A General Propensity Score for Signal Detection using Tree-Based Scan Statistics

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Disclosures

- This work was funded by the FDA Sentinel Initiative
- The presentation reflects the views of the authors and should not be construed to represent FDA's views or policies
- At the time that this work was conducted, Dr. Wang received salary support from investigator-initiated grants to Brigham and Women's Hospital from Novartis, J & J, Boehringer Ingelheim for unrelated work
- Dr. Wang was a consultant for Aetion Inc. (2 years ago)

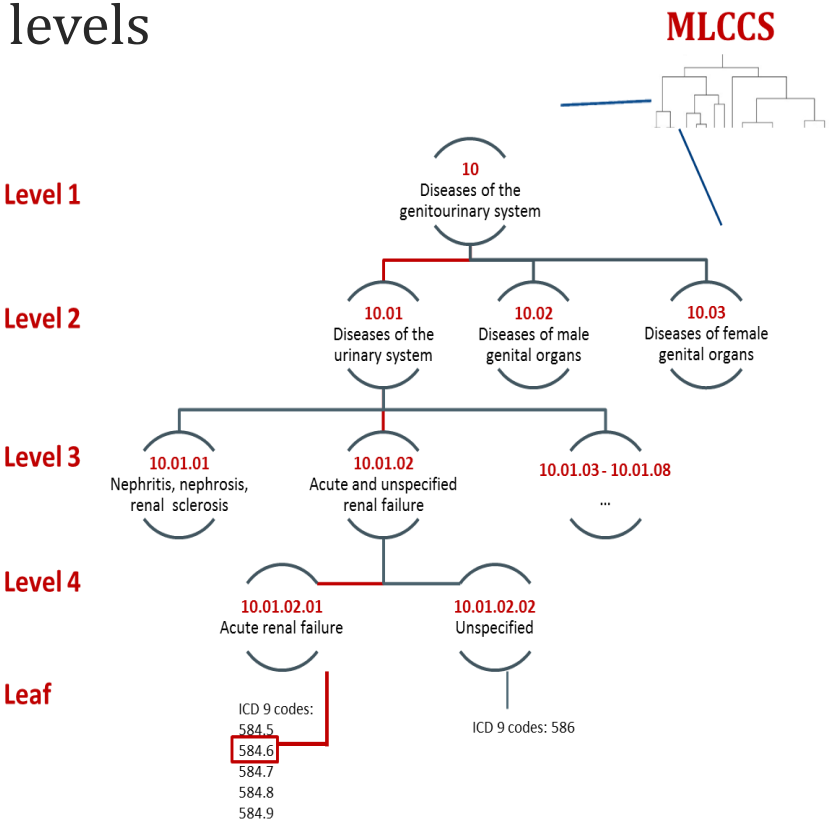
What is TreeScan™?

- A statistical data mining tool for signal detection
  - Utilizes tree-based scan statistics
  - Adjust p-values for multiple testing of correlated hypotheses when screening thousands of potential adverse events

The Tree

Hierarchically grouped diagnosis codes

- Multi-Level Clinical Classification Software (MLCCS)[2]
- ICD9 codes grouped in 4 hierarchical levels
  - Grouped by body systems



The Scan Statistic

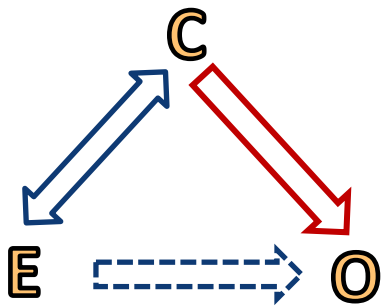
- Null hypothesis: there are no nodes for which there is an effect of exposure
- Statistical alerts at specified threshold ($p<0.01$) if the test statistic for observed data is greater than 99% of test statistics generated under the null
- Statistical Alert ≠ Safety Signal

An alert by itself is not a safety signal and always requires further clinical correlation and evaluation for bias and confounding

