Use of propensity scores for multivariate distributed analytics in a Sentinel-type system

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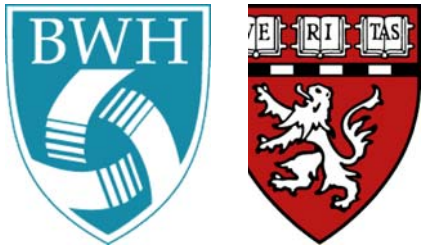


FDA Sentinel from one perspective

- **Overall goal:** Use available data, collected and stored by parties across the United States, to generate, refine, and evaluate drug safety signals in an ongoing monitoring effort.

- **Epidemiology goal:** Understand that most questions will require substantial efforts to control confounding due to treatment selection driven by disease severity and prognosis.

- **Privacy goal:** Be respectful of patient and organizational privacy and operate within all guidelines and regulations.

The challenge of distributed data

- Established methods of [horizontally] combing data require either:
  - Sharing of individual covariates (often impossible) *or*
  - Minimal covariate adjustment (often unsuitable).

- A Sentinel-type system requires:
  - Maintaining privacy of individual patients.
  - Maintaining proprietary data from contributing organizations.
  - Executing signal refinement and evaluation with full multivariate adjustment.
  - A system that supports sites with minimal amounts of statistical expertise.

Confounding bias can lead to false alerts

- Confounding bias is a major challenge, except in limited cases like childhood vaccines.

- A drug given to sicker patients than the comparator drug may have a high probability of false positive alerts. False negative decisions are also possible.

- Full multivariate adjustment with use of maximal recorded information is required in all phases of signal assessment.

Various methods explored (i)

1. **Sharing individual covariates**
   - Definition: amalgamate all data into a "master dataset", including all patient covariates
   - Problems:
     - Does not maintain privacy or proprietary data
     - Time-consuming to implement and standardize variable definitions
2. **Meta-analysis**
   - Definition: compute point estimates and variances at each site; do a pooled analysis with just these figures.
   - Problems:
     - Requires statistical ability at each site
     - Limited ability to do *post hoc* (or "*intra hoc*") changes to analytic plan

Various methods explored (ii)

