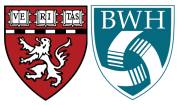
Comparative Effectiveness of Treatments in Large Healthcare Databases

The Value of High-Dimensional Propensity Score Approaches

Sebastian Schneeweiss, MD, ScD
Professor of Medicine and Epidemiology



Division of Pharmacoepidemiology and Pharmacoeconomics,
Dept of Medicine, Brigham & Women's Hospital/ Harvard Medical School

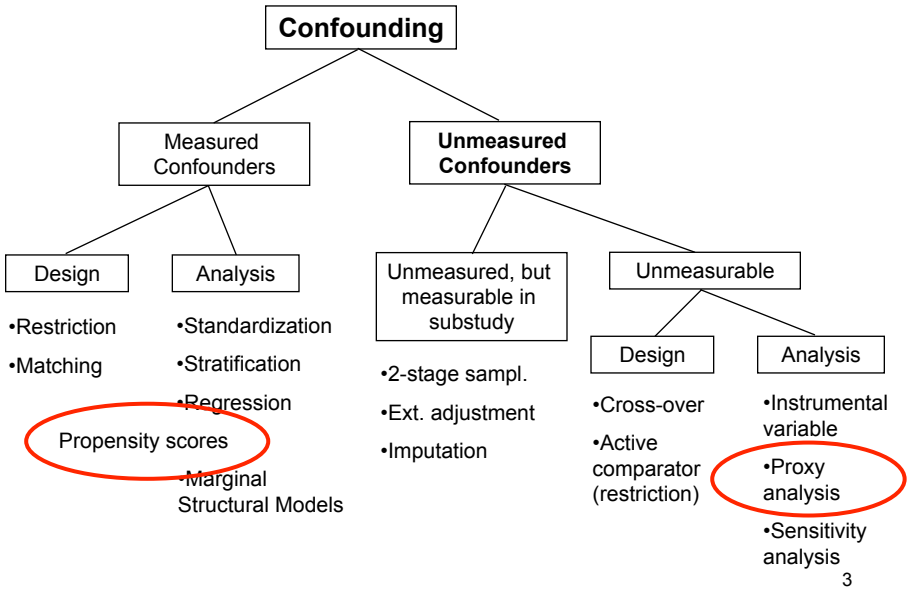
1

Effectiveness Research with Healthcare Databases

- **Reduce bias**
  - Analyses that support causal interpretations
- **Reduce investigator error**
- **Increase meaningfulness for decision making**
  - Analyses that run in near real-time as data refresh
  - Analyses that produce absolute effect sizes
  - Analyses that are representative of routine care outcomes
  - Analyses that can be reproduced by others

2

Dealing with Confounding

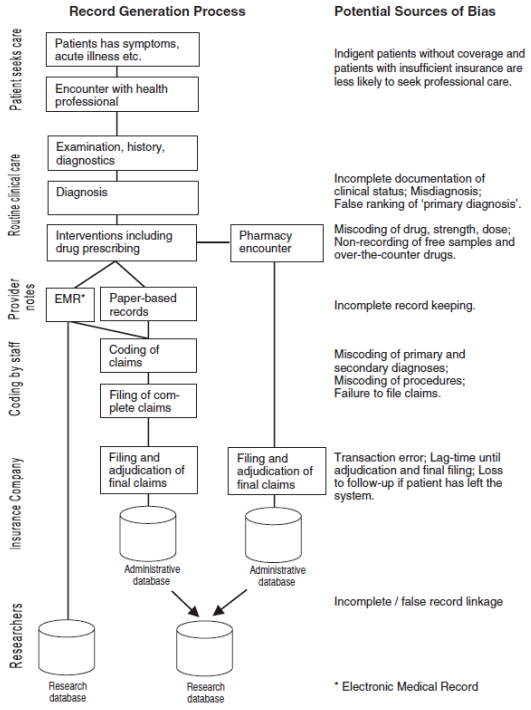


Schneeweiss, PDS 2006

3

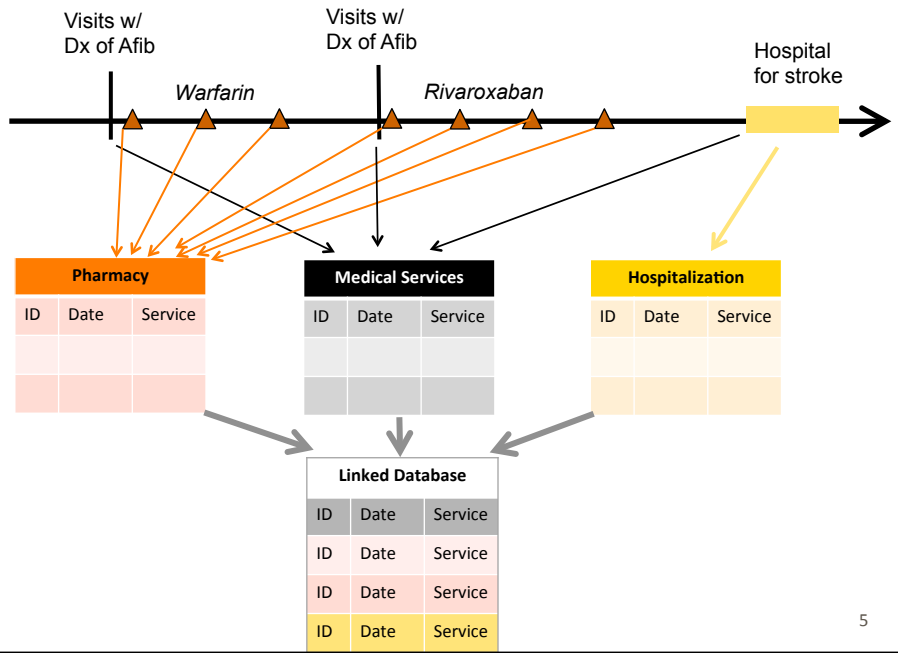
Secondary Healthcare Databases

Claims data describe the sociology of health care and its recording practice in light of economic interests