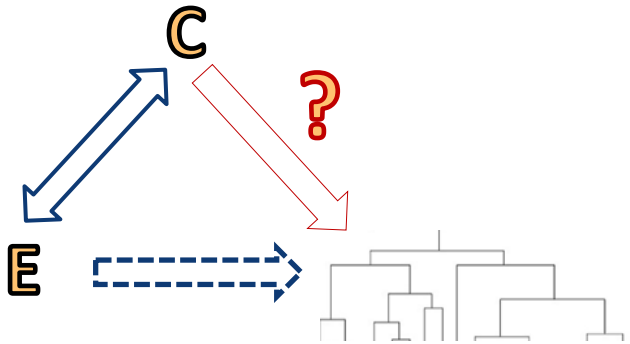
Key Challenge to Using TreeScan with Propensity Score (PS) Matching

- When scanning across thousands of outcomes it is infeasible to select confounders for the PS based on risk for each/all outcomes in the tree

Usual PS matched analysis



TreeScan PS matched analysis



- What should be included in a PS for applied signal detection activities?
  - Consider practicality as well as bias reduction
  - Looking for broad proxy coverage of confounders
  - Good enough for first pass signal detection, to be followed with refinement of potential signals

Objective

Develop **candidate "general" propensity scores** for general application in cohort studies with TreeScan and **compare performance** by evaluating 4 drug examples with well characterized safety profiles

- Review of alerts using the *a priori* specified primary general propensity score to adjust for confounding

Methods

Empirical approach evaluating 4 examples with established safety profiles, reflecting different populations and indications

- All apply TreeScan with active comparator, new initiator design and 1:1 PS matching

Exposures	Indication	Expected alerts?
Macrolide vs Fluoroquinolone	Community Acquired Pneumonia	None
Azithromycin vs Clarithromycin	Community Acquired Pneumonia	None
Meloxicam vs Celecoxib	Osteoarthritis	None
Valproate vs Lamotrigine	Any	Yes

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- Short term exposure
- Used immediately
- Between class vs within class

Methods

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- Intended chronic use
- Older, sicker population
- ↑ comorbidity

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Balanced on indication in design phase

- Intended chronic use
- ↑ comorbidity (different)
- Need to adjust for multiple indications

Methods

- Evaluated candidate PSs that included a combination of 3 types of covariates
  - **Predefined general:** based on characteristics* that are risk factors for a variety of outcomes
  - **High dimensional PS (hdPS):** empirically selected based on relationship to exposure
  - **Tailored:** investigator selected variables tailored to each exposure pair

	Predefined general	hdPS	Tailored
1		x	
2	x		
3	x	x	
4	x		x
5	x	x	x

*combined comorbidity score[3], frailty index[4], health seeking (e.g. screening, vaccination), utilization

Methods

- Compared candidate PSs on
  - Sample size after 1:1 matching (related to power)
  - Covariate balance
  - Alerting patterns

	Expected effect of exposure?		
	Yes	**No**	**Unknown**
Alert	True Positive	False Positive	?
No Alert	False Negative	True Negative	?

Summary Results

Exposures	Covariate[1] imbalance before matching
Macrolide vs Fluoroquinolone	Age (older)
Azithromycin vs Clarithromycin	# prior ED visits
Meloxicam vs Celecoxib	DME Anticoagulants Opioids Peptic ulcer/GI bleed # IP stays
Valproate vs Lamotrigine	Gender Anxiety Bipolar disorder Depression Other antidepressants Migraine Schizophrenia TCA # prior IP stays

[1] Standardized differences > 0.1 for predefined general or tailored covariates

DME = durable medical equipment, ED = emergency department, GI = gastrointestinal, TCA = tricyclic antidepressants, IP = inpatient

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Matched on indication in design phase
Fairly well balanced before matching

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Matched on indication in design phase
Comparator patients were sicker

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Initiators allowed to enter cohort with different indications

More baseline imbalances, reflective of indications

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Matching balanced every baseline covariate that was included in the PS