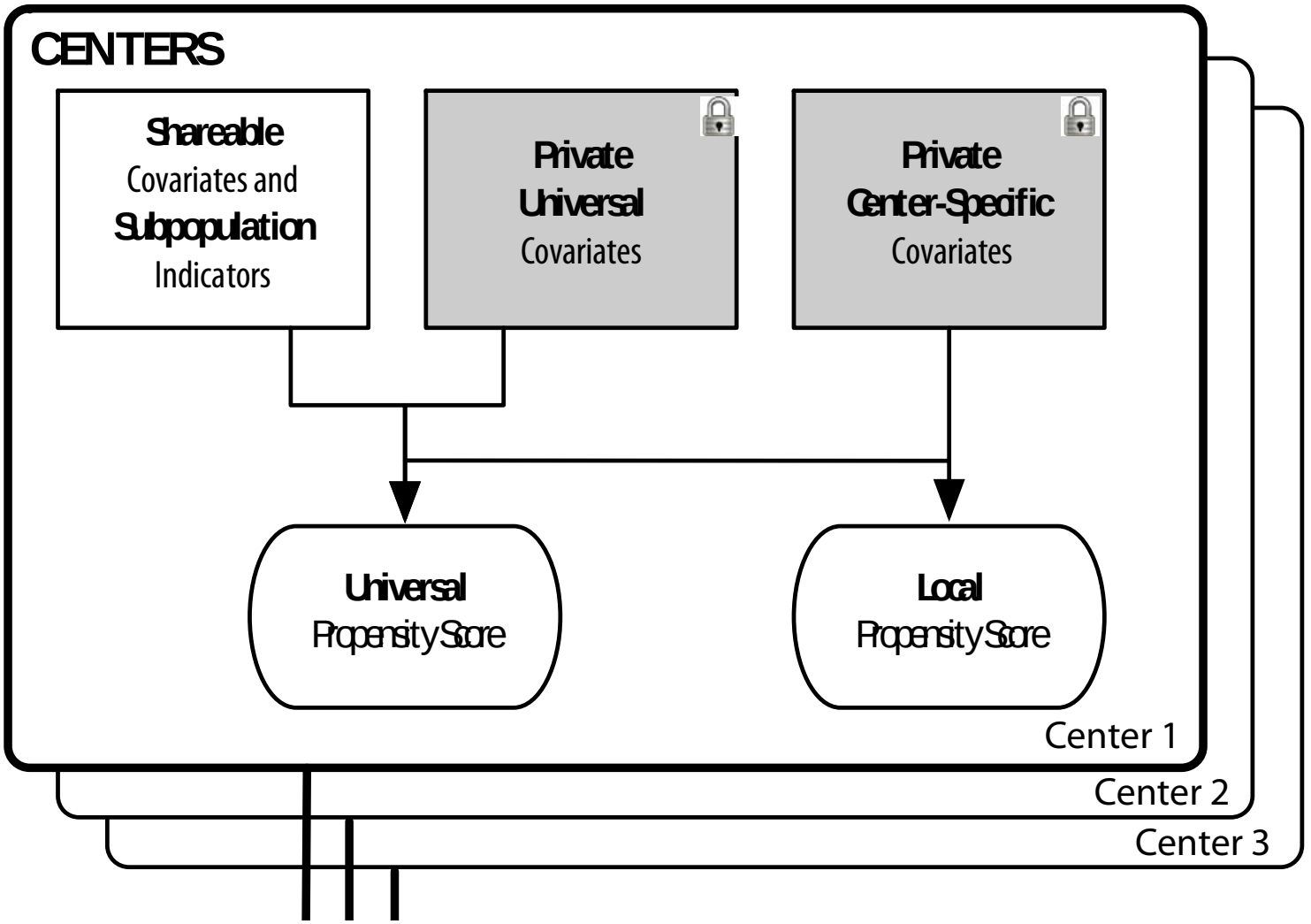
3. **Sharing cell counts (or cell counts masked cryptographically)**
   - Definition: summarize data into cells of counts, then pool counts. Analyze data at the cell level.
   - Problems:
     - If data are stratified by outcome and a reasonable number of confounders are considered then most important cells would be small and thus make patients identifiable.
4. **Propensity score based method***
   - Based on propensity scores – a value that predicts an individual's probability of exposure given his/her vector of measured covariates.
   - PS methods are robust, proven, and can maximize site-specific information content.