Schneeweiss J Clin Epi 2005

From healthcare encounters to data and analyzable databases

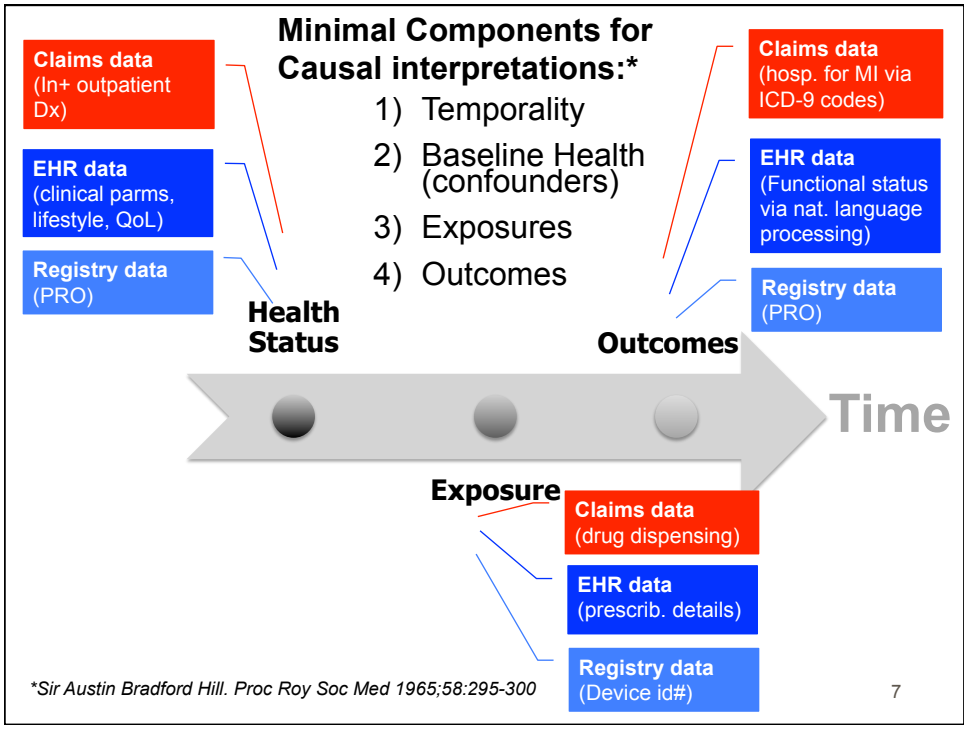


5

Longitudinal insurance claims databases

```
---------- ID********** dob=**/**/1948 sex=M eligdt=1/2000 indexdt=6/2001  --------------------

Service  Site of                    ___________Drug or Procedure________  ________Diagnosis_____
Date     Service  Prov Type         Code   Description                    * Code  Description
-------------------------------------------------------------------------------------------
10/01/00 OFFICE   Family Practice  90658  INFLUENZA VIRUS VACC/SPLIT     V048  VACC FOR INFLUEN
10/01/00 Rx       Pharmacy                CIPROFLOXACIN 500MG TABLETS          10
11/05/00 OFFICE   Family Practice  17110  DESTRUCT OF FLAT WARTS, UP     0781  VIRAL WARTS
11/07/00 Rx       Pharmacy                CIPROFLOXACIN 500MG TABLETS          10
01/15/01 Rx       Pharmacy                CIPROFLOXACIN 500MG TABLETS          10
06/25/01 OFFICE   Emerg Clinic    99070  SPECIAL SUPPLIES               * 84509 SPRAIN OF ANKLE
                                                                        E927  ACC OVEREXERTION
06/30/01 OFFICE   Orthopedist     99204  OV,NEW PT.,DETAILED H&P,LOW    * 72767 RUPT ACHILL TEND
06/30/01 OFFICE   Internist/Gener 99202  OV,NEW PT.,EXPD.PROB-FOCSD     * 84509 SPRAIN OF ANKLE
         OUTPT HP Anesthesiologis 01472  REPAIR OF RUPTURED ACHILLES  * 84509 SPRAIN OF ANKLE
                  Hospital        27650  REPAIR ACHILLES TENDON         * 84509 SPRAIN OF ANKLE
                                  85018  BLOOD COUNT; HEMOGLOBIN        * 84509 SPRAIN OF ANKLE
                  Orthopedist     27650  REPAIR ACHILLES TENDON         * 84509 SPRAIN OF ANKLE
06/30/01 OFFICE   Orthopedist     29405  APPLY SHORT LEG CAST           * 72767 RUPT ACHILL TEND
07/30/01 OFFICE   Orthopedist     29405  APPLY SHORT LEG CAST           * 72767 RUPT ACHILL TEND
08/13/01 OFFICE   Orthopedist     L2116  AFO TIBIAL FRACTURE RIGID      * 72767 RUPT ACHILL TEND
```



Why we like propensity score matching when working with healthcare databases:

Propensity scores:

- Many exposed patients
- Few outcomes
- Many covariates

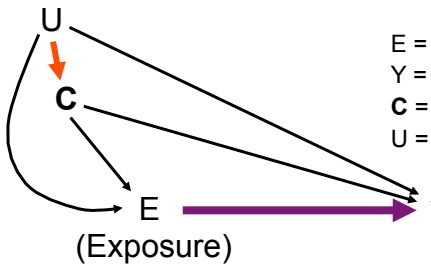
Primary data collection	**Secondary** use of data
▪ Precisely identified covariates ▪ Well-defined measurement ▪ A small number of selected covariates	▪ Known constructs of covariates ▪ **No control of covariate measurement** ▪ **Large numbers of covariates can be generated**

Matching:

- Transparency in the achieved balance
- Trimming of subjects that cannot be matched (areas of no support)

8

Unobservable confounding and proxy measures



E = Exposure; e.g.
Y = Outcome of interest
C = observable confounder (serves as a proxy)
U = unobservable confounder

Unobserved confounder	Observable proxy	Coding
Very frail health	Use of **oxygen canister**	CPT-4:
Acutely sick but not that bad off	Receiving a **code for hypertension** during a hospital stay	ICD-9:
Health seeking behavior	**Regular check-up** visit; regular screening exams	ICD-9, CPT-4 # GP visits
Fairly healthy senior	Receiving the **first lipid-lowering medication** at age 70	NDC
Chronically sick	Regular visits with specialist, hospitalization; many prescription drugs	# specialist visits, NDC

Longitudinal insurance claims databases

---------- ID=********** dob=**/**/1948 sex=M eligdt=1/2000 indexdt=6/2001 ----------