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Summary Results

Exposures	Covariate[1] imbalance before matching	Sample size % Matched[2] using general predefined covariates	Decrease in sample after adding hdPS/tailored covariates to predefined*
Macrolide vs Fluoroquinolone	Age (older)	87% of macrolide	1-4%
Azithromycin vs Clarithromycin	# prior ED visits	100% of clarithromycin	0%
Meloxicam vs Celecoxib	DME Anticoagulants Opioids Peptic ulcer/GI bleed # IP stays	97% of celecoxib	3-5%
Valproate vs Lamotrigine	Gender Anxiety Bipolar disorder Depression Other antidepressants Migraine Schizophrenia TCA antidepressants # prior IP stays	90% of valproate	10-15%

1:1 matching on general covariates → small reductions in sample size

[1] Standardized differences > 0.1 for predefined general or tailored covariates [2] % of smaller exposure group

DME = durable medical equipment, ED = emergency department, GI = gastrointestinal, TCA = tricyclic antidepressants, IP = inpatient

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Adding variables → smaller sample
May subtly change matched pop characteristics
Consider potential effect modification and impact on power to detect alerts

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Summary Results

Exposures	Characteristics of example	Statistical alerting pattern
Macrolide vs Fluoroquinolone	• Short term exposure • Used immediately • Between class comparison	• 4 unique alerts in crude analyses • 1-4 alerts across candidate general PS matched • Alerts indicated need to modify approach to better capture and exclude based on pregnancy
Azithromycin vs Clarithromycin	• Within class comparison	• 3 alerts in crude analyses • 0 alerts after any PS matching
Meloxicam vs Celecoxib	• Intended chronic use • Older, sicker population • High comorbidity (physical)	• 0 alerts in crude analysis • 1-3 unique alerts after any PS matching • All alerts were labeled events

Valproate vs Lamotrigine	• Intended chronic use
	• High comorbidity (mental health)
	• Multiple indications
		• Crude analysis
		  • 85 alerts (most clearly confounded)
		  • 3 alerts were labeled events
		• Predefined primary PS (general + hdPS)
		  • 7 indication related
		  • 1 alert related to labeled event
		  • 2 unclassified alerts pending further characterization for confounding
		• Other candidate PS similar pattern

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Limitations

- Evaluation of empirical examples only

  → Lack strong reference standard "truth" for all outcomes being scanned

  – Why didn't expected adverse events alert after adjustment?
    - Not strong evidence to begin with
    - Warning may be effective, prescribers are not giving drug to high risk patients
    - Outcome misclassification (nodes may not be sensitive/specific)
    - Loss of power
  – Relative ability of different PS adjusted analysis to detect true adverse effects depends on interplay between misspecification and sample size
    - Bias-variance tradeoff could be further investigated with simulation

Take home points

- Alerting pattern
  - ~8,000 outcomes screened → handful of alerts after PS adjustment
  - Few false positives
  - Unknown magnitude of false negatives

- Design matters
  - Requiring active-comparators to match on drug indication makes patients more similar even when comorbidities aren't measured well

    → fewer confounding related false alerts
  - Well balanced on predefined/tailored covariates before matching

- With selection of a good active comparator, no major differences in alerting pattern for candidate general PS

Take home points

- Consider scalability for active surveillance/signal detection
  - Predefined general covariates are risk factors for many outcomes, broadly relevant as confounders across the tree
  - Covariates selected based on relationship to exposure may not be confounders for most outcomes (instruments?)
    - Potentially increasing bias and variance[5]/decreasing power for real signals

	Predefined general	Empirically selected	Tailored to indication
Easy to apply "out-of-the-box"	✓	✓	⊘
Potential to increase variance		⊘	⊘
Broad proxy coverage for potential confounders not pre-specified		✓	

Take home points

When should we include hdPS exposure-based selection of covariates in a TreeScan signal detection activity?