* *Rassen, Avorn, Schneeweiss, 2009.*

Propensity scores

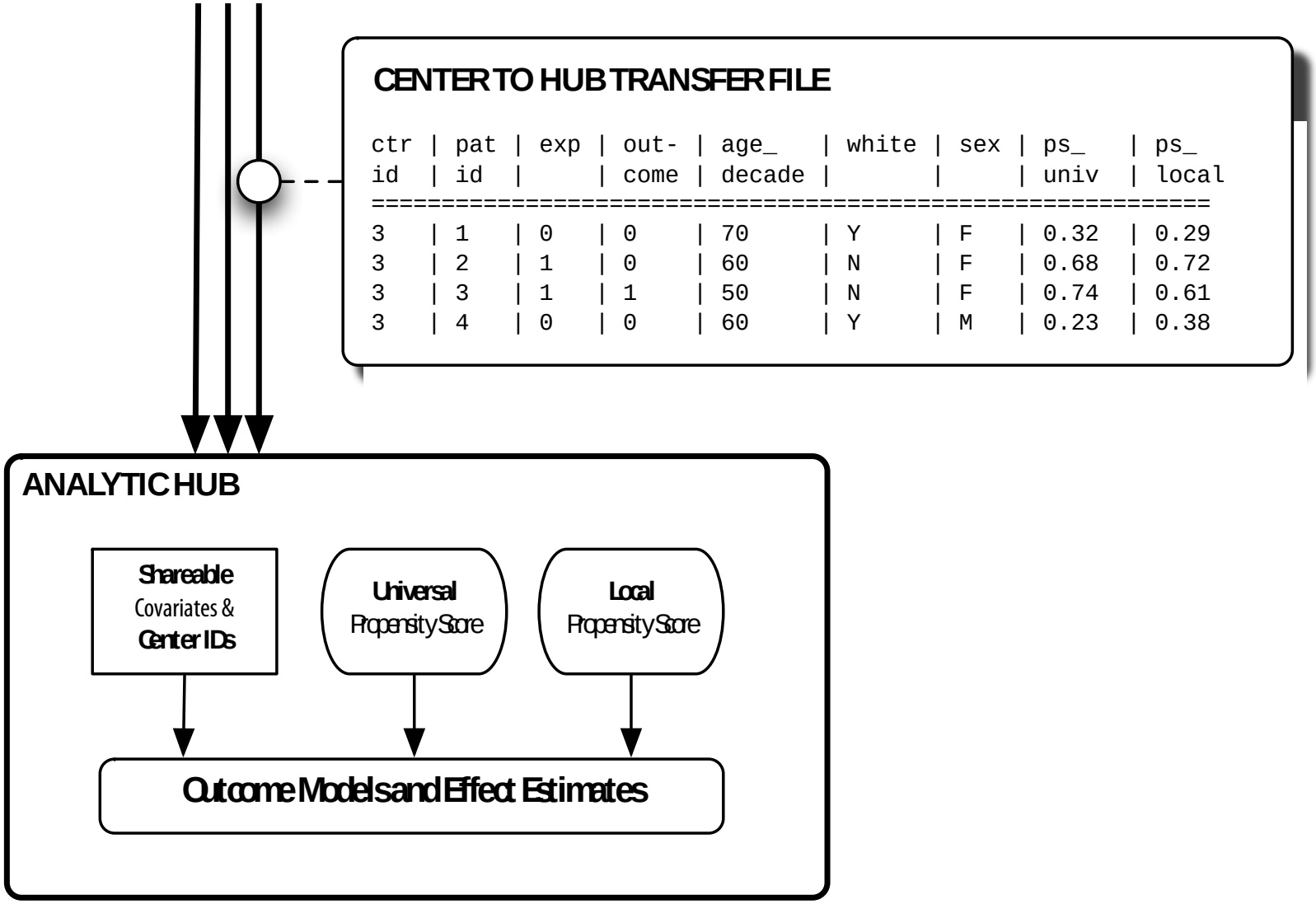
- One of several confounder summary scores: a single value that encapsulates all important information about a patient's disease status.
- If a patient receiving saxagliptin has a PS of 0.2836, and a patient receiving metformin has a PS of 0.2836, then they should be generally balanced on their covariates.
- No knowledge of *why* their PS is 0.2836 needs to be shared. 0.2836 is essentially useless for identifying a single patient.
- Any observed increase in MI incidence can then be causally attributed to the drug.
- Other summary scores could work just as well.

PS-based method (i)



* *Rassen, Avorn, Schneeweiss, 2009.*

PS-based method (ii)



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Example

- PS-based analysis should yield substantially similar results to analysis based on full, unblinded information.
- Example: drug-drug interaction between clopidogrel and PPIs; two outcomes.
- Four centers contribute information to a single analytic hub
- 29 covariates with private patient information

Example outcome 1 (strong confounding)

	B.C. n=19,979	PA Medicr. n=4,201	NJ Medicr. n=4,030	Commerc. n=3,451	POOLED n=31,661	META-ANALY.
Unadj.	1.87	2.03	1.32	*~1.21*	1.74	1.74
Age/sex adj.	1.66	2.12	1.25	*~1.18*	1.60	1.60
Cov. adj.	1.34	1.99	1.19	*~0.75*	1.34	1.34
Univ. PS adj.	1.35	2.11	1.22	*~0.88*	1.32	1.32

Difference < 1%

* *n was too small for model to converge.*

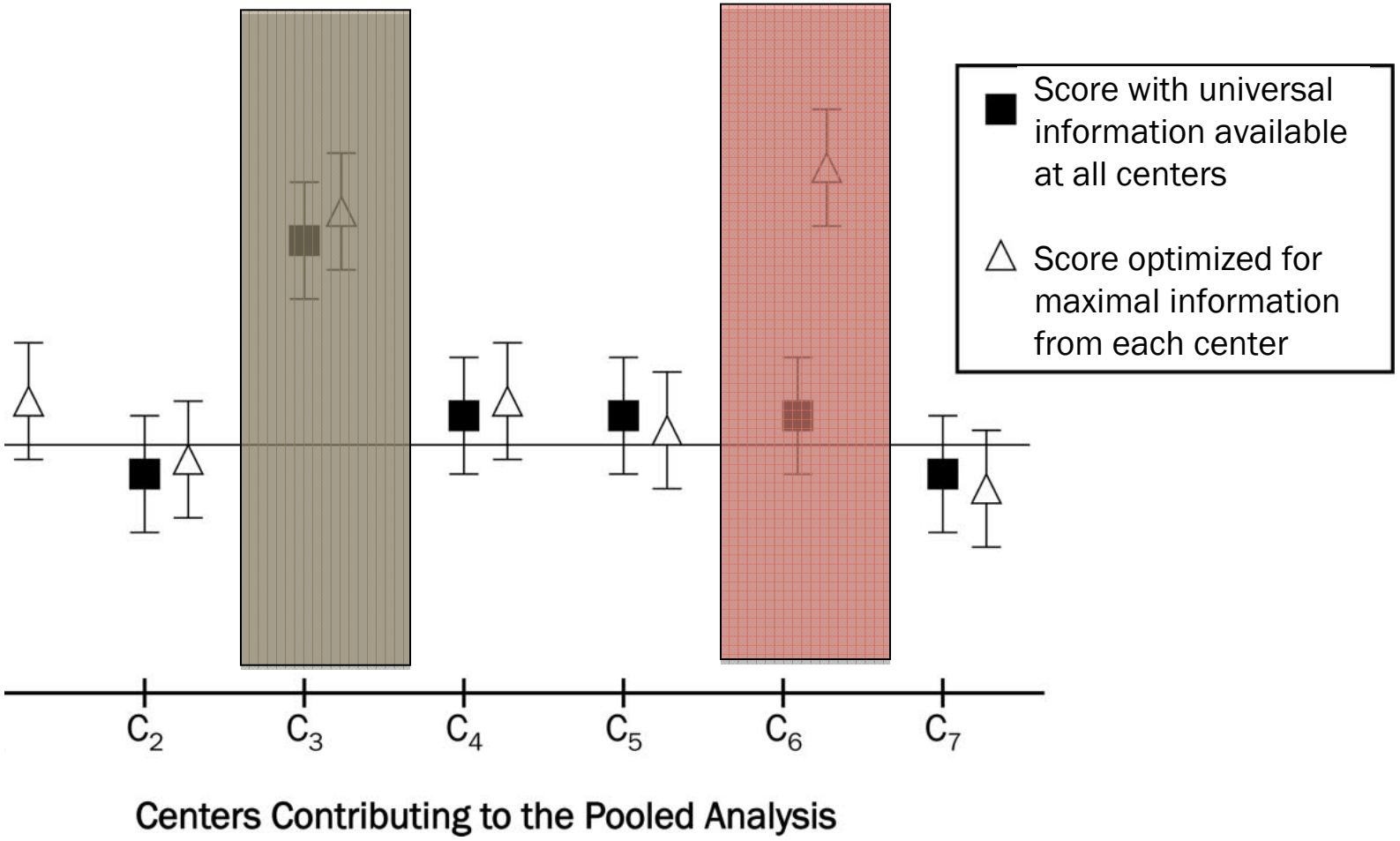
Example outcome 2 (weaker confounding)

	B.C. n=19,979	PA Medicr. n=4,201	NJ Medicr. n=4,030	Commerc. n=3,451	POOLED n=31,661	META-ANALY.
Unadj.	1.41	0.96	0.77	*~1.34*	1.12	1.12
Age/sex adj.	1.5	0.95	0.78	*~1.34*	1.14	1.14
Cov. adj.	1.42	0.96	*0.78*	*~1.34*	1.14	1.14
Univ. PS adj.	1.44	0.93	0.76	*~1.32*	1.11	1.11

Difference = 2%

* *n was too small for model to converge.*

PS's can shed light on heterogeneity



Limitations

- Limited flexibility for *post hoc* subgroup analyses.
- Perceived as a black box.
  - *But one that can be opened by having each site automatically generate copious pre-defined diagnostics.*
- Gleaning private information from propensity scores is all but impossible, but not cryptographically iron-clad.
  - *It is particularly difficult if the information is shared with a (mostly) trusted third party.*
- PS traditionally used for 2 exposures
  - *This fits most Sentinel monitoring scenarios*
  - *Can be expanded to >2 exposures using, eg, multi-way matching*

Conclusions

- Any methodology for a Sentinel-type system must be
  - (a) built on sound epidemiologic principles; and
  - (b) built with the Sentinel goals in mind.

- The PS-based approach maintains privacy and simplicity without sacrificing validity. It also allows for maximal information usage from each data partner.

- The method has served well in several projects to date.