The journey toward Clinical Characterization

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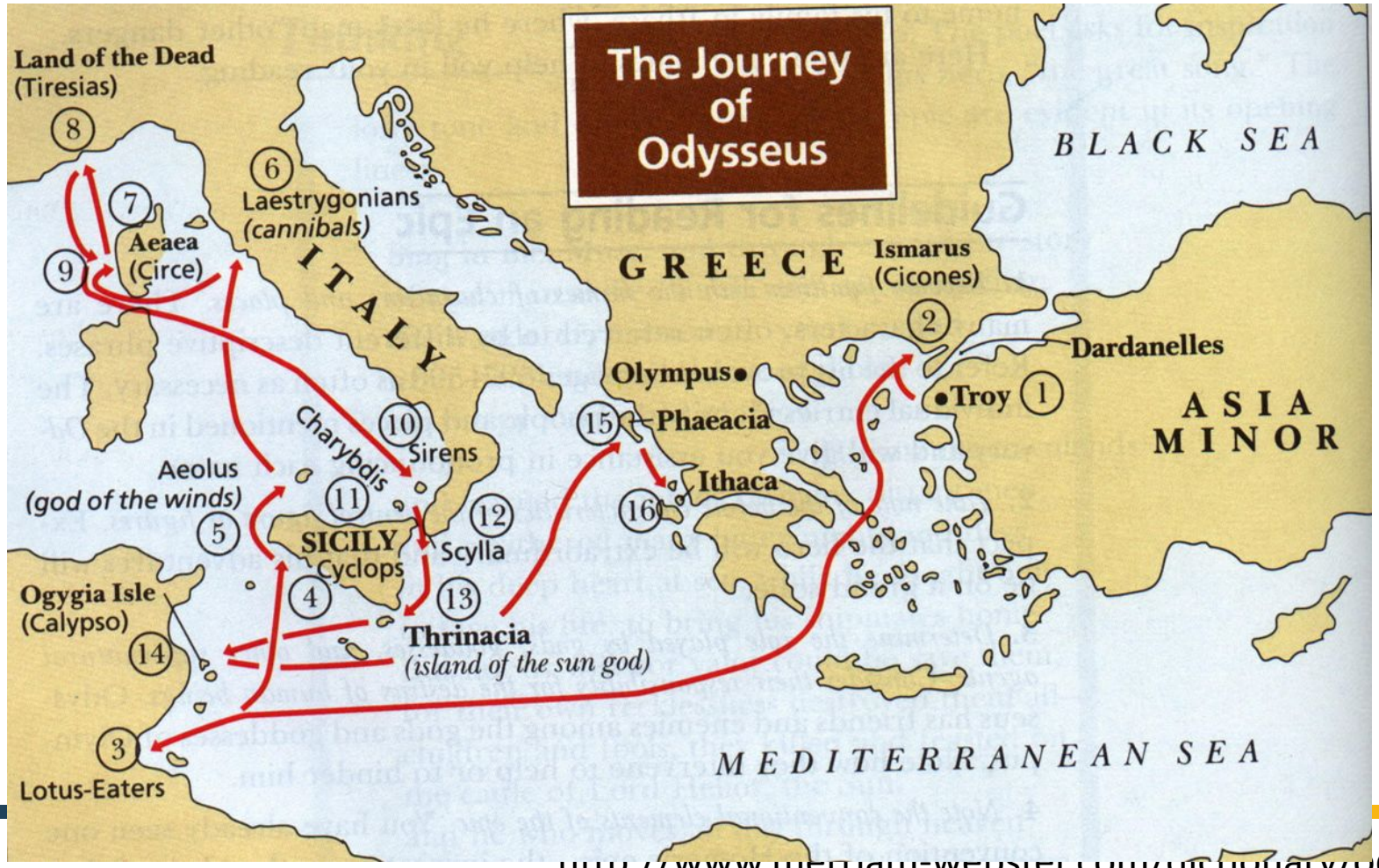
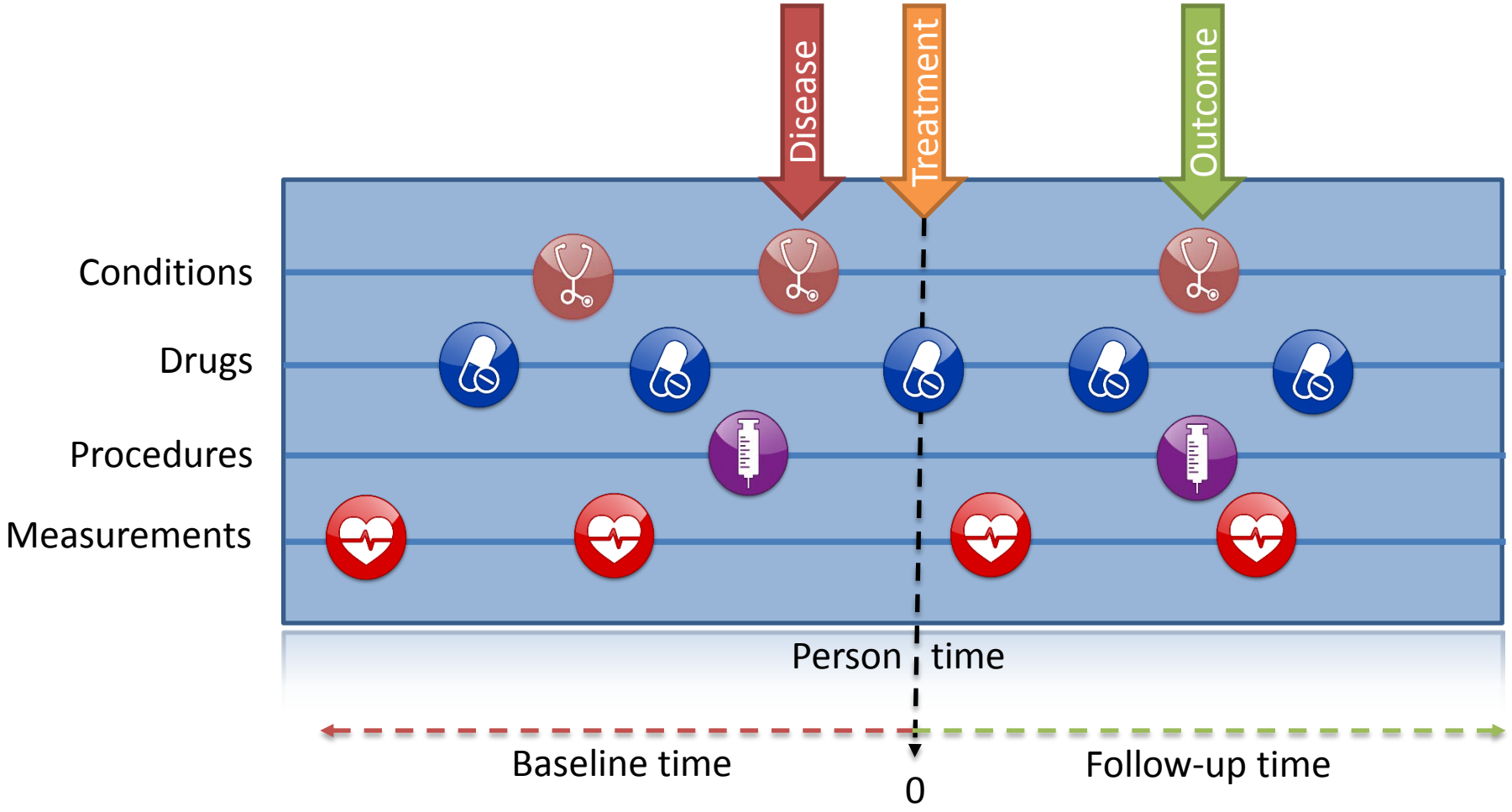
Odyssey (*noun*): \oh-d-si\