It depends

Consider design choices and level of concern about remaining confounding (given the comparator and inclusion/exclusion criteria) versus loss of power

Strong active comparator

- Within class
- Same line of therapy
- Same indication
- A lot of unmeasured potential confounding handled by design

Predefined general

Weaker active comparator

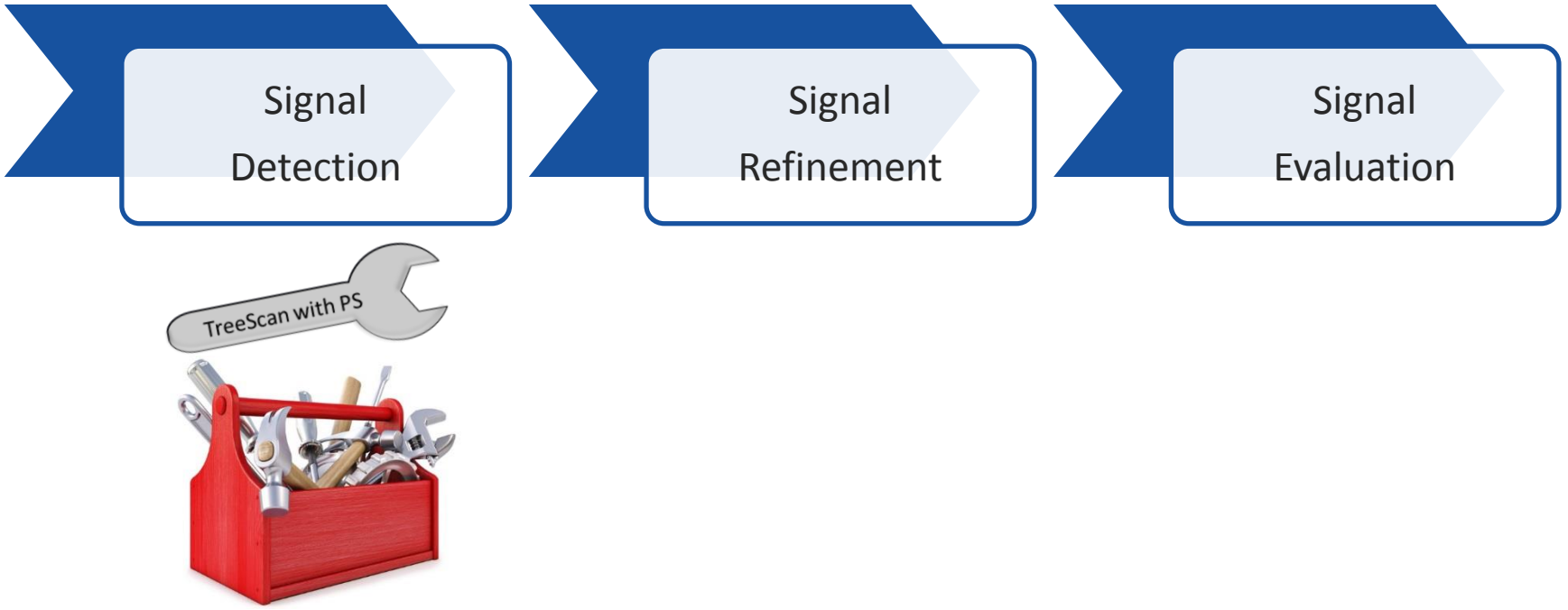
- Cross class comparison
- Different line of therapy (e.g. 1st vs 2nd)
- Different indications for use
- *Consider* possibility of adding more broad proxy adjustment (bias/variance tradeoff)

Predefined general + hdPS?

Can always do both as sensitivity analyses and evaluate how the PS affects sample size, covariate balance and alerting patterns

Take home points

- TreeScan with a general PS is a first pass for signal detection
  - Relevant alerts should be refined with pharmacoepidemiologic assessment where confounding control is tailored to the specific outcome(s) under investigation



Questions?