Service Date	Site of Service	Prov Type	Drug or Procedure Code	Drug or Procedure Description	Diagnosis *	Diagnosis Code	Diagnosis Description
10/01/00	OFFICE	Family Practice	90658	INFLUENZA VIRUS VACC/SPLIT		V048	VACC FOR INFLUEN
10/01/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
11/05/00	OFFICE	Family Practice	17110	DESTRUCT OF FLAT WARTS, UP		0781	VIRAL WARTS
11/07/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
01/15/01	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
06/25/01	**OFFICE**	**Emerg Clinic**	**99070**	**SPECIAL SUPPLIES**	*	**84509**	**SPRAIN OF ANKLE**
						E927	**ACC OVEREXERTION**
06/30/01	**OFFICE**	**Orthopedist**	**99204**	**OV,NEW PT.,DETAILED H&P,LOW**	*	72767	**RUPT ACHILL TEND**
06/30/01	OFFICE	Internist/Gener	99202	OV,NEW PT.,EXPD.PROB-FOCSD	*	84509	SPRAIN OF ANKLE
	OUTPT HP	Anesthesiologis	01472	REPAIR OF RUPTURED ACHILLES	*	84509	SPRAIN OF ANKLE
		Hospital	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
			85018	BLOOD COUNT; HEMOGLOBIN	*	84509	SPRAIN OF ANKLE
		Orthopedist	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
06/30/01	OFFICE	Orthopedist	29405	APPLY SHORT LEG CAST	*	72767	RUPT ACHILL TEND
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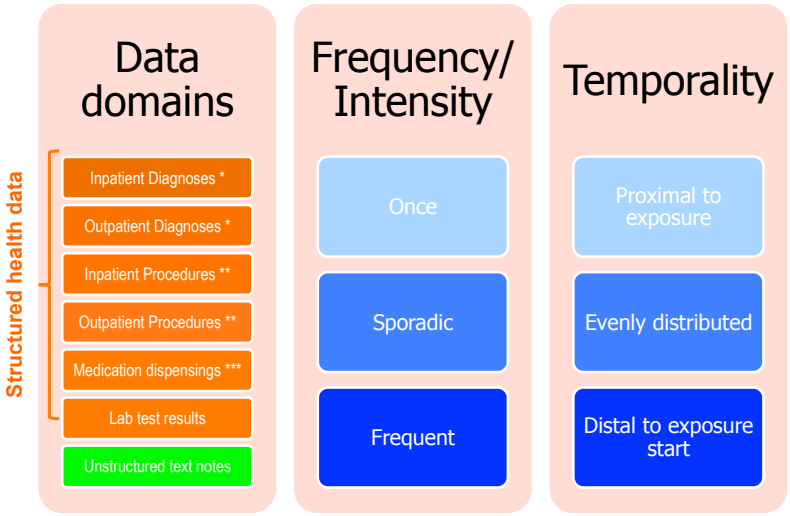
08/13/01	OFFICE	Orthopedist	L2116	AFO TIBIAL FRACTURE RIGID	*	72767	RUPT ACHILL TEND

Longitudinal patterns of codes of any type (Dx, Px, Rx, Lx etc.) are proxies of disease activity, severity and general health state.

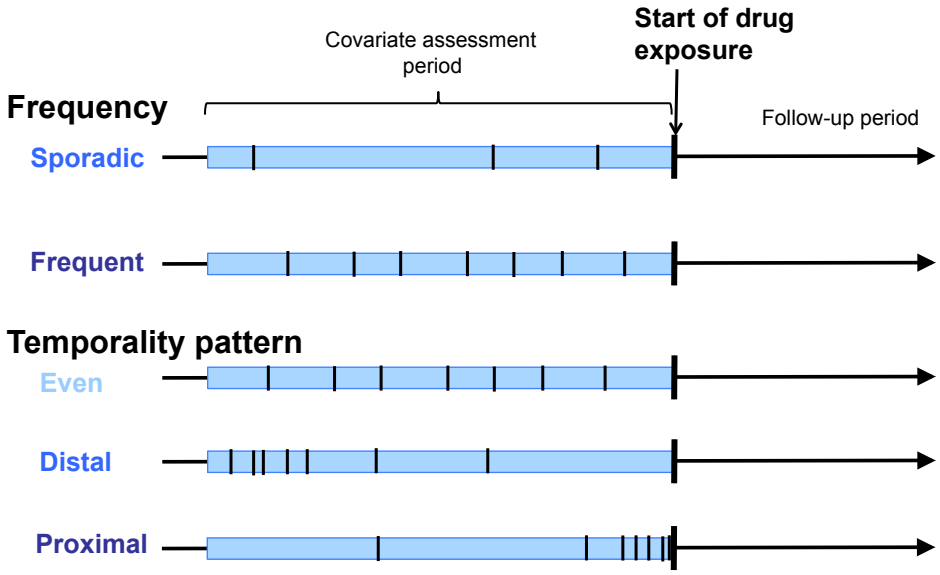
Three main data dimensions



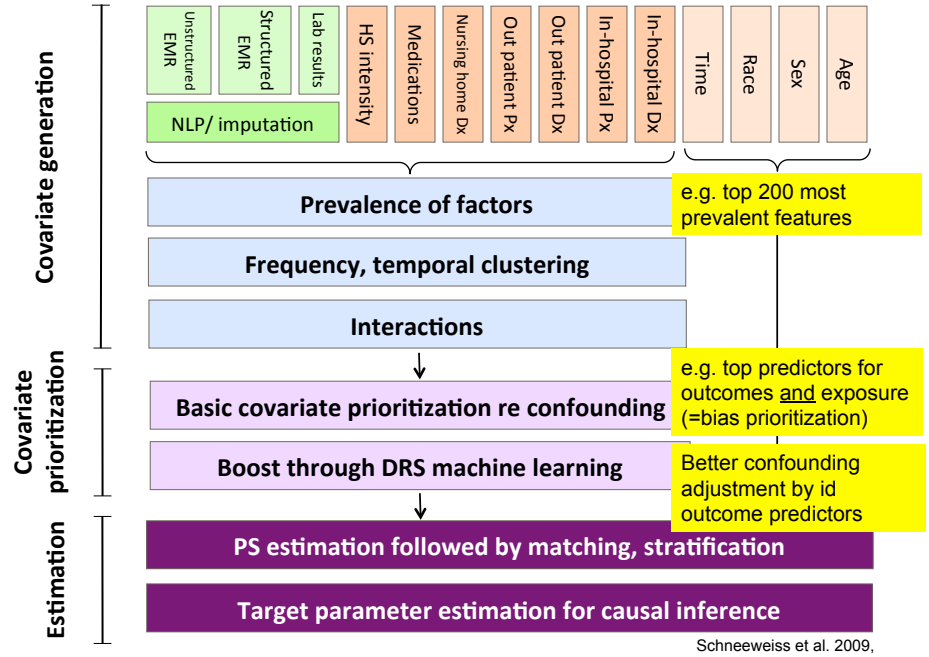
Standard coding examples: * ICD: International classification of disease; ** CPT: Current procedure terminology; *** NDC: National Drug Code, ATC: Anatomical Therapeutic Classification

Schneeweiss et al. 2009, Rassen et al 2011

Confounding frequency and temporality patterns



Data adaptive adjustment using hdPS



Schneeweiss et al. 2009,

Comparative Safety of Antidepressant Agents for Children and Adolescents Regarding Suicidal Acts

AUTHORS: Sebastian Schneeweiss, MD, ScD,[a] Amanda R. Patrick, MS,[a] Daniel H. Solomon, MD, MPH,[a] Colin R. Dormuth, MA, MS, ScD,[b] Matt Miller, MD, ScD,[c] Jyotsna Mehta, MS,[a] Jennifer C. Lee, BS,[a] and Philip S. Wang, MD, DrPH[a,d]

Pediatrics 2010;125:e000

TABLE 3 Event RRs for Suicidal Acts and Violent Suicidal Acts During 1-Year Follow-up Period

	RR (95% CI)			
	Suicidal Acts			
	Unadjusted	Adjusted for Age, Gender, and Calendar Year	Adjusted for Propensity Score Decile[a]	Adjusted for High-Dimensional Propensity Score Decile[b]
Children and adolescents with no antidepressant use in past 3 y				
Tricyclic drugs	0.59 (0.28–1.27)	0.66 (0.31–1.42)	0.71 (0.33–1.52)	0.92 (0.43–2.00)