1. A long journey full of adventures

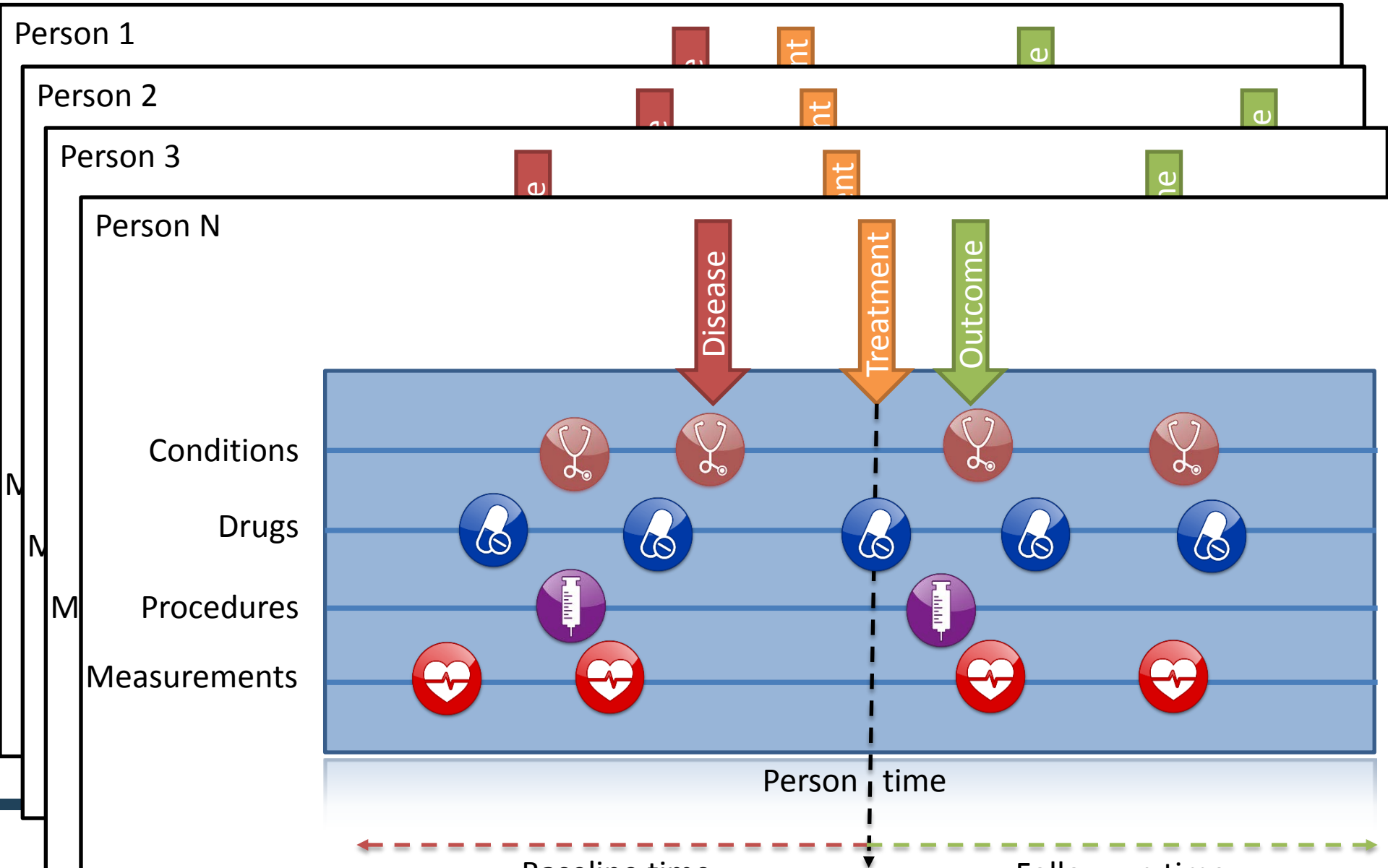


http://www.merriam-webster.com/dictionary/odyssey

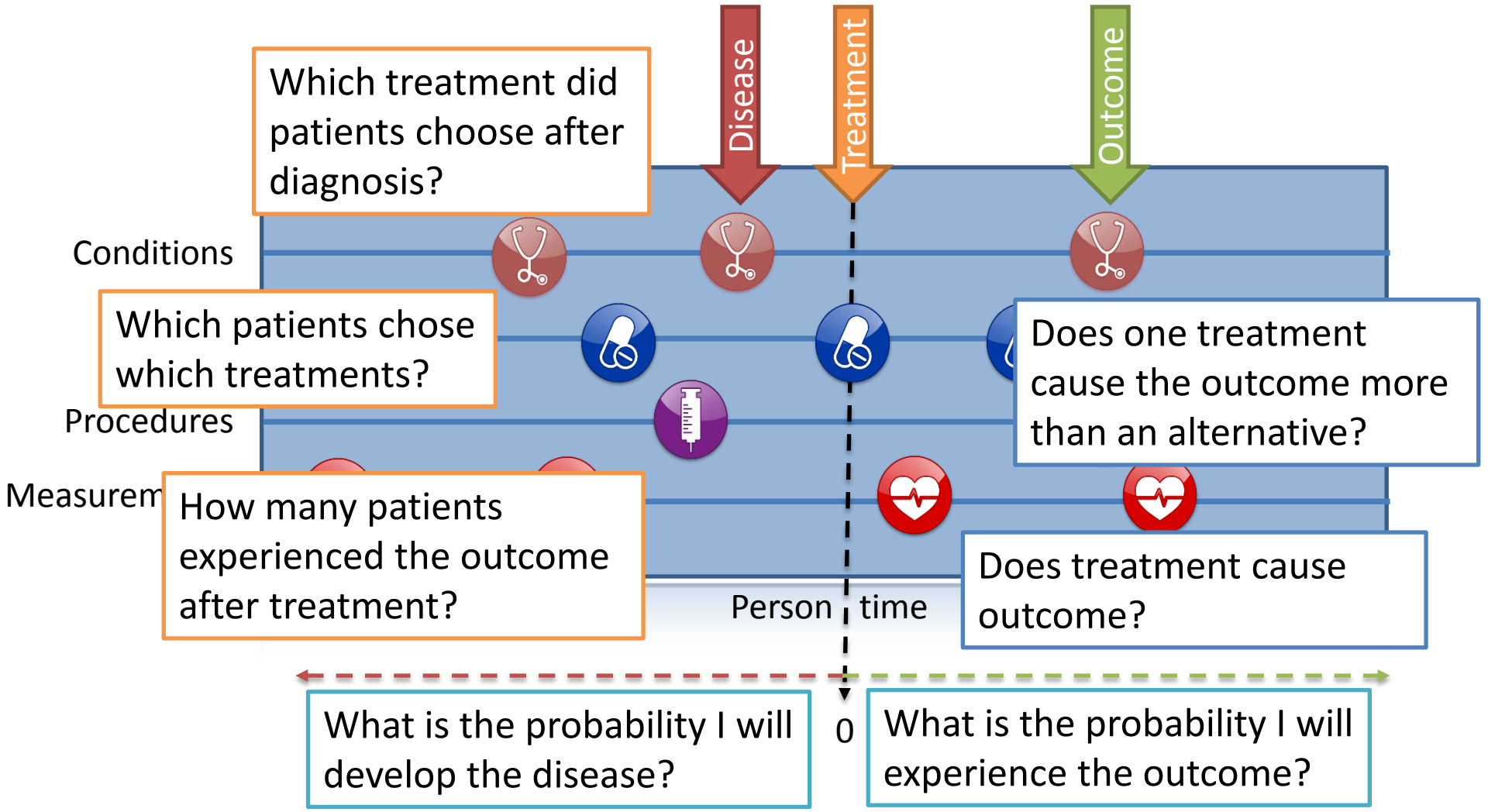
A caricature of the patient journey



Each observational database is just an (incomplete) compilation of patient journeys