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Back up slides

The Scan Statistic

T = unconditional Bernoulli scan statistic

$$LLR(G) = ln\left(\frac{\left(\frac{c_G}{c_G + n_G}\right)^{c_G}\left(\frac{n_G}{c_G + n_G}\right)^{n_G}}{(p)^{c_G}(1-p)^{n_G}}\right) I\left(\frac{c_G}{c_G + n_G} > p\right)$$

$$T = \max_G LLR(G)$$

G = node of interest

c_G = cases in the treatment group for a given node

n_G = cases in the reference group for a given node

p = probability of being in the treatment group (for 1:1 matched this is 0.5)

Maro, J et al. Using tree-based scan statistics to evaluate outcomes following incident antibiotic use. Sentinel Methods Protocol.
Kulldorff, M. Drug safety data mining with a tree-based scan statistic. PDS, 2013
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Meloxicam label

----------**WARNINGS AND PRECAUTIONS**----------

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease/risk factors may be at greater risk. (5.1)
- Serious gastrointestinal (GI) adverse events which can be fatal. The risk is greater in patients with a prior history of ulcer disease or GI bleeding, and in patients at higher risk for GI events, especially the elderly. (5.2)
- Elevated liver enzymes, and rarely, severe hepatic reactions. Discontinue use imme worsen. (5.3)
- New onset or worseni monitored closely dur
- Fluid retention and ed fluid retention or hear
- Renal papillary necros with caution in the elc failure, liver dysfunct angiotensin II antagor renal impairment is nc
- Serious skin adverse e Johnson syndrome (S can be fatal and can o appearance of rash or

Table 1a Adverse Events (%) Occurring in ≥2% of MOBIC Patients in a 12-Week Osteoarthritis Placebo- and Active-Controlled Trial

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 100 mg daily
No. of Patients	**157**	**154**	**156**	**153**
Gastrointestinal	17.2	20.1	17.3	28.1
Abdominal pain	2.5	1.9	2.6	1.3
Diarrhea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	3.2	3.9	3.8	7.2
Body as a Whole				
Accident household	1.9	4.5	3.2	2.6
Edema[1]	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-like symptoms	5.1	4.5	5.8	2.6
Central and Peripheral Nervous System				
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Respiratory				
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3
Skin				
Rash[2]	2.5	2.6	0.6	2.0

Valproate label

CONTRAINDICATIONS

- Hepatic disease or significant hepatic dysfunction (4, 5.1)
- Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG) (4, 5.1)
- Suspected POLG-related disorder in children under two years of age (4, 5.1)
- Known hypersensitivity to the drug (4, 5.12)
- Urea cycle disorders (4, 5.6)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity; evaluate high risk populations and monitor serun (5.1)
- Birth defects and decreased IQ following *in utero* exposure; only treat pregnant women with epilepsy if other medications are una should not be administered to a woman of childbearing potential essential (5.2, 5.3, 5.4)
- Pancreatitis; Depakene should ordinarily be discontinued (5.5)
- Suicidal behavior or ideation; Antiepileptic drugs, including Depakene, increase the risk of suicidal thoughts or behavior (5.7)
- Bleeding and other hematopoietic disorders; monitor platelet counts and coagulation tests (5.8)
- Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation of valproate therapy (5.6, 5.9, 5.10)
- Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate (5.11)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction; discontinue Depakene (5.12)
- Somnolence in the elderly can occur. Depakene dosage should be increased slowly and with regular monitoring for fluid and nutritional intake (5.14)

ADVERSE REACTIONS

- Most common adverse reactions (reported >5%) are abdominal pain, alopecia, amblyopia/blurred vision, amnesia, anorexia, asthenia, ataxia, bronchitis, constipation, depression, diarrhea, diplopia, dizziness, dyspepsia, dyspnea, ecchymosis, emotional lability, fever, flu syndrome, headache, increased appetite, infection, insomnia, nausea, nervousness, nystagmus, peripheral edema, pharyngitis, rhinitis, somnolence, thinking abnormal, thrombocytopenia, tinnitus, tremor, vomiting, weight gain, weight loss. (6.1)
- The safety and tolerability of valproate in pediatric patients were shown to be comparable to those in adults (8.4).