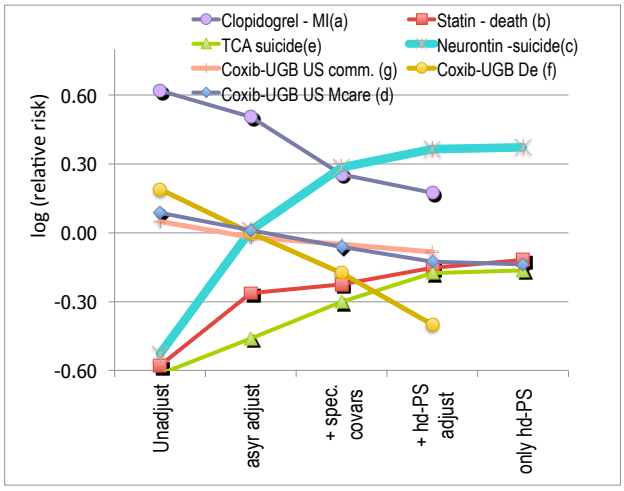
14

Performance in empirical database studies

hdPS is data source indep't

<u>Claims databases:</u>
U.S. Medicare
U.S. commercial
Canada
Germany

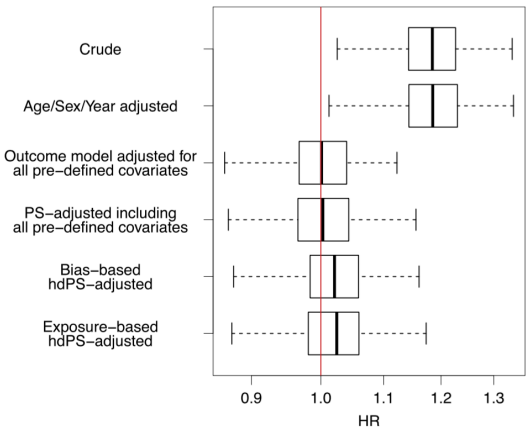
<u>HER databases:</u>
United Kingdom
Regenstrief

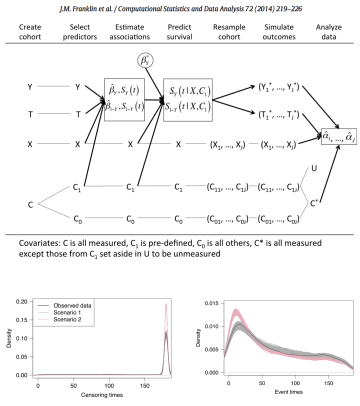


(a) Rassen JA, et al.. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention. Circulation 2009;120:2322-9.
(b + d) Schneeweiss S, et al.. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512–22.
(c) Patorno E, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401-9
(e) Schneeweiss S, et al. The comparative safety of antidepressant agents in children regarding suicidal acts. Pediatrics 2010;125: 876–88
(f) Garbe E, et al. High-dimensional versus conventional propensity scores in a comparative effectiveness study of coxibs and reduced upper gastrointestinal complications. Eur J Clin Pharmacol. 2012 Jul 5.
(g) Le, et al. Effects of aggregation of drug and diagnostic codes on the performance of the hdPS algorithm. BMC Med Res Methodology 2013;13:142.

Plasmode simulations studies confirmed excellent performance in real-world data

Plasmode simulations inject a defined causal effect of E on Y|C in a given healthcare database preserving the underlying data structure and information content.





Franklin et al. Comp Stat Data Analysis 2013

16

American Journal of Epidemiology Advance Access published April 19, 2006

American Journal of Epidemiology

DOI: 10.1093/aje/kwj149

Practice of Epidemiology

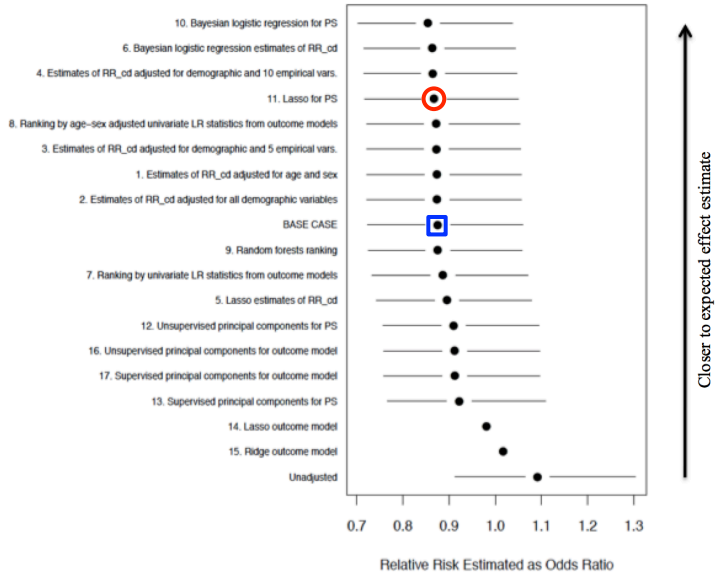
Variable Selection for Propensity Score Models

M. Alan Brookhart[1], Sebastian Schneeweiss[1], Kenneth J. Rothman[1,2], Robert J. Glynn[1,3], Jerry Avorn[1], and Til Stürmer[1,3]

1) Variables that are unrelated to the exposure but **related to the outcome should always be included in a PS** model.
2) Including variables that are related to the exposure but not to the outcome will increase the variance of the estimated exposure effect without decreasing bias
3) In small studies, the inclusion of variables that are strongly related to the exposure but only weakly related to the outcome can increase bias

17

Using Lasso to ID outcome predictors, then feeding into PS

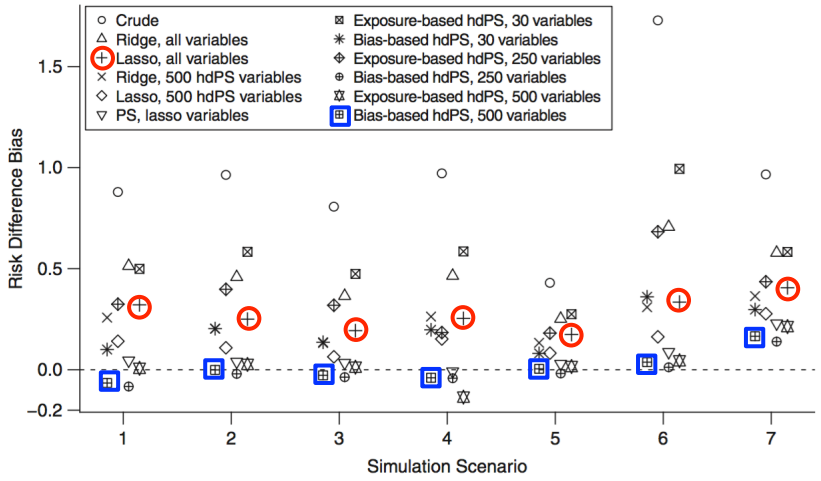


Schneeweiss et al. Epidemiology 2016 in press

18

Direct effect estimation (outcome model) with Lasso

Why PS? Why not use statistical learning techniques like Lasso for direct outcome estimation in an high-dimensional covariate space