Questions asked across the patient journey



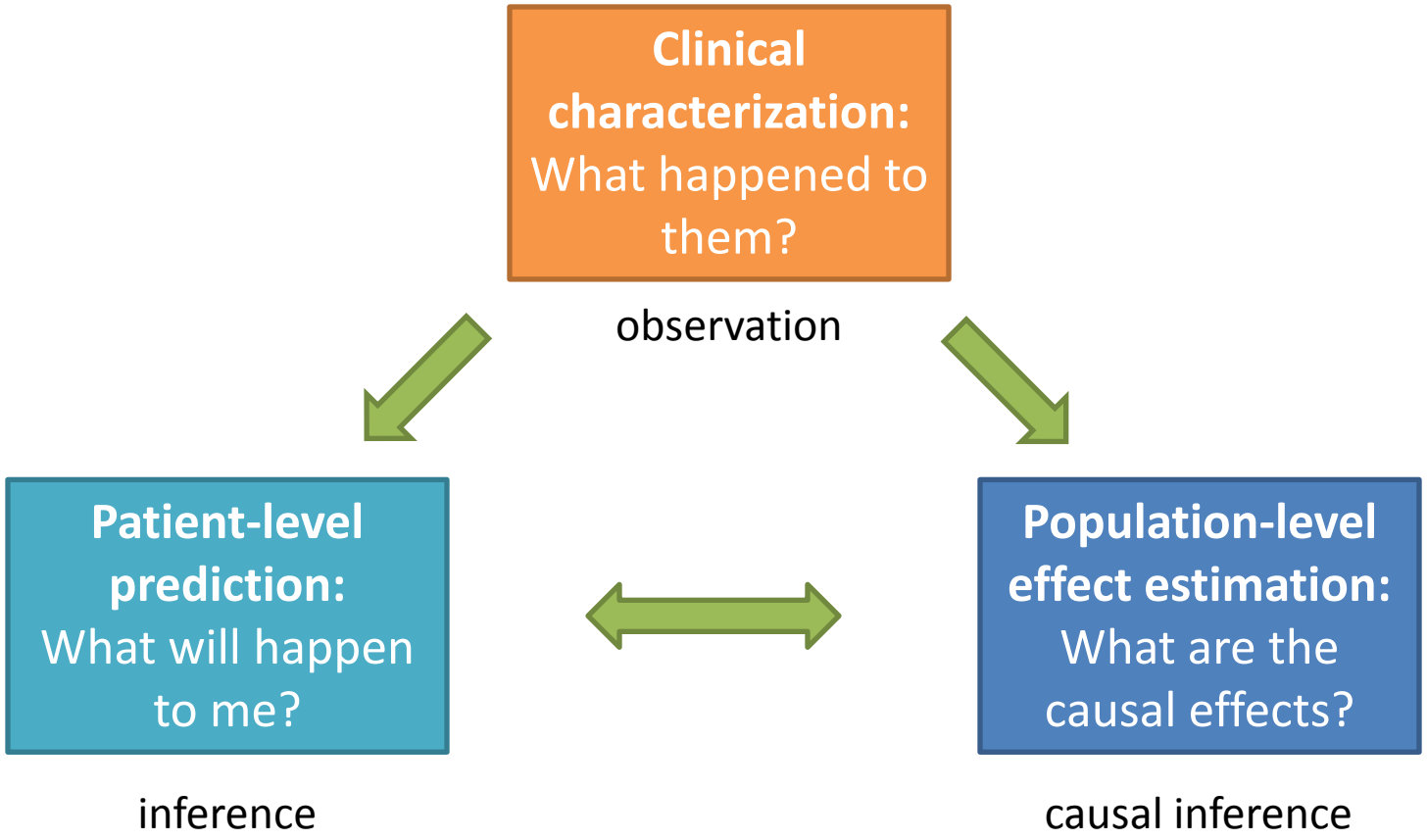
Classifying questions across the patient journey

- **Clinical characterization:** What happened to them?
  - What treatment did they choose after diagnosis?
  - Which patients chose which treatments?
  - How many patients experienced the outcome after treatment?

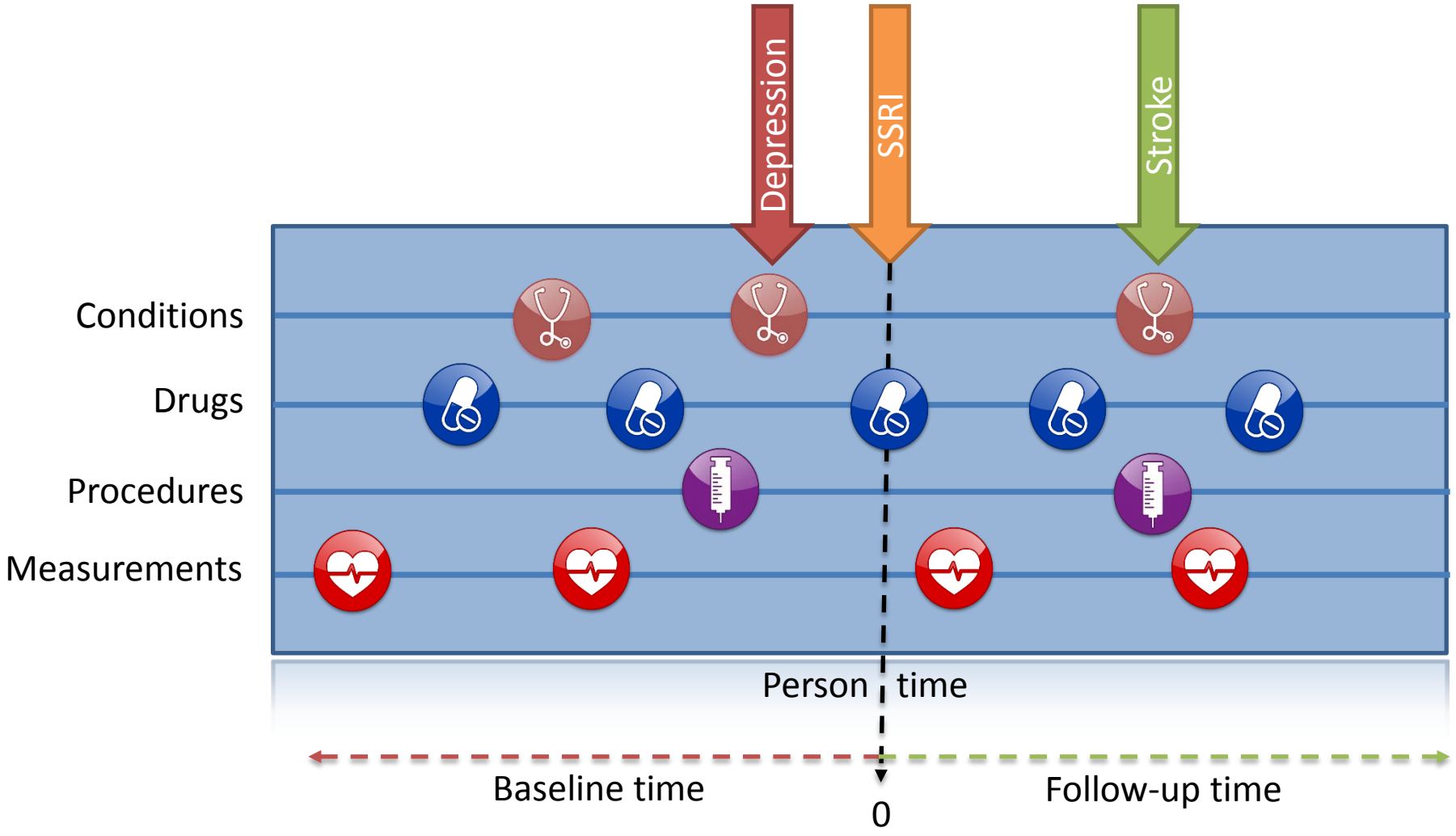
- **Patient-level prediction:** What will happen to me?
  - What is the probability that I will develop the disease?
  - What is the probability that I will experience the outcome?

