Aplastic Anemia #1	0.70	13	1
OMOP Bisphosphonates	Acute Liver Failure #6	0.69	14	0
OMOP Antibiotics	Aplastic Anemia #5	0.67	15	0
OMOP Antibiotics	Acute Renal Failure #4	0.65	16	0
OMOP Antibiotics	Acute Renal Failure #1	0.64	17	0
OMOP Tricyclic antidepressants	Acute Renal Failure #2	0.59	18	0
OMOP Benzodiazepines	Acute Liver Failure #5	0.59	19	0
OMOP Warfarin	Aplastic Anemia #1	0.59	20	0
OMOP Amphotericin B	Acute Liver Failure #7	0.58	21	0
OMOP Typical antipsychotics	Acute Renal Failure #4	0.56	22	0
OMOP Typical antipsychotics	Acute Renal Failure #1	0.56	23	0
OMOP Benzodiazepines	Aplastic Anemia #4	0.55	24	0
OMOP Beta blockers	Acute Liver Failure #6	0.54	25	0
OMOP Antibiotics	Aplastic Anemia #1	0.52	26	0
OMOP Benzodiazepines	Aplastic Anemia #5	0.51	27	0
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #2	0.50	28	0
OMOP Antiepileptics	Acute Renal Failure #2	0.50	29	0
OMOP Warfarin	Bleeding #2	0.49	30	1
OMOP Typical antipsychotics	Upper GI Ulcer Hospitalization #1	0.47	31	0
OMOP Benzodiazepines	Aplastic Anemia #3	0.47	32	0
OMOP Benzodiazepines	Aplastic Anemia #2	0.47	33	0
OMOP Warfarin	Bleeding #1	0.46	34	1
OMOP Typical antipsychotics	Acute myocardial Infarction #1	0.41	35	1
OMOP Benzodiazepines	Acute Renal Failure #3	0.38	36	0
OMOP Typical antipsychotics	Acute myocardial Infarction #3	0.38	37	1
OMOP Bisphosphonates	Acute Liver Failure #5	0.37	38	0
OMOP Warfarin	Aplastic Anemia #5	0.37	39	0
OMOP Benzodiazepines	Angioedema #2	0.36	40	0
OMOP Beta blockers	Angioedema #1	0.35	41	0
OMOP Benzodiazepines	Angioedema #1	0.35	42	0
OMOP Beta blockers	Angioedema #2	0.35	43	0
OMOP ACE Inhibitor	Aplastic Anemia #1	0.33	44	0
OMOP Warfarin	Aplastic Anemia #4	0.32	45	0
OMOP Antiepileptics	Aplastic Anemia #2	0.32	46	1
OMOP Antiepileptics	Aplastic Anemia #3	0.32	47	1
OMOP Antibiotics	Bleeding #2	0.32	48	0
OMOP Warfarin	Hip Fracture #2	0.30	49	0
OMOP Typical antipsychotics	Acute myocardial Infarction #2	0.29	50	1
OMOP Antiepileptics	Acute Renal Failure #4	0.29	51	0
OMOP Antiepileptics	Acute Renal Failure #1	0.29	52	0
OMOP Tricyclic antidepressants	Acute Liver Failure #3	0.27	53	0
OMOP Benzodiazepines	Hip Fracture #4	0.27	54	1
OMOP Benzodiazepines	Hip Fracture #3	0.27	55	1
OMOP Warfarin	Aplastic Anemia #2	0.26	56	0
OMOP Warfarin	Aplastic Anemia #3	0.26	57	0
OMOP Antibiotics	Bleeding #3	0.26	58	0
OMOP Antibiotics	Bleeding #1	0.25	59	0
OMOP Warfarin	Hip Fracture #1	0.25	60	0
OMOP Benzodiazepines	Acute Liver Failure #3	0.25	61	0
OMOP Benzodiazepines	Aplastic Anemia #1	0.24	62	0
OMOP ACE Inhibitor	Upper GI Ulcer Hospitalization #2	0.23	63	0
OMOP Warfarin	Bleeding #3	0.22	64	1
OMOP Benzodiazepines	Bleeding #2	0.19	65	0
OMOP Bisphosphonates	Aplastic Anemia #4	0.19	66	0
OMOP Antibiotics	Acute myocardial Infarction #2	0.19	67	0
OMOP Antibiotics	Acute myocardial Infarction #3	0.19	68	0
OMOP Antibiotics	Acute Liver Failure #7	0.17	69	1
OMOP Antibiotics	Acute Liver Failure #1	0.16	70	1
OMOP Beta blockers	Upper GI Ulcer Hospitalization #2	0.15	71	0
OMOP Benzodiazepines	Acute myocardial Infarction #1	0.14	72	0
OMOP ACE Inhibitor	Upper GI Ulcer Hospitalization #1	0.13	73	0
OMOP Beta blockers	Aplastic Anemia #5	0.12	74	0
OMOP Beta blockers	Aplastic Anemia #1	0.12	75	0
OMOP Beta blockers	Upper GI Ulcer Hospitalization #1	0.11	76	0
OMOP Antibiotics	Acute Liver Failure #2	0.10	77	1
OMOP Benzodiazepines	Acute myocardial Infarction #3	0.10	78	0
OMOP ACE Inhibitor	Aplastic Anemia #3	0.10	79	0
OMOP ACE Inhibitor	Aplastic Anemia #2	0.10	80	0
OMOP Beta blockers	Aplastic Anemia #3	0.10	81	0
OMOP Beta blockers	Aplastic Anemia #2	0.10	82	0
OMOP Beta blockers	Acute Renal Failure #1	0.10	83	0
OMOP Benzodiazepines	Bleeding #1	0.10	84	0
OMOP Beta blockers	Acute Renal Failure #4	0.10	85	0
OMOP Benzodiazepines	Acute Renal Failure #4	0.10	86	0
OMOP Bisphosphonates	Acute Liver Failure #7	0.09	87	0
OMOP Benzodiazepines	Acute Renal Failure #1	0.09	88	0
OMOP Benzodiazepines	Bleeding #3	0.09	89	0
OMOP Warfarin	Acute Renal Failure #3	0.09	90	0
OMOP Warfarin	Hip Fracture #3	0.08	91	0
OMOP Warfarin	Hip Fracture #4	0.08	92	0
OMOP Amphotericin B	Acute Liver Failure #2	0.07	93	0
OMOP Benzodiazepines	Acute myocardial Infarction #2	0.07	94	0
OMOP Bisphosphonates	Upper GI Ulcer Hospitalization #1	0.07	95	1
OMOP Antibiotics	Acute myocardial Infarction #1	0.07	96	0
OMOP Bisphosphonates	Acute Renal Failure #2	0.06	97	0
OMOP Tricyclic antidepressants	Acute Renal Failure #1	0.06	98	0
OMOP Warfarin	Acute Renal Failure #4	0.06	99	0
OMOP Benzodiazepines	Acute Liver Failure #1	0.06	100	0

- ‘Precision-at-k’ provides a statistic to describe: ‘Among the top k scores, what fraction of the scores are for true positive drug-outcome pairs?’
- HOI experiment has 213 pairs, 35 are true relationships
- p@100 measures the proportion of true pairs in the top half (100/213) of the ranking
- Maximum score p@100 for HOI experiment is 0.35.

USCCS in MSLR: p@100 = 0.22

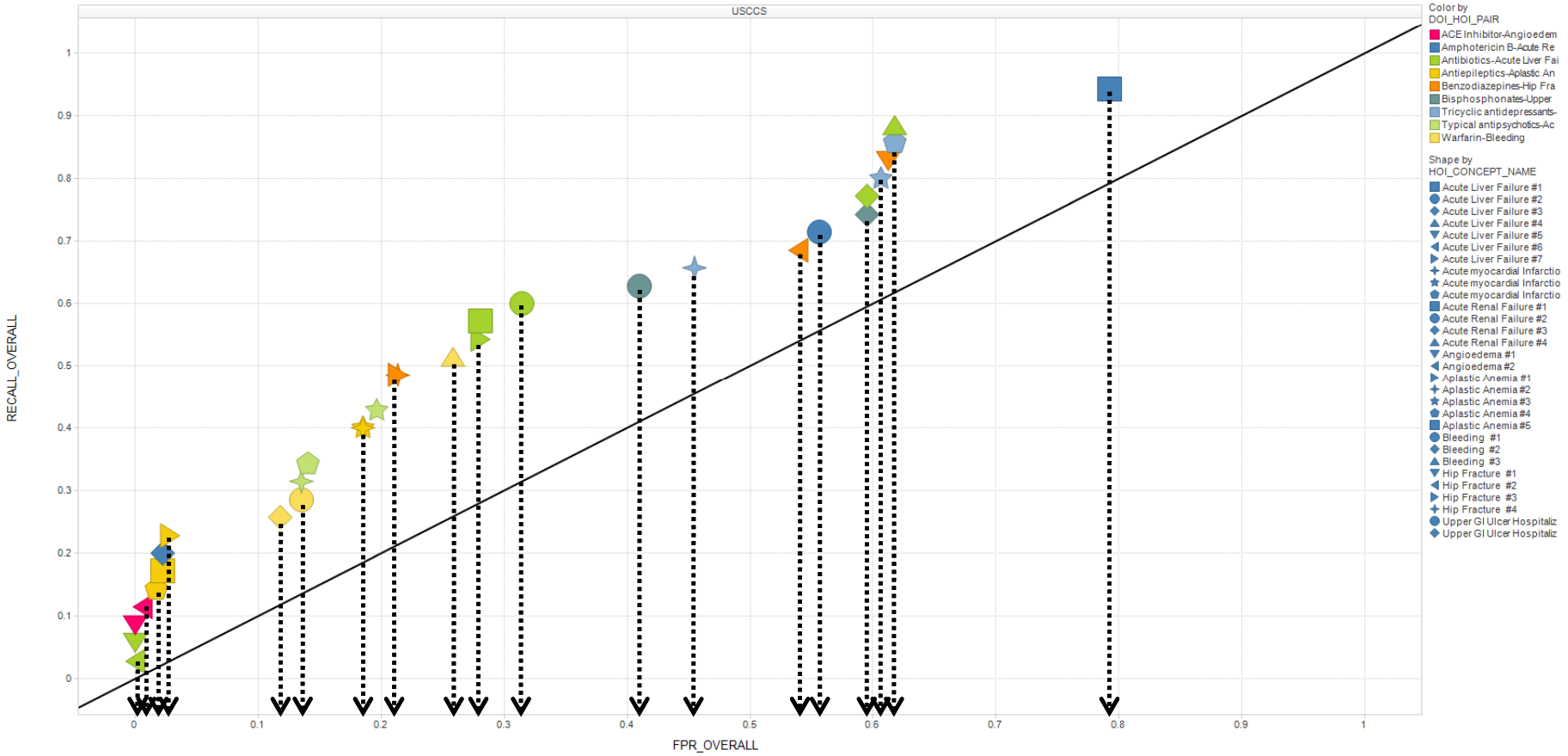
Recall @ FPR



- ROC curve shows all possible thresholds, but some have unreasonably high false positive rates that may not be useful in practice
- An alternative approach: specify the percentage of false positives that can be tolerated (e.g. 5%)
- Measure the fraction of the true positive pairs that can be identified before hitting the target false positive rate
- R@FPR is equivalent to reading “up-and-over” on the ROC curve for a defined FPR value

USCCS in MSLR: R@5%FPR = 0.229

Average false positive rate



- Average false positive rate (AFPR) provides a composite summary that estimates what fraction of false positives you can expect to observe on average at the score of any given true drug-outcome pair
- AFPR is equivalent to reading “down” for all true positives on the ROC curve, then taking the average of those values
- Unscored ‘true pairs’ are assigned a maximum false positive rate (FPR=1)
- For AFPR, lower performance measure is better (fewer average false positives)

USCCS in MSLR: AFPR = 0.341

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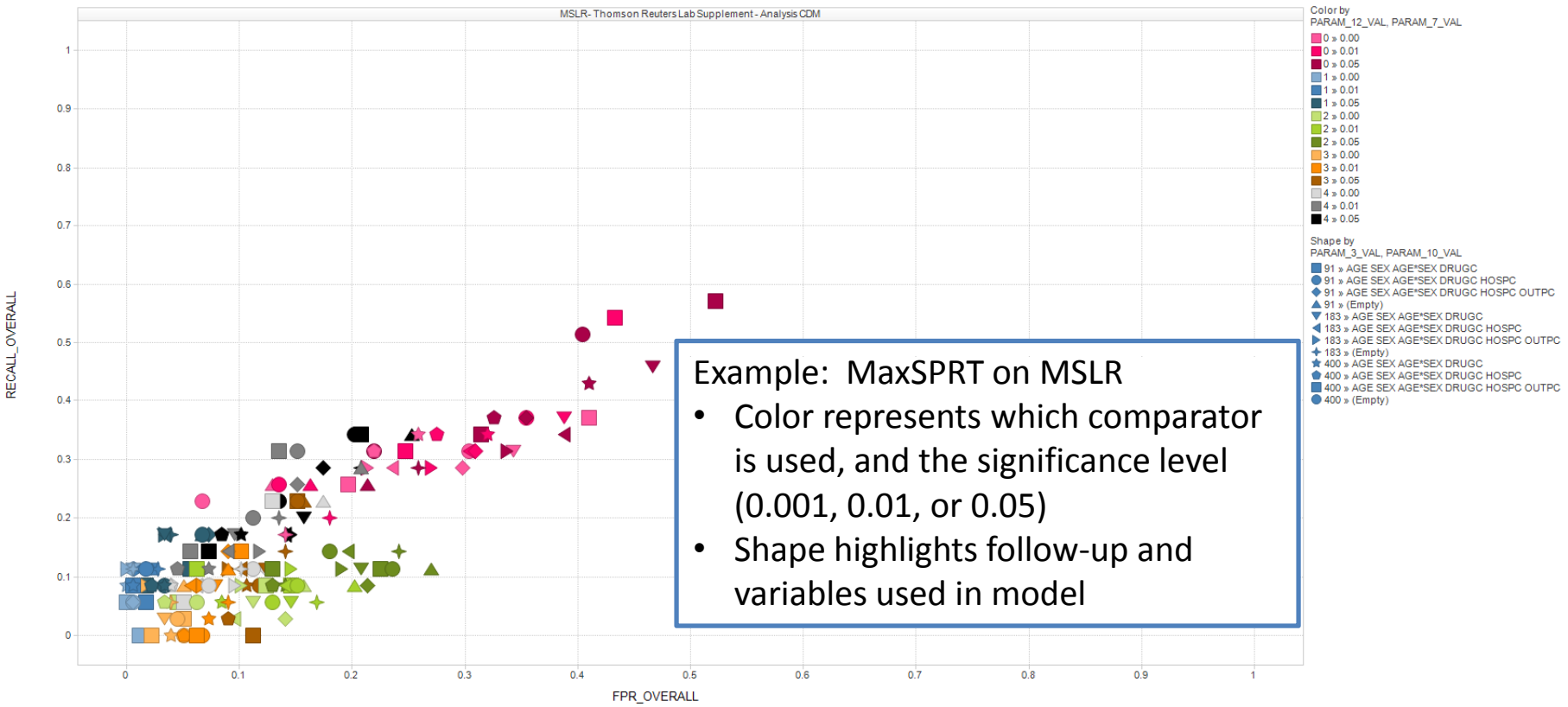
Threshold-based analysis for dichotomized scores



Example: MaxSPRT on MSLR

- Color represents which comparator is used, and the significance level (0.001, 0.01, or 0.05)
- Shape highlights follow-up and variables used in model

- Plot recall vs. false positive rate for a specific method-threshold pair (each dot represents a different method-parameter setting)
- Whereas methods that produce real-valued scores can be plotted to produce a full ROC curve, methods that dichotomize scores as 1-'signal', 0-'no signal' (e.g. maxSPRT) only produce one point on a ROC curve
- Continuous-valued methods can also be plotted here by specifying the threshold for the score (e.g. USCCS score >= 0.49 provides recall=0.26, false positive rate = 0.12)
- Analyses with lower recall and higher false positive rate than another setting are 'inferior', but all other points reflect reasonable tradeoffs between sensitivity and specificity

Summary

- Performance measures allow for comparisons across all methods and all data sources
- Performance measures can be estimated across any subset of the test cases, enabling exploratory subgroup analyses, including:
  - With and without HOIs that require laboratory values
  - High vs. low prevalence drugs and conditions
  - Strong vs. weak drug-outcome association
  - Acute vs. non-acute time-to-event
  - High vs. low expected confounding

Proposed analysis strategy

- Calculate performance measures for all parameters of all methods, against all databases
- For a given method (e.g. USCCS)
  - Within a particular database (e.g. MSLR):
    - Characterize the 'overall optimal' parameter setting: the configuration that yields the maximum overall AUC (or other chosen performance measure)
      - Performance measures across all test cases and within subgroups
      - Identify which true drug-outcome pairs were 'successfully identified': the pair produced a score at a threshold <=5% FPR
      - Identify which true drug-outcome pairs were 'failures': the method incorrectly produced a negative score for the pair
    - Explore 'suboptimal' parameter settings: what is the consequence on performance if one of the 'optimal' parameters is changed to a different value?
      - Measure change in performance measures when changing one parameter at a time
      - Identify drug-outcome pairs where FPR changes >= 0.20 and pair moves between 'success' and 'non-success'
    - Identify the 'subgroup optimal' parameter settings for each subgroup
      - Compare to 'overall optimal' performance within subgroup
      - Identify subgroup drug-outcome pairs where FPR changes >= 0.20 and pair moves between 'success' and 'non-success'

Proposed analysis strategy (cont)

- For a given method (cont)
  - Repeat analysis for each database
    - Assess how 'optimal' parameters vary by data source
  - Identify 'community optimal' parameter setting: configuration that yields maximum average AUC across databases
- Repeat analysis for each method
- Compare 'optimal' methods within a database and assess consistency in 'identified' drug-outcome pairs
- Compare 'optimal' methods across data sources to understand how data characteristics influence method performance

Complementary analyses from Phase 3 results

- Evaluate performance of alternative definitions within each Health Outcome of Interest
  - Which definition(s) yield the maximum average AUC across 'optimal' methods and databases
  - Assess the relative contribution of procedure codes and laboratory values to definitions based on diagnosis codes
- Develop strategies for combining predictions across methods within a data source
- Develop strategies for combining method scores across data sources (meta-analysis or other modeling approaches?)
- Use results from HOI and NSA experiments to create simulated data scenarios to attempt to replicate findings

Discussion

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Backup

- Review of methods library
- Parameter settings for all released Phase 3 methods

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OMOP's Methods Landscape

Disproportionality Analysis

	AE j = Yes	*AE j = No*
Drug *i* = Yes	*a*=20	*b*=100
Drug *i* = No	*c*=100	*d*=1080

- Distinct Patients
- SRS
- Modified SRS

X

MGPS
BCPNN
PRR
Chi
etc.

X

Stratified

- Temporal Pattern Discovery (WHO)

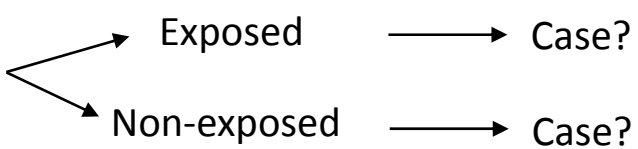
Sequential Methods

	AE j = Yes	*AE j = No*
Drug *i* = Yes	*a*=20	
Drug *i* = No		

Compare to baseline Poisson

- Maximized Sequential Probability Ratio Teat (MaxSPRT)
- Conditional Sequential Sampling Procedure (CSSP)

Exposure Based Methods



- Observational screening
- HSIU
- Incident User Designs
- High-Dimensional Propensity Scoring
- Local control

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

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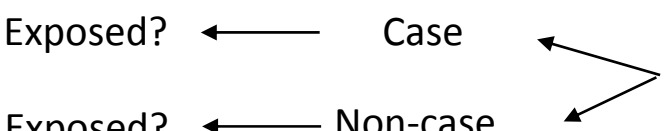
OMOP's Methods Landscape

Case Based Methods



- Case control surveillance
- Multiset case control
- Self-controlled case series
- Case crossover

Other Methods

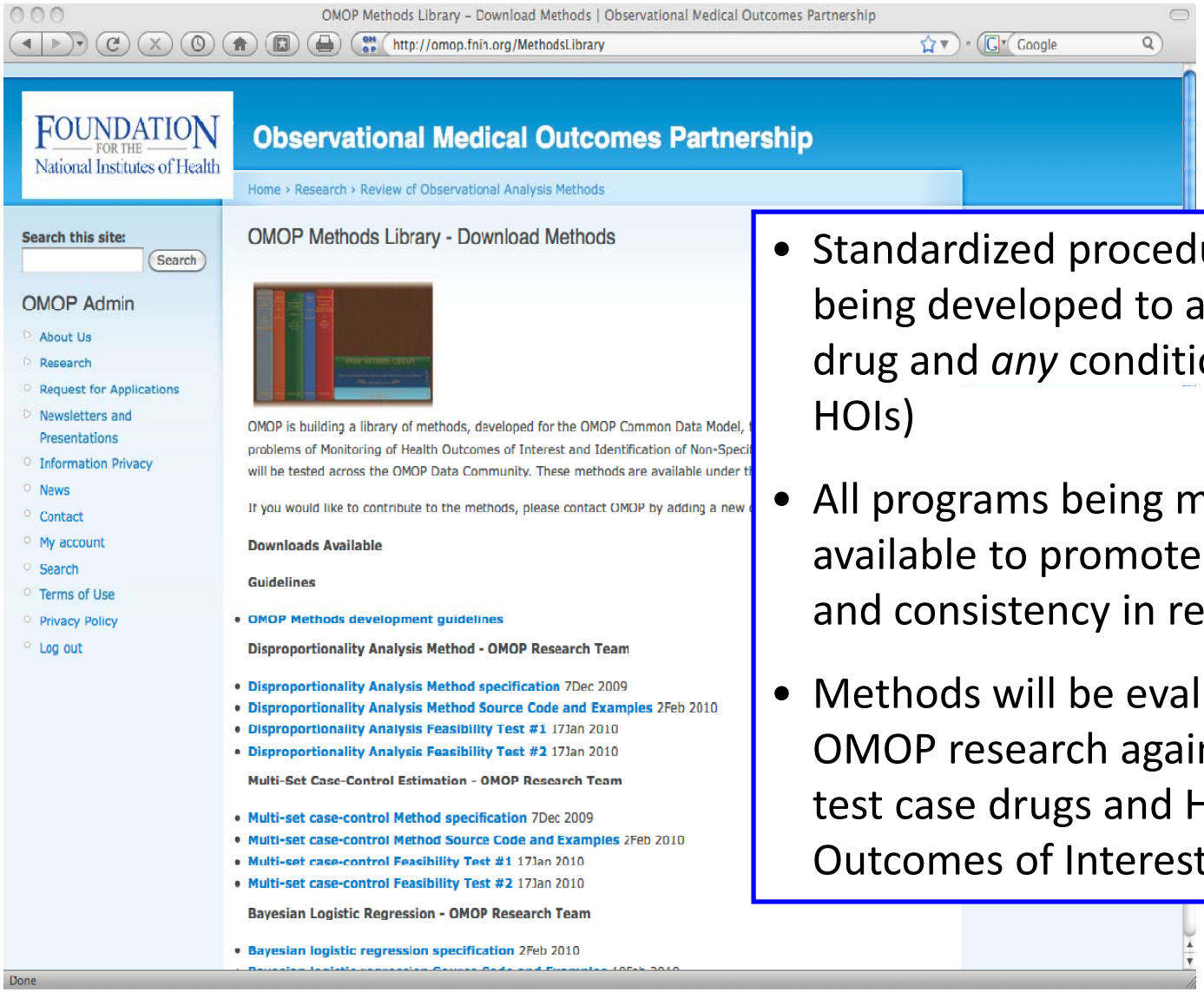
- Hi-Dimensional logistic regression
- Statistical relational learning

Future Methods

- Multivariate self-controlled case series
- Case-time control
- Lasso propensity scoring
- Online algorithms
- OMOP Cup (50+ submissions)

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

OMOP Methods Library



- Standardized procedures are being developed to analyze *any* drug and *any* condition (including HOIs)
- All programs being made publicly available to promote transparency and consistency in research
- Methods will be evaluated in OMOP research against specific test case drugs and Health Outcomes of Interest

http://omop.fnih.org/MethodsLibrary

Methodological considerations common across multiple methodological approaches

- Exposure definition
  - Incident vs. prevalent exposure
  - Source of data capture
- Outcome definition
  - Incident vs. prevalent events
  - Diagnosis codes vs. HOI
- Defining temporal relationship
  - Time from exposure start
  - Time after exposure end
- Comparator selection
- Inclusion/exclusion criteria
  - Baseline history
  - Follow-up time
- Covariate selection and adjustment
  - Matching
  - Stratification
  - Multivariate modeling
- Output metric/statistic
  - Estimation vs. testing
  - Relative vs. attributable risk
  - Measure of uncertainty

Each method has input parameters that encode these choices

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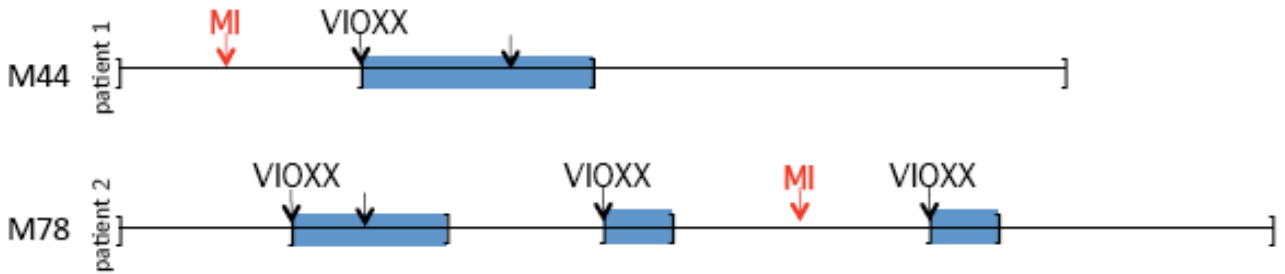
Univariate self-controlled case series overview

- **Self-controlled case series (SCCS)** - developed to estimate relative incidence of AEs to assess vaccine safety [**?**]
- Focus on **one** adverse event and **one** drug (data is in days):



- Person i is observed for τ_i days and (i, d) is their dth day

y_{id} = number of AEs observed on (i, d)

Drug exposure is known each day: $x_{id} = \begin{cases} 1 & \text{exposure on } (i,d) \\ 0 & \text{otherwise} \end{cases}$

Univariate self-controlled case series overview

- Assume that events arise according to a non-homogeneous Poisson process, where drug exposure modulates the baseline event rate

- Poisson intensity on day (i, d) $= e^{\phi_i + \beta x_{id}}$

where
e^{ϕ_i} = fixed individual intensity rate
e^{β} = multiplicative effect of drug exposure

$$y_{id} \mid x_{id} \sim \text{Poisson}(e^{\phi_i + \beta x_{id}})$$

- The likelihood contribution of (i, d) is

$$P(y_{id} \mid x_{id}) = \frac{e^{-e^{\{\phi_i + \beta x_{id}\}}} (e^{\phi_i + \beta x_{id}})^{y_{id}}}{y_{id}!}$$

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Univariate self-controlled case series overview

- Joint probability of events for i over all observed days

$$L_i = P(y_{i1}, \ldots, y_{i\tau_i} \mid x_{i1}, \ldots, x_{i\tau_i}) = P(\mathbf{y}_i \mid \mathbf{x}_i) = \prod_{d=1}^{\tau_i} P(y_{id} \mid x_{id})$$

$$= exp\{-\sum_d e^{\phi_i + \beta x_{id}}\} \times \prod_{d=1}^{\tau_i} \frac{(e^{\phi_i + \beta x_{id}})^{y_{id}}}{y_{id}!}$$

- **Assumptions**
  1. Conditionally independent events

$$y_{id} \perp\!\!\!\perp y_{id'} \mid \mathbf{x_i} \quad \text{for } d \neq d'$$

  2. Events are conditionally independent of exposures

$$y_{id} \perp\!\!\!\perp x_{id'} \mid x_{id} \quad \text{for } d \neq d'$$

USCCS parameters

- Condition type (2): first occurrence or all occurrences of outcome
- Defining exposure time-at-risk:
  - Days from exposure start (2): should we include the drug start index date in the period at risk?
  - Surveillance window (4):
    - 30 d from exposure start
    - Duration of exposure (drug era start through drug era end)
    - Duration of exposure + 30 d
    - Duration of exposure + 60 d
- Precision of Normal prior (4): 0.5, 0.8, 1, 2
- Total parameters: 2x2x4x4 = 64 settings

- An example configuration applied to MSLR (ANALYSIS_ID=503005)
  - Condition type = all occurrences
  - Days from exposure start = 1
  - Surveillance window = 30d from exposure start
  - Precision of prior = 0.8

DP parameters under study

- Condition type (2): first occurrence or all occurrences of outcome
- Metric (7): PRR, BCPNN/IC, MGPS/EBGM, signed chisq, PRRLB95, ICLB95, MGPS/EB05
- Stratification (2): with or without age and sex
- Surveillance window (4):
  - 30 d from exposure start
  - Duration of exposure (drug era start through drug era end) + 30 d
  - Duration of exposure + 60 d
  - All time post-exposure start
- Total parameters: 2x7x2x4 = 112 settings

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MSPRT parameters under study

- Washout period (3): 91d, 183d, or 400d
- Significance level (3): 0.001, 0.01, or 0.05
- Comparator group (4): 'Other drugs with same indications', 'drugs in same class', 'drugs with same indications not in same class', or 'most prevalent drug with same primary indication'
- For propensity model approach:
  - Variables to include (3):
    - AGE SEX AGE*SEX DRUGC
    - AGE SEX AGE*SEX DRUGC HOSPC
    - AGE SEX AGE*SEX DRUGC HOSPC OUTPC ERC NURSING

- Total parameter combinations: 3x3x4 (original) + 3x3x4x3 (propensity model) = 144 settings

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OS parameters under study

- Drug exposures used (2): first exposure only or all exposures
- Outcome occurrence (3): first occurrence only, all occurrences, or first occurrence within exposure period
- Comparator group (2): Self-controlled cohort design (post vs. pre-exposure), or Relative assessment (post vs. overall)
- Surveillance window (3):
    - 30 d from exposure start
    - Duration of exposure (drug era start through drug era end) + 30 d
    - All time post-exposure start
- Metric (3): Point estimate, LB95, or UB95
- Include index date in post-exposure time-at-risk (2): Yes or No
- For self-controlled design:
  - Surveillance window length pre-exposure:
    - Length of exposure + 30d
    - 30d
    - 180d
    - 365d
    - All time pre-exposure (used for all time post-exposure comparison)
  - Include index date in pre-exposure time-at-risk (2): Yes or No

- Total parameter combinations: 2x3x3x3x2 (relative) + 2x3x5x3x2x2 (self-controlled) = 162 settings

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ICTPD parameters under study

- Observation period (3): 1d to 30d; 1d to 60d; or, 1d to 360d
- Control period (4): -1080d to -361d; -810d to -361d; -180d to-1d; or, -30d to -1d
- Multiple control periods:
  - (4) 100, 101, 110, or 111 when control period <> -30d
  - (2) 010, 011 when control period = -30d
- Metric (2): IC or IC025

- Total parameter combinations: 3x3x4x2 + 3x1x2x2 = 84 settings

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CCS parameters under study

- Lead time (3): 30d, 91d, or 183d
- Follow up time (2): 30d or 180d
- Controls per case (2): 4 or 100
- Matching variables (2): with or without race and location
- Exposure window (2): 30d from exposure start or all time post-exposure

- Total parameter combinations: 3x2x2x2x2= 48 settings

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BLR parameters under study

- Condition type (2): First occurrence or all occurrences of outcome
- Prior variance (3): 0.5, 1, or 2
- Demographic covariates (2): with and without age and gender
- Surveillance window (2):
  - 30d from exposure start
  - Exposure length (drug era start – drug era end) + 30d

- Total parameter combinations: 2x3x2x2= 24 settings

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MSCCE parameters under study

- Controls (2): 10 or 1000
- Days enrolled for washout period (4): 30, 91, 183, or 400
- Surveillance window (3):
  - 30d from exposure start
  - Exposure length (drug era start – drug era end) + 30d
  - Exposure length (drug era start – drug era end) + 60d
- Metric (2):
  - Crude OR
  - Mantel-Haenszel-adjusted OR

- Total parameter combinations: 2x4x3x2= 32 settings

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CCO parameters under study

- Days enrolled for washout period (2): 91d, or 180d
- Days in case window (3): 30d, 90d, or 180d
- Days in control window:
  - For 30d: 30d, 90d, or 180d
  - For 90d: 90d, or 180d
  - For 180d: 180d
- Control window lag (2): 0d or 180d
- Control windows sampled(2): 1 or 2

- Total parameter combinations: 2x3x2x2 + 2x2x2x2 + 2x1x2x2= 48 settings

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HSIU parameters under study

- Outcome relation to exposure (2): In exposure or after exposure start
- Stratification variables (3):
  - None
  - Sex and Age
  - Sex, Age, and Number of drugs

- Total parameter combinations: 2x3 = 6 settings

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