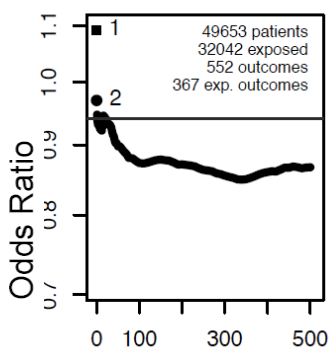
Franklin et al. AJE 2015

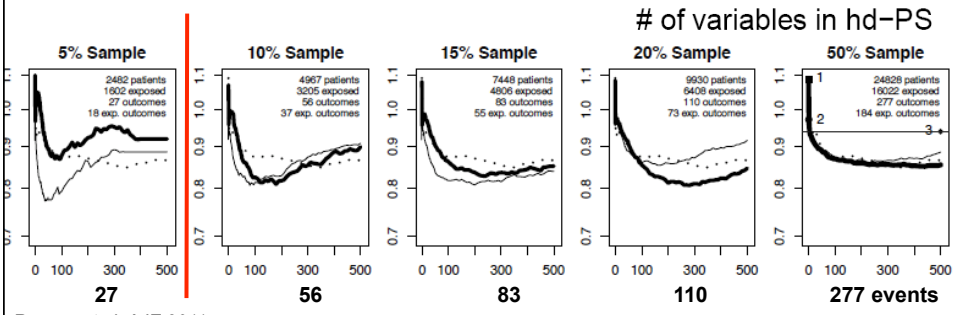
19

hd-PS small sample performance (simulations)

Use case: **Newly marketed medications**

- Initially few exposed patients and a handful of events
- Want to know adverse events early on
- Sequential estimation as data refresh

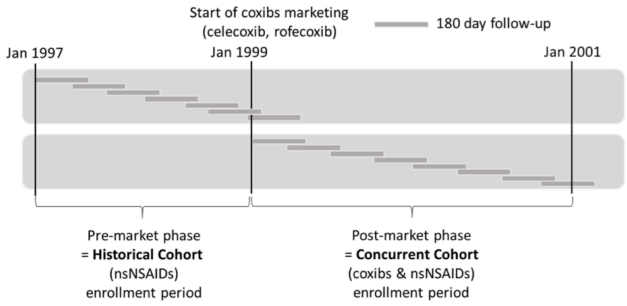




Rassen et al. AJE 2011

New medications: Can historical data help with covariate identification when there are few exposed subjects

coxibs vs. nsNSAIDs study



	Full cohort	Sampled Cohort			
		10%	15%	20%	50%
	Odds Ratio	Geometric Mean of ORs (Monte-Carlo 95% CI)			
Unadjusted	1.09	1.11 (1.06-1.15)	1.10 (1.07-1.14)	1.10 (1.07-1.12)	1.08 (1.07-1.10)
PS (predefined[†])	0.92	0.93 (0.89-0.97)	0.94 (0.91-0.97)	0.93 (0.90-0.95)	0.92 (0.91-0.93)
e-hdPS	0.90	0.86 (0.82-0.90)	0.88 (0.85-0.91)	0.87 (0.85-0.89)	0.88 (0.87-0.89)
op-hdPS$_{Hx+}$	0.92	0.94 (0.90-0.99)	0.94 (0.91-0.98)	0.92 (0.90-0.95)	0.92 (0.90-0.93)
b-hdPS$_{Hx+}$	0.88	0.81 (.78-.85)	0.83 (.80-.86)	0.83 (.81-.85)	0.84 (.83-.85)
b-hdPS	0.86	0.78 (0.75-0.82)	0.80 (0.77-0.83)	0.79 (0.77-0.81)	0.82 (0.81-0.83)
b-hdPS with correction	0.88	0.78 (0.75-0.82)	0.81 (0.78-0.84)	0.80 (0.78-0.82)	0.83 (0.82-0.84)
hdDRS	0.96	0.98 (0.94-1.02)	0.97 (0.94-1.01)	0.97 (0.95-0.99)	0.96 (0.95-0.97)

Kamamaru et al. J Clin Epi 2016 in press

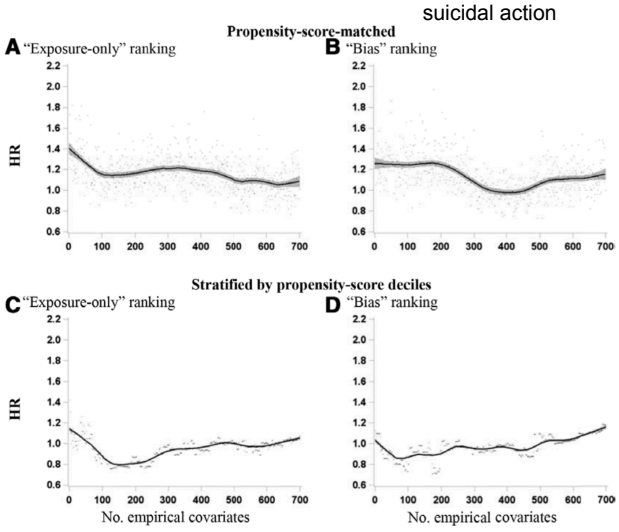
21

Automatic variable selection: When is it enough?

Anticonvulsants and suicidal action

Change in estimate?
(Schneeweiss)

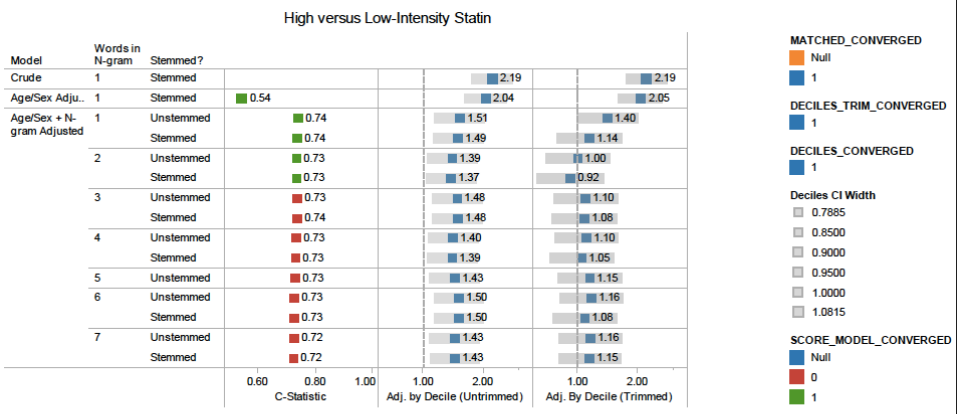
X-validated outcome prediction via CTMLE?
(van der Laan)