- **Population-level effect estimation:** What are the causal effects?
  - Does treatment cause outcome?
  - Does one treatment cause the outcome more than an alternative?

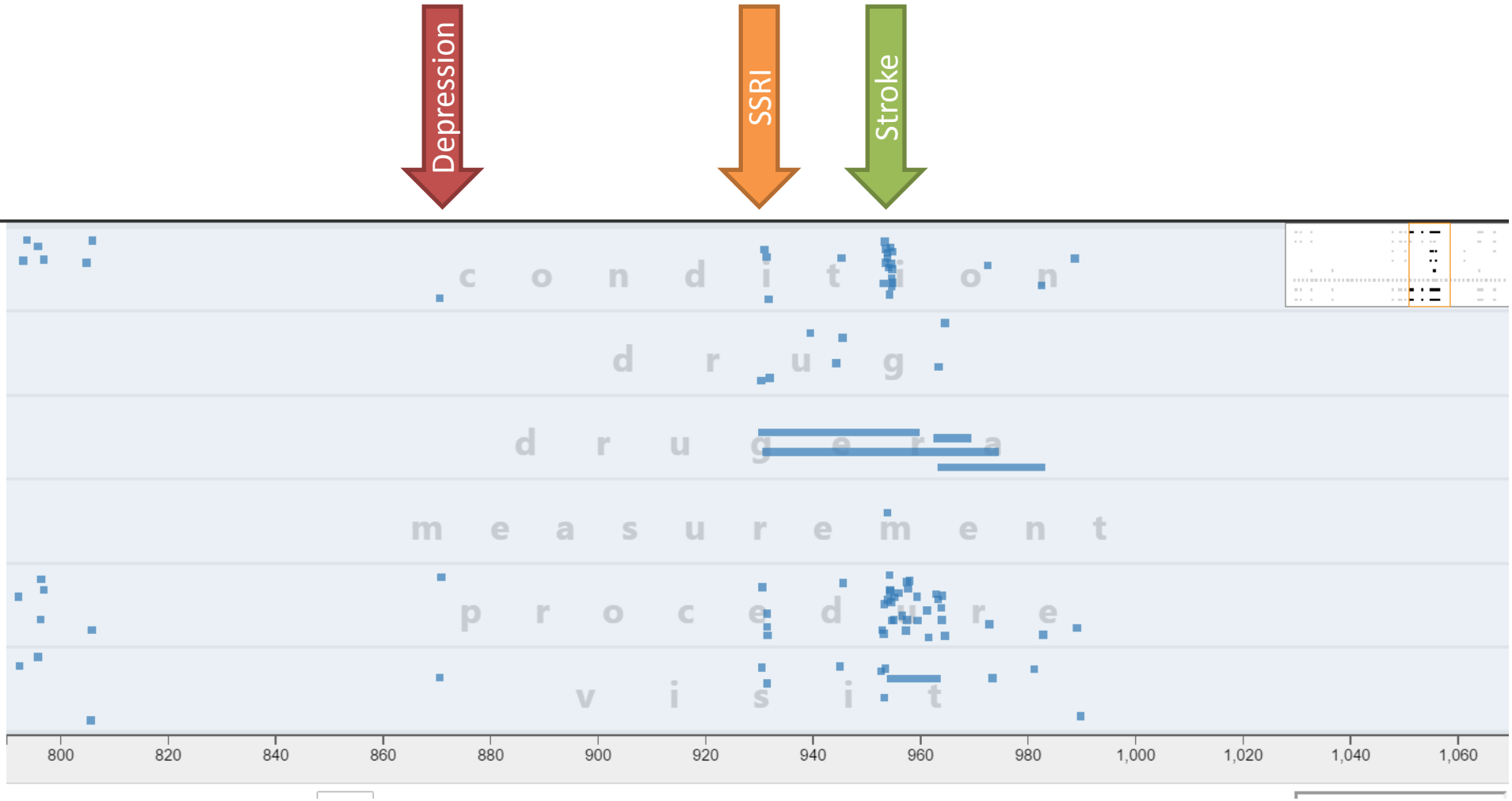
Complementary evidence to inform the patient journey