Patorno et al. Epidemiology 2014

22

Performance of algorithmic EHR word stem adjustment



1 Word:
leukocytosi
oxycontin
haptic
extracrani
scleral
splenomengali
valium
cardizem

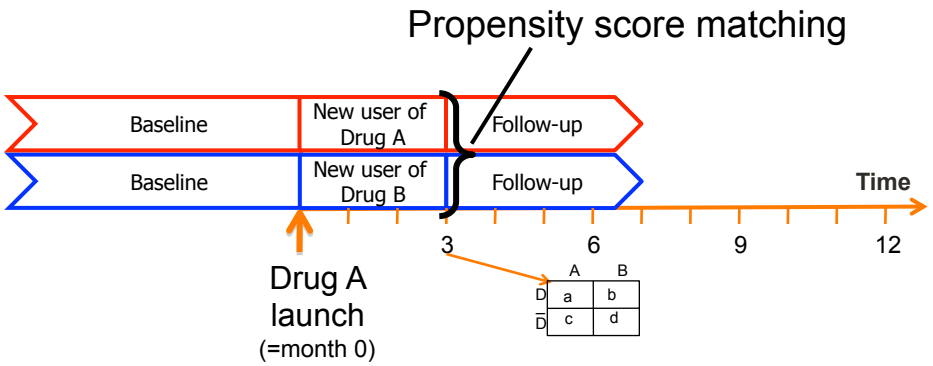
2 Words:
site cervix
categori within
specimen
categori
peripher edema
maxillari sinus
differenti diagnos
high bpv

3 Words:
specimen site cervix
site cervix endocervix
categori within normal
impress ct abdomen
or 3 view
white female a
exam ct abdomen

Rassen et al. 2013

From one-off to ongoing monitoring

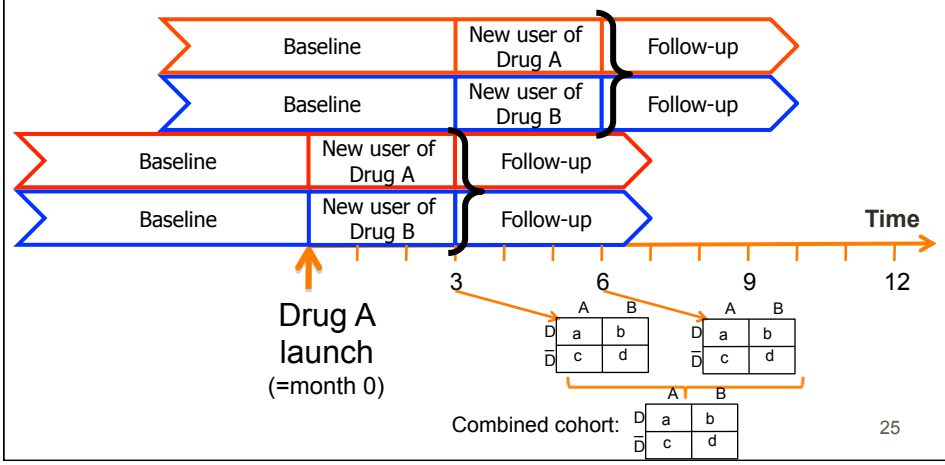
Now that we have developed an automated approach to optimized confounding adjustment with healthcare data



Schneeweiss et al. CPT 2011

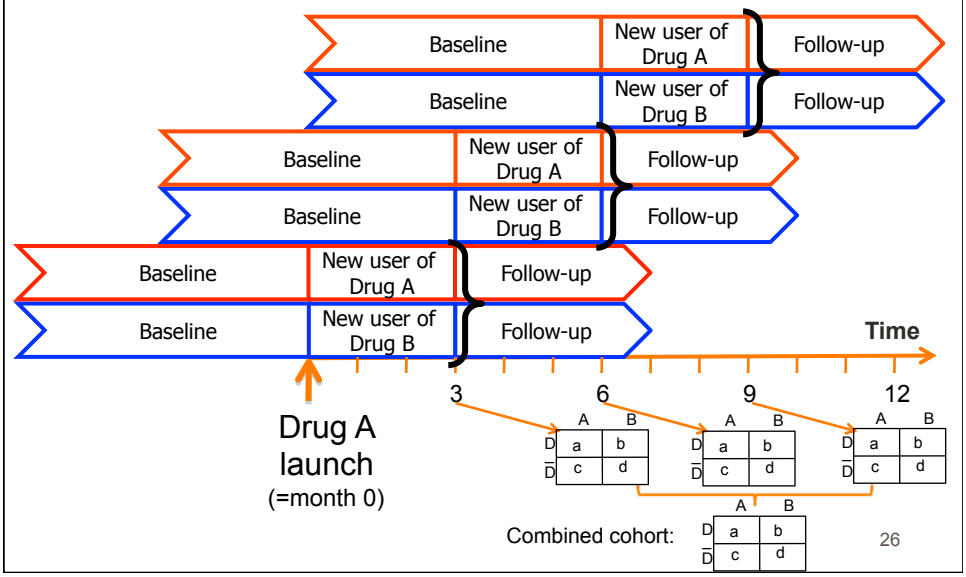
24

Evidence generation as data refresh
A sequential cohort design



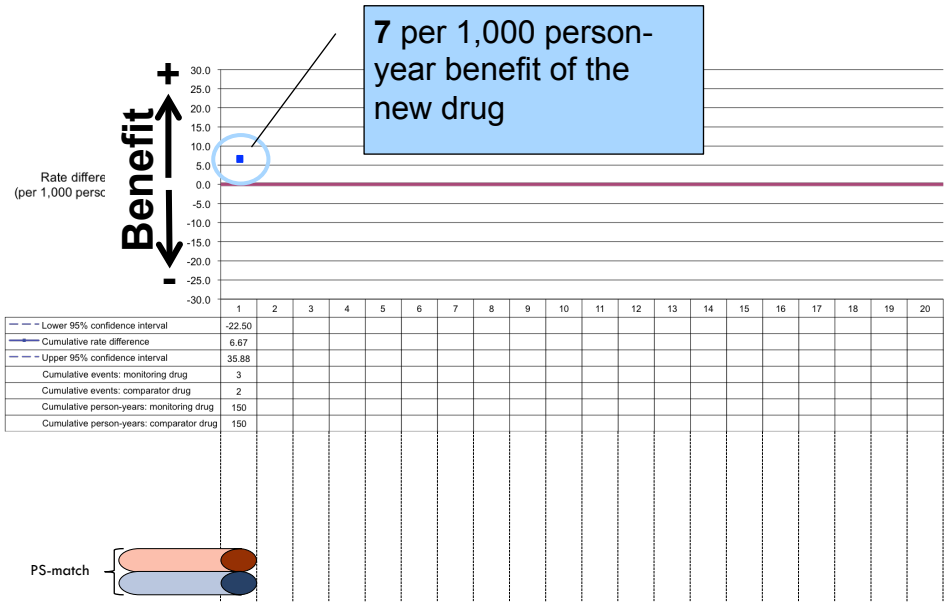
25

Evidence generation as data refresh
A sequential cohort design

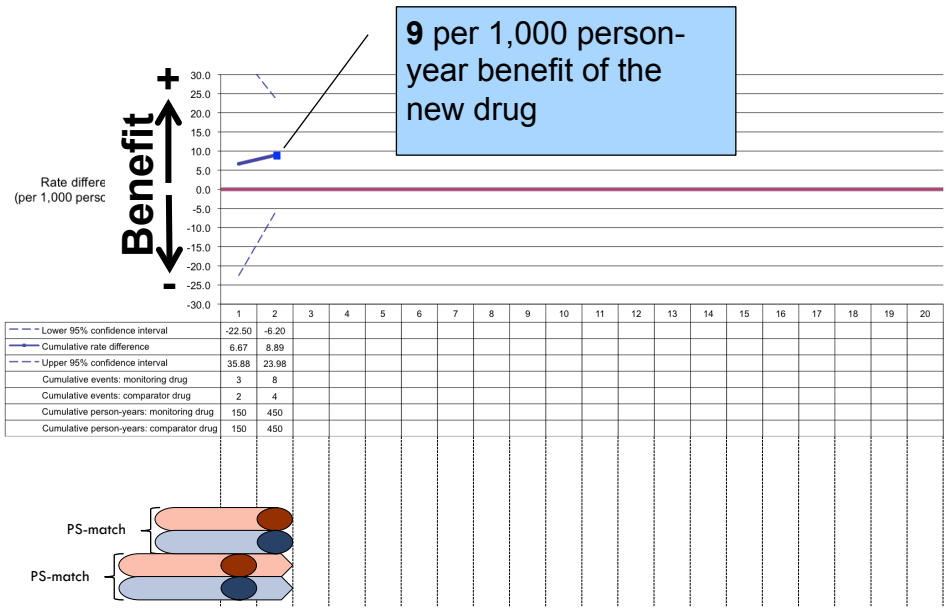


26

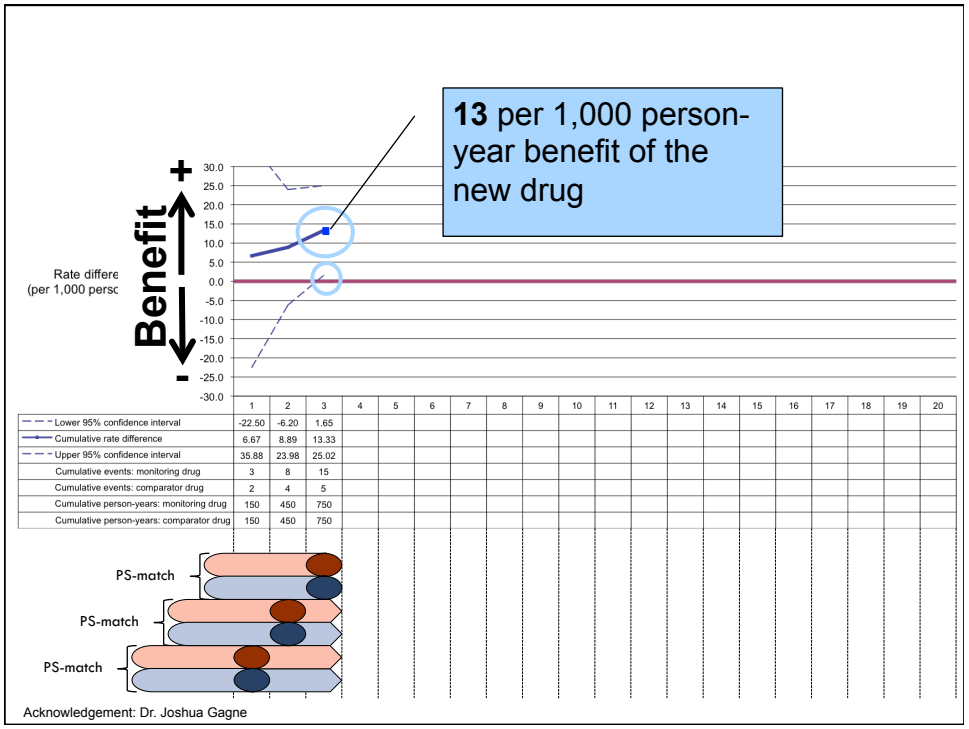
When is a benefit real?

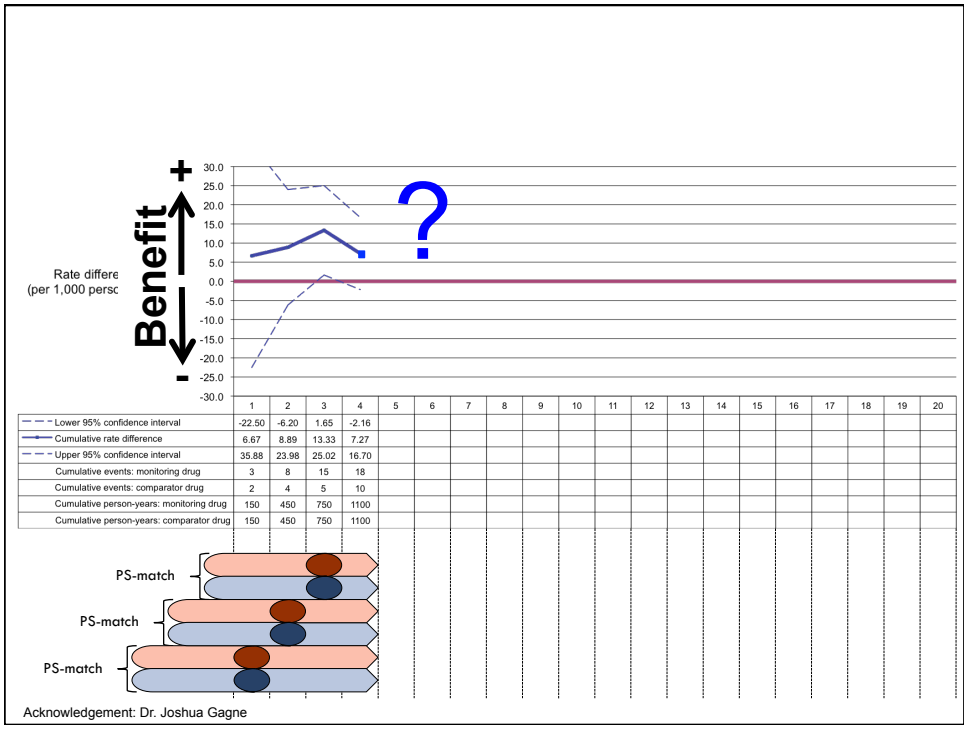


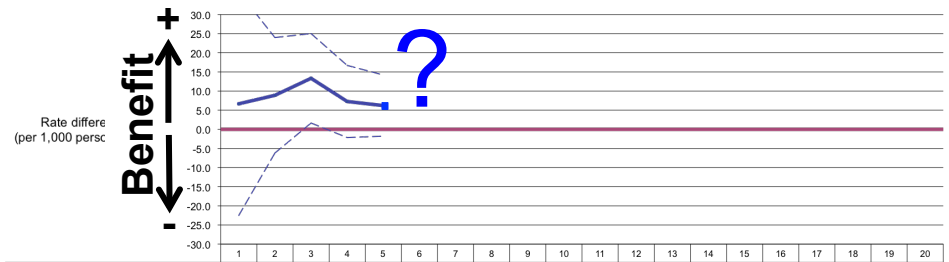
Acknowledgement: Dr. Joshua Gagne



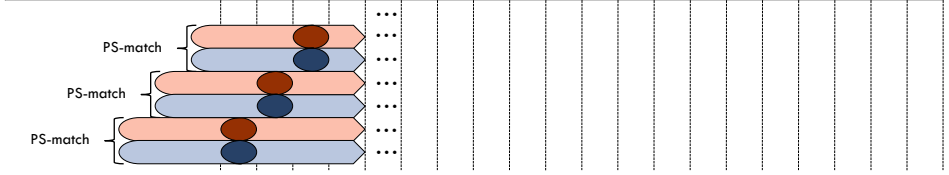
Acknowledgement: Dr. Joshua Gagne


13 per 1,000 person-year benefit of the new drug
Benefit
Rate differe
(per 1,000 persc
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Lower 95% confidence interval -22.50 -6.20 1.65
Cumulative rate difference 6.67 8.89 13.33
Upper 95% confidence interval 35.88 23.98 25.02
Cumulative events: monitoring drug 3 8 15
Cumulative events: comparator drug 2 4 5
Cumulative person-years: monitoring drug 150 450 750
Cumulative person-years: comparator drug 150 450 750
PS-match
PS-match
PS-match
Acknowledgement: Dr. Joshua Gagne

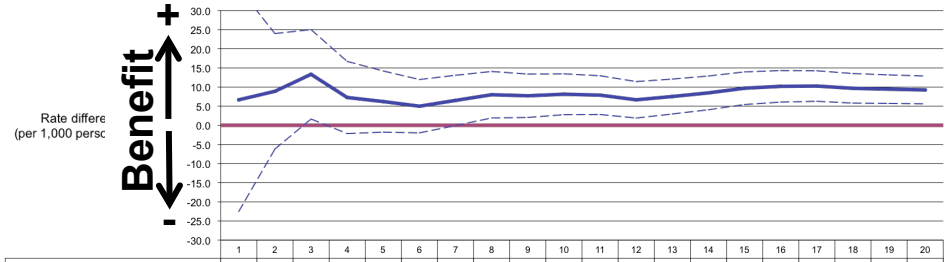

Benefit
Rate differe
(per 1,000 persc
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
-30.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Lower 95% confidence interval -22.50 -6.20 1.65 -2.16
Cumulative rate difference 6.67 8.89 13.33 7.27
Upper 95% confidence interval 35.88 23.98 25.02 16.70
Cumulative events: monitoring drug 3 8 15 18
Cumulative events: comparator drug 2 4 5 10
Cumulative person-years: monitoring drug 150 450 750 1100
Cumulative person-years: comparator drug 150 450 750 1100
PS-match
PS-match
PS-match
Acknowledgement: Dr. Joshua Gagne



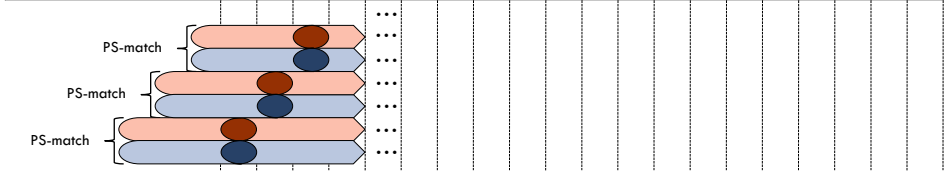
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79															
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21															
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20															
Cumulative events: monitoring drug	3	8	15	18	22															
Cumulative events: comparator drug	2	4	5	10	13															
Cumulative person-years: monitoring drug	150	450	750	1100	1450															
Cumulative person-years: comparator drug	150	450	750	1100	1450															



Acknowledgement: Dr. Joshua Gagne



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79	-1.97	-0.06	1.93	2.05	2.79	2.83	1.90	2.96	4.07	5.43	6.07	6.28	5.80	5.72	5.62
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21	5.00	6.51	8.00	7.72	8.13	7.89	6.67	7.53	8.48	9.70	10.19	10.27	9.67	9.45	9.25
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20	11.97	13.08	14.07	13.39	13.46	12.95	11.43	12.09	12.89	13.96	14.31	14.25	13.53	13.18	12.88
Cumulative events: monitoring drug	3	8	15	18	22	25	33	40	45	51	56	58	65	73	82	89	95	99	103	108
Cumulative events: comparator drug	2	4	5	10	13	16	19	20	23	25	28	32	33	34	34	35	37	41	43	46
Cumulative person-years: monitoring drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700
Cumulative person-years: comparator drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700



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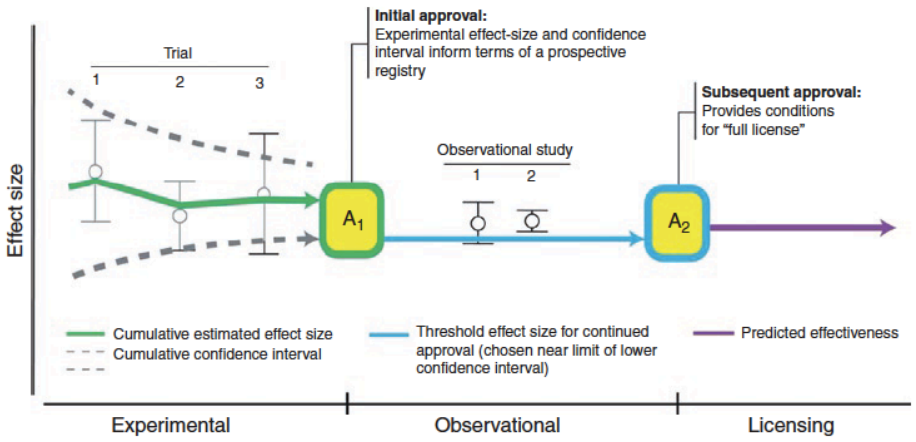
Sequential approaches using healthcare databases for accelerated approval and adaptive licensing



Eichler et al, Clin Pharmacol Therap 2012
Woodcock J, CPT 2012

33

Summary

Tremendous possibilities:

- High-dimensional PS as a confounding adjustment strategy tailored towards healthcare databases:
  - Few outcomes
  - Many exposed patients
  - Many proxies of covariates
  - Automated and data adaptive

Practical notes:

- Used by the FDA Sentinel system
- Used by OMOP
- Training and guidelines
- Validated software tools

Not much value outside secondary databases

34