A caricature of the journey of a patient with major depressive disorder

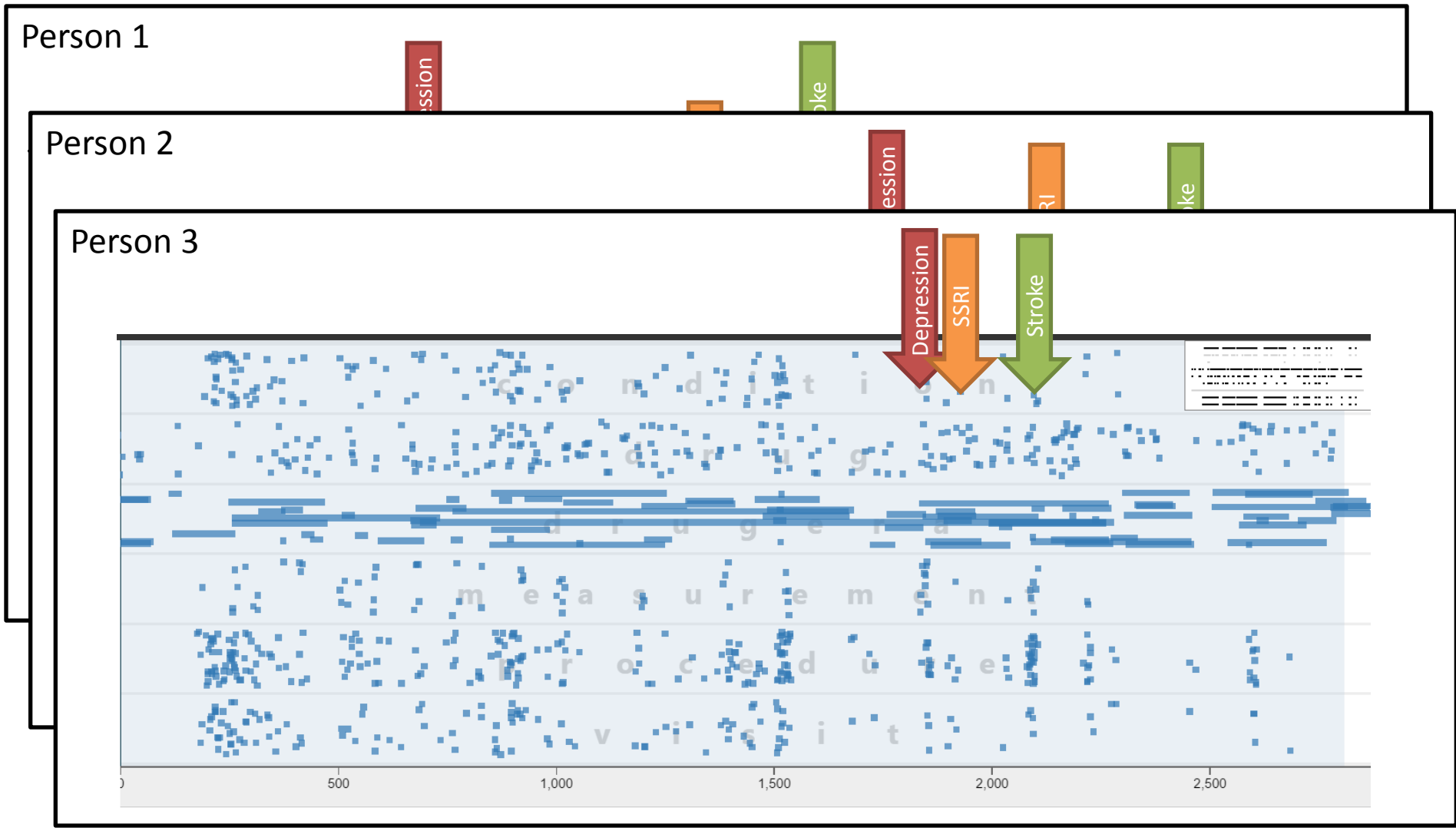


In practice, a patient's journey is a bit more complicated…



*See CHRONOS poster by Sigfried Gold!

…and every patient's journey is quite different



Clinical questions that deserve reliable evidence to inform patients with depression

- **Clinical characterization:** What happened to them?
  - What antidepressant did they choose after their MDD diagnosis?
  - Which patients chose which antidepressant treatments?
  - How many patients had ischemic stroke after antidepressant exposure?

- **Patient-level prediction:** What will happen to me?
  - What is the probability that I will develop major depressive disorder?
  - What is the probability that I will experience an ischemic stroke?

- **Population-level effect estimation:** What are the causal effects?
  - Do SSRIs cause ischemic stroke?
  - Does sertraline cause ischemic stroke more than duloxetine?

How *should* patients with major depressive disorder be treated?

Treating Major Depressive Disorder

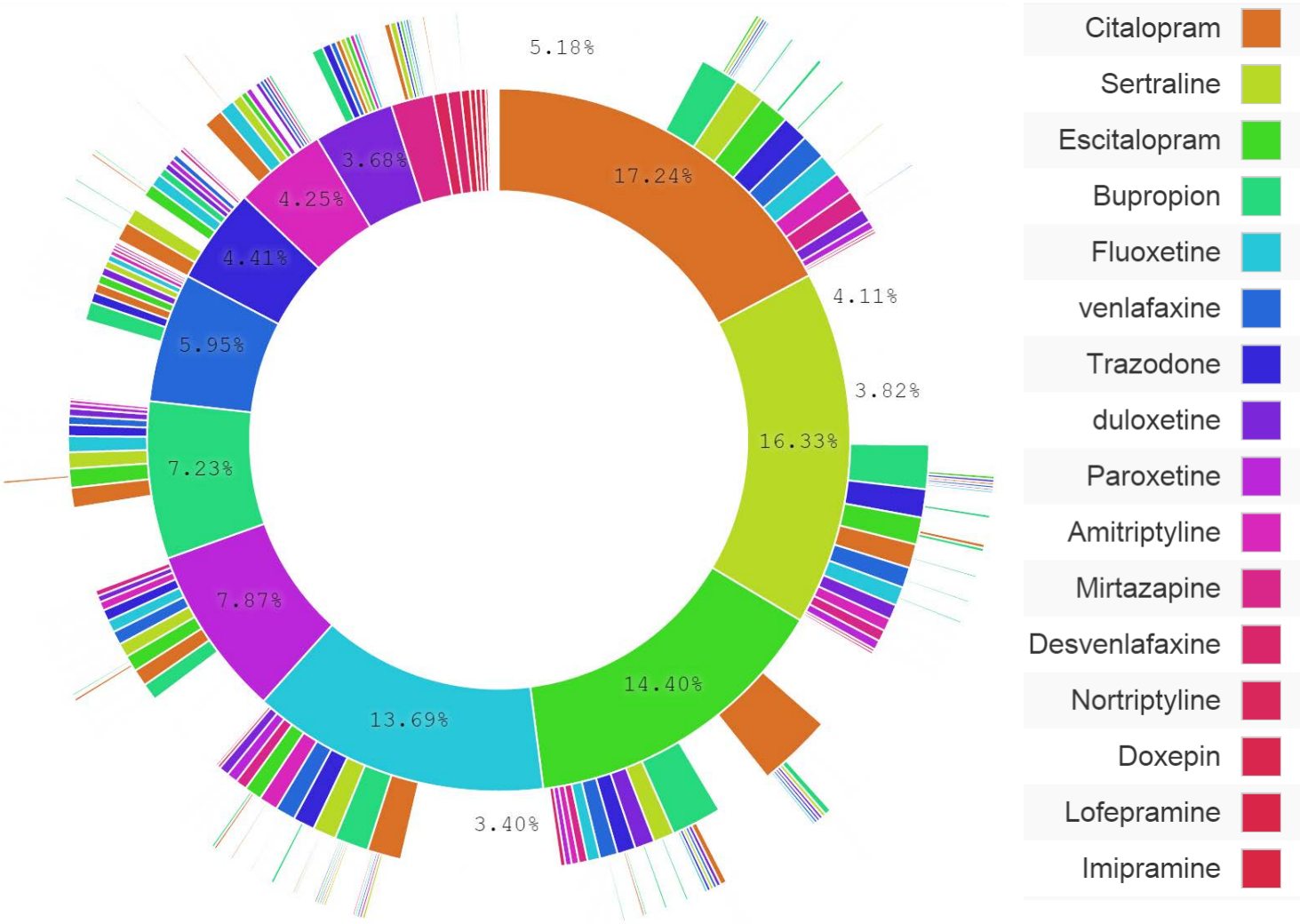
A Quick Reference Guide

Based on *Practice Guideline for the Treatment of Patients With Major Depressive Disorder,* Third Edition, originally published in October 2010. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available.

Pharmacotherapy

- The effectiveness of antidepressant medications is generally comparable between and within classes of medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Therefore, choose a medication largely based on the following:
  - Patient preference
  - Nature of prior response to medication
  - Safety, tolerability, and anticipated side effects
  - Co-occurring psychiatric or general medical conditions
  - Pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions; consult the full guideline or a current drug database)
  - Cost
- For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal.
- In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

How are patients with major depressive disorder *ACTUALLY* treated?



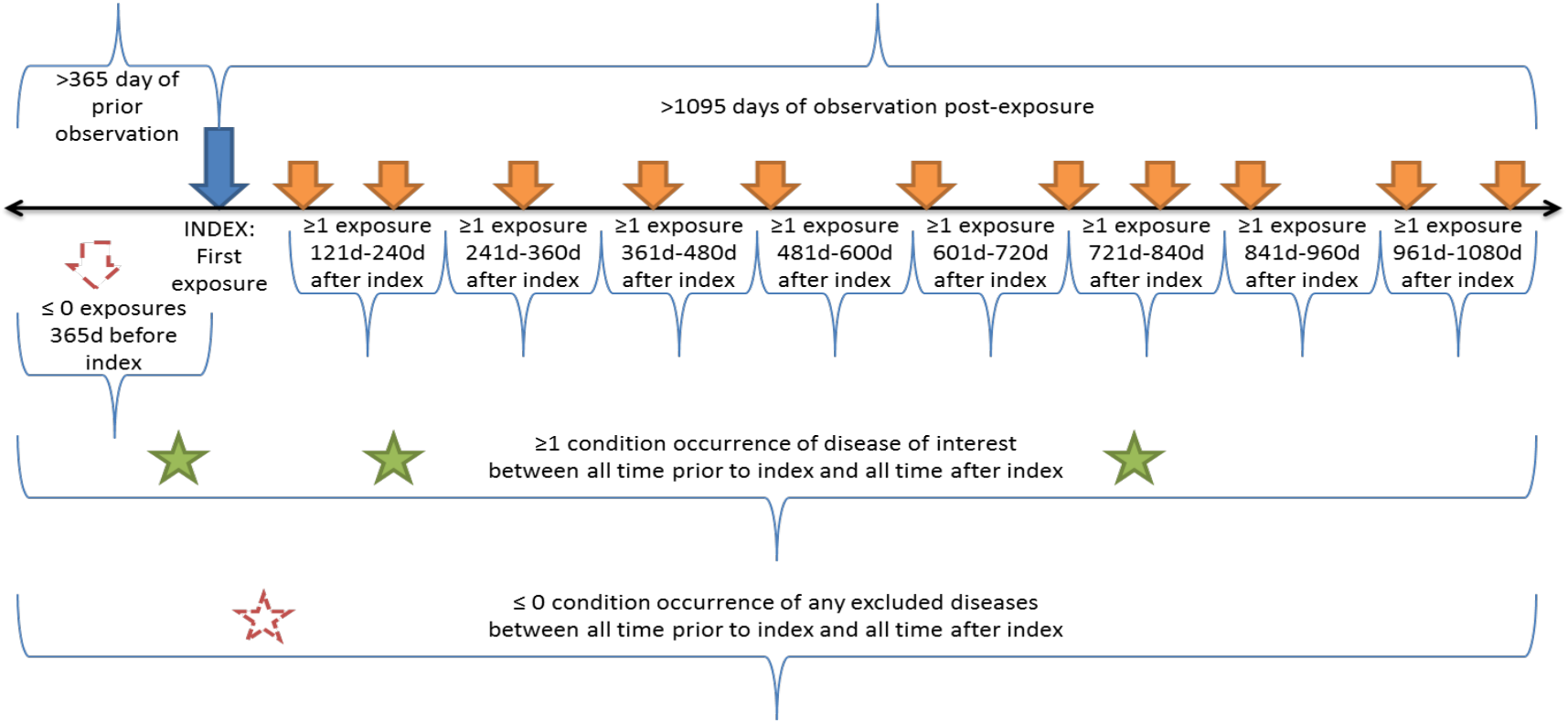
Hripcsak et al, PNAS, 2016

OHDSI participating data partners

Code	Name	Description	Size (M)
AUSOM	Ajou University School of Medicine	South Korea; inpatient hospital EHR	2
CCAE	MarketScan Commercial Claims and Encounters	US private-payer claims	119
CPRD	UK Clinical Practice Research Datalink	UK; EHR from general practice	11
CUMC	Columbia University Medical Center	US; inpatient EHR	4
GE	GE Centricity	US; outpatient EHR	33
INPC	Regenstrief Institute, Indiana Network for Patient Care	US; integrated health exchange	15
JMDC	Japan Medical Data Center	Japan; private-payer claims	3
MDCD	MarketScan Medicaid Multi-State	US; public-payer claims	17
MDCR	MarketScan Medicare Supplemental and Coordination of Benefits	US; private and public-payer claims	9
OPTUM	Optum ClinFormatics	US; private-payer claims	40
STRIDE	Stanford Translational Research Integrated Database Environment	US; inpatient EHR	2
HKU	Hong Kong University	Hong Kong; EHR	1

Hripcsak et al, PNAS, 2016

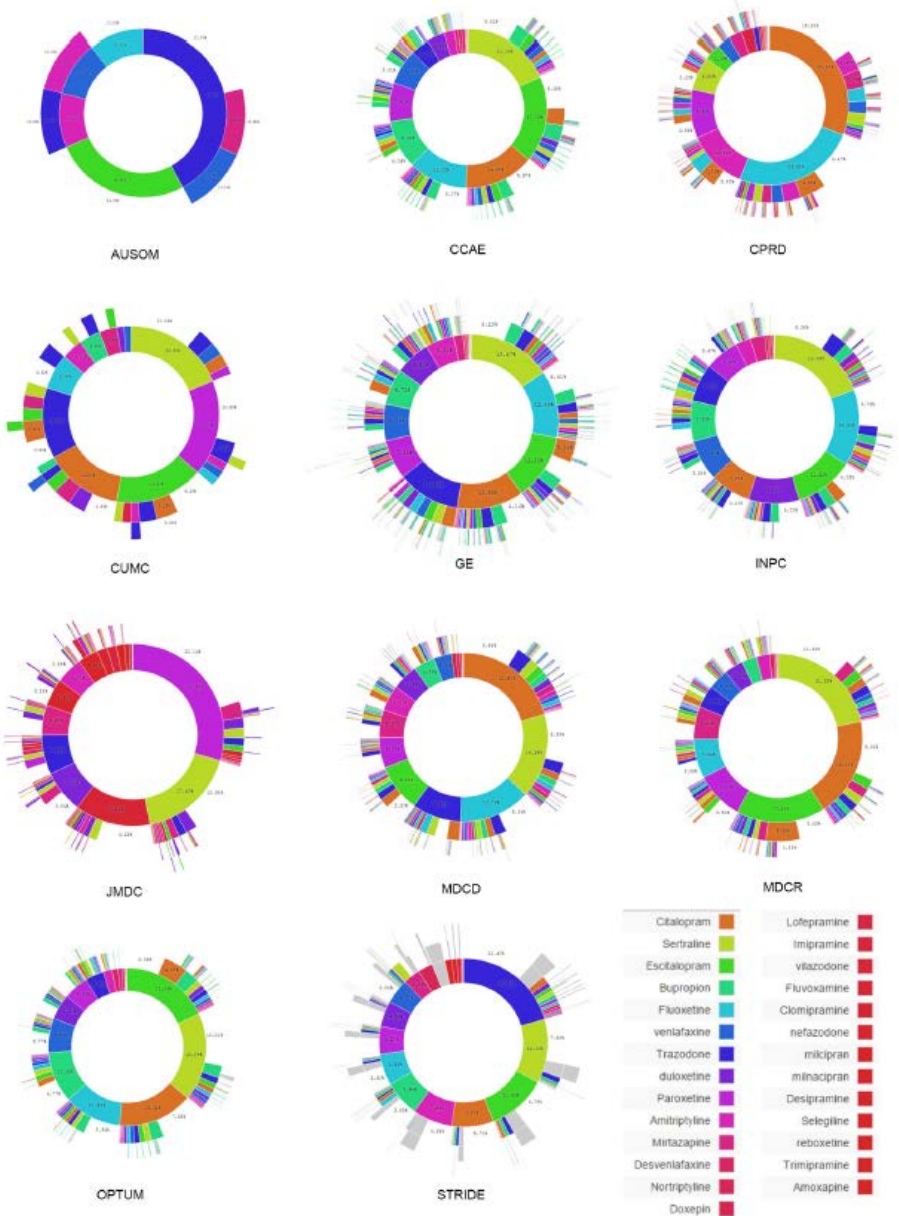
Treatment pathway study design



- >250,000,000 patient records used across OHDSI network
- >=4 years continuous observation
- >=3 years continuous treatment from first treatment
- N=264,841 qualifying patients with depression

Hripcsak et al, PNAS, 2016

How are patients with major depressive disorder ACTUALLY treated?

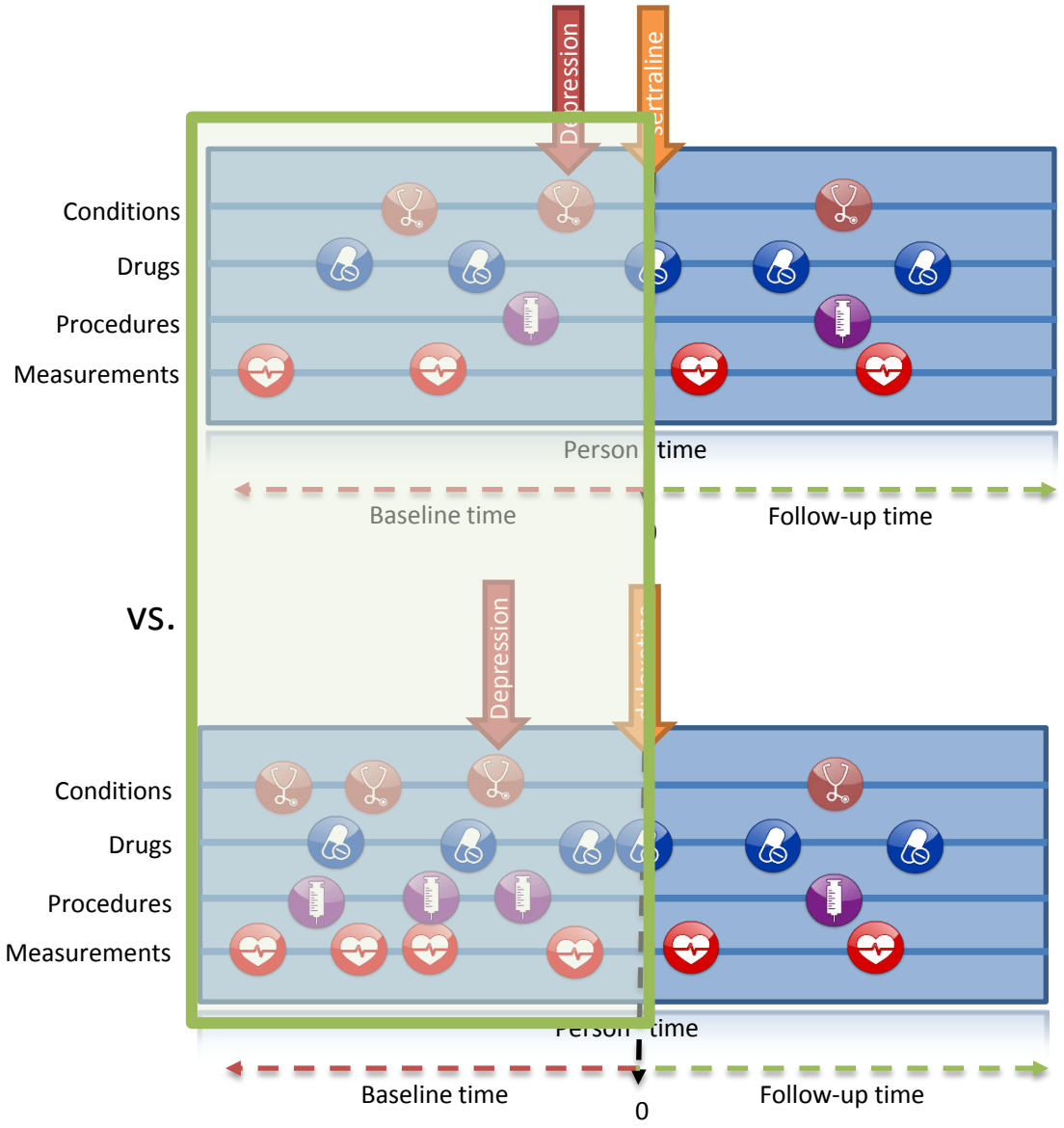


- Substantial variation in treatment practice across data sources, health systems, geographies, and over time
- Consistent heterogeneity in treatment choice as no source showed one preferred first-line treatment
- 11% of depressed patients followed a treatment pathway that was shared with no one else in any of the databases

Hripcsak et al, PNAS, 2016

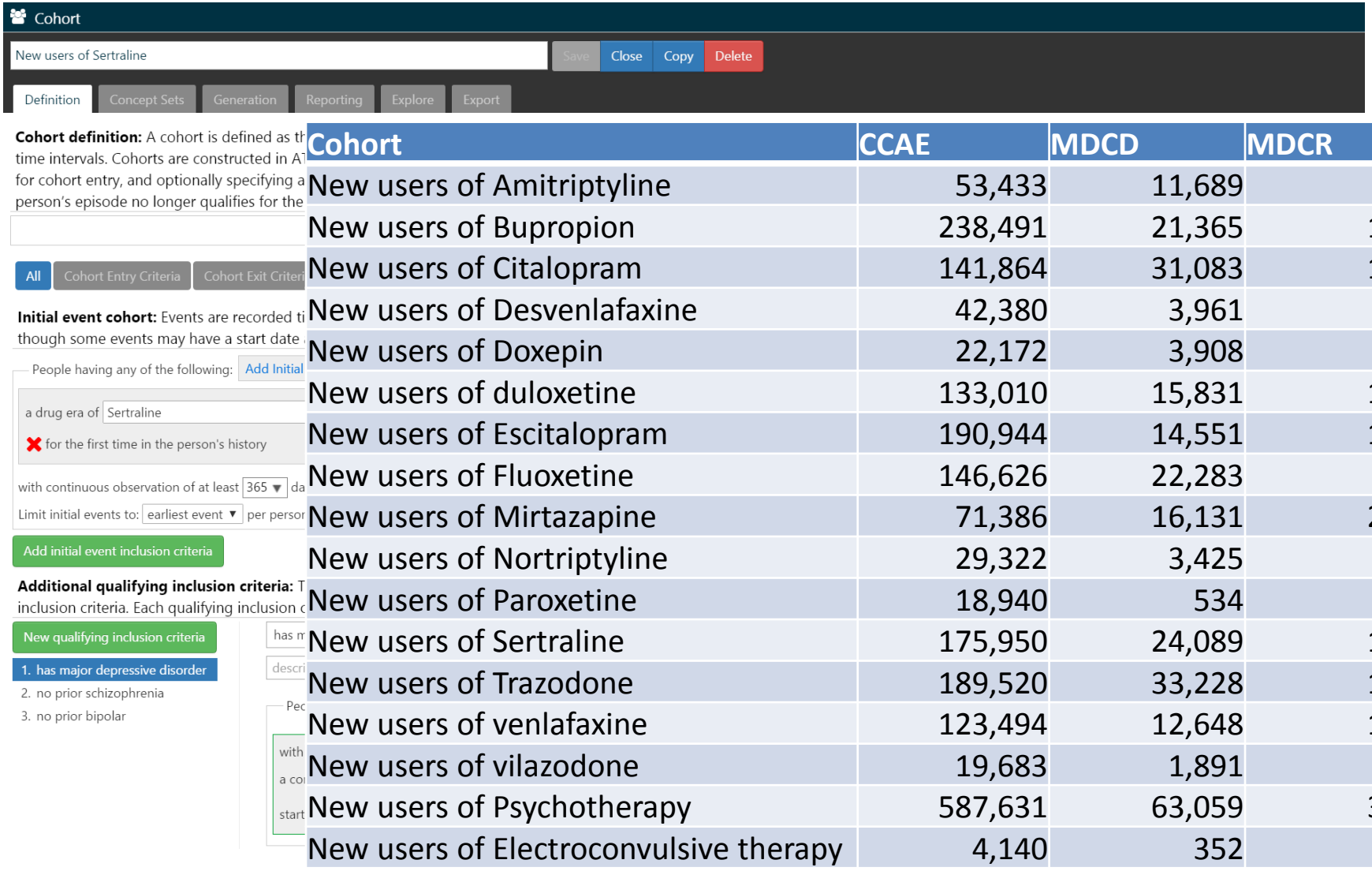
*See TxPath demo by Jon Duke!

Which patients chose which antidepressant treatments?



- Create cohorts for all antidepressant treatments
- Summarize all baseline characteristics
- Systematically explore differences in populations

Standardized cohort construction*



Cohort	CCAE	MDCD	MDCR
New users of Amitriptyline	53,433	11,689	5,242
New users of Bupropion	238,491	21,365	15,549
New users of Citalopram	141,864	31,083	17,533
New users of Desvenlafaxine	42,380	3,961	2,450
New users of Doxepin	22,172	3,908	2,505
New users of duloxetine	133,010	15,831	15,171
New users of Escitalopram	190,944	14,551	19,414
New users of Fluoxetine	146,626	22,283	8,620
New users of Mirtazapine	71,386	16,131	22,618
New users of Nortriptyline	29,322	3,425	3,925
New users of Paroxetine	18,940	534	2,419
New users of Sertraline	175,950	24,089	16,937
New users of Trazodone	189,520	33,228	18,263
New users of venlafaxine	123,494	12,648	11,998
New users of vilazodone	19,683	1,891	1,121
New users of Psychotherapy	587,631	63,059	39,839
New users of Electroconvulsive therapy	4,140	352	1,604

17 depression treatment cohorts

*See ATLAS demo by Chris Knoll!

Large-scale clinical characterization

- Demographics: age, gender, race, ethnicity, index year and month
- Conditions
  - SNOMED verbatim concepts and all ancestral groupings
  - 365 days, 30d, 180d inpatient, all-time prior, overlapping
- D
  - 365 days, 30d, all-time prior, overlapping
- Procedures, Measurements, Observations
- Concept density: # of visits, distinct drugs, conditions
- Risk scores, such as Charlson index

The same types of covariates you'd be using for your Table 1 of your paper and for fitting propensity score and f outcome model…only bigger…

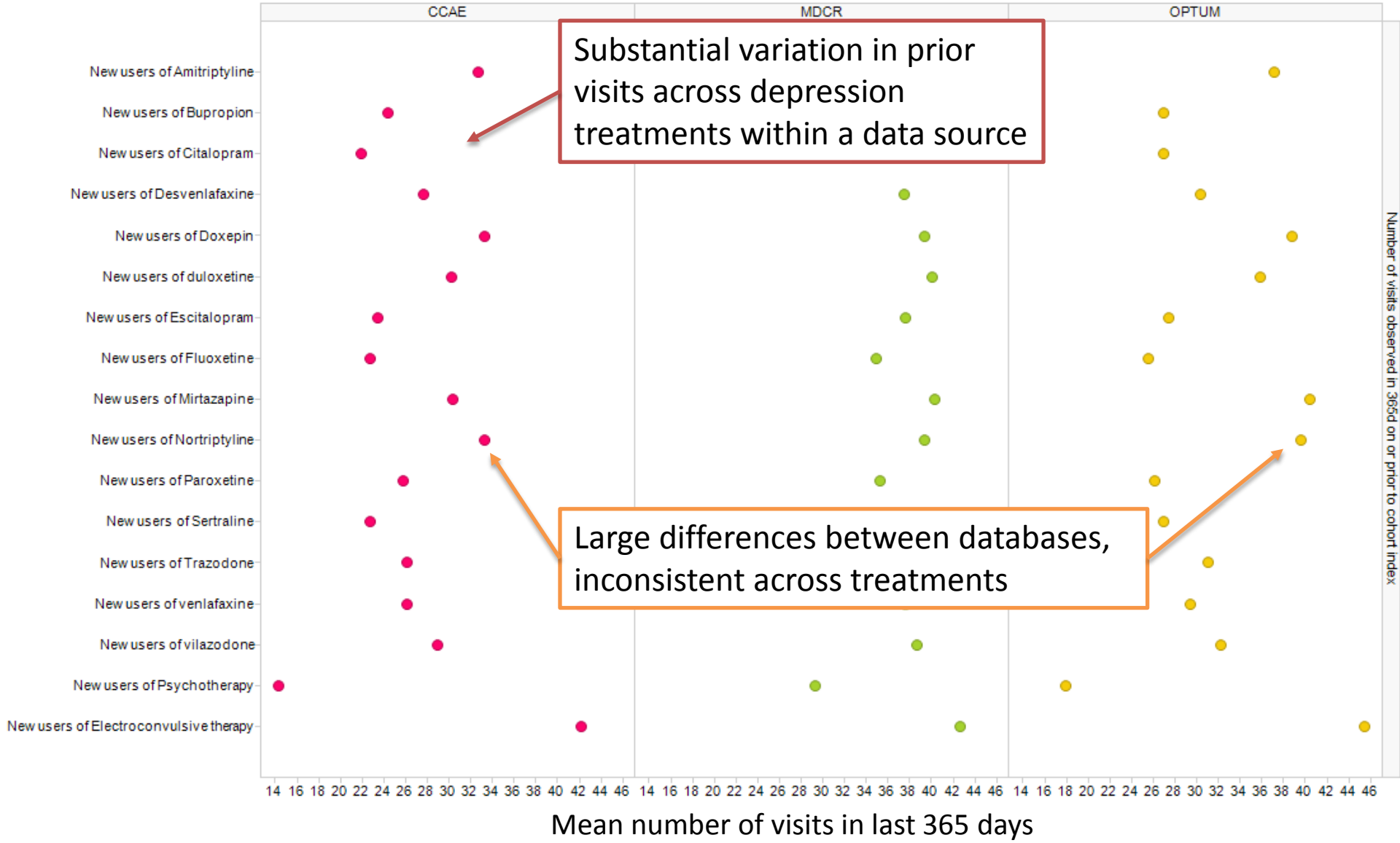
Large-scale baseline characterization for depression

- 17 **treatments**
- 232,542 **baseline characteristics**
- 4 **databases** (so far)

- 17*232,542*4 = 15,812,856 **summary statistics**

- Large-scale analysis is not ‘data mining’!

Baseline health service utilization by depression treatment across databases



How can we find current evidence for outcomes that patients with depression might care about?

APA Treatment Guidelines

TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS *(continued)*

Side Effect	Antidepressant Associated With Effect
Other *(continued)*	
Diaphoresis	TCAs, some SSRIs, SNRIs
Fall risk	TCAs, SSRIs
Gastrointestinal (GI) bleeding	SSRIs
Hepatotoxicity	Nefazodone
Insomnia	SSRIs, SNRIs, bupropion
Nausea, vomiting	SSRIs, SNRIs, bupropion

Published literature

TABLE 40–1 Agents Implicated i

Drug		
Loxapine[17,18]		
Monoamine oxidase inhibitors[1-14,29-31]		
Methylphenidate[1-14]		
Molindone[17,18]		
Nefazodone[1-14,20,29-31]		
Olanzapine[1-14,21]		
Pemoline[1-14]		
Phenytoin[1-14,17,18,21]		
Prochlorperazine[17,18]		
Promazine[17,18]		
Riluzole[15,16]		
Risperidone[17,18]		
Selective serotonin-reuptake inhibitor		
Tacrine[1-16]		
Thioridazine[15-18]		
Tolcapone[1-14,20]		
Topiramate[1-14,21]		
Trazodone[1-14,17,18,29-31]		
Tricyclic antidepressants[15-18,,29-31]		
Valproic acid[1-16,21,23]		
Venlafaxine[1-14,21,29-31]	1%	C
	NK	B
	NK	C

FDA Product labeling, DailyMed

ZOLOFT- sertraline hydrochloride tablet, film coated
ZOLOFT- sertraline hydrochloride solution, concentrate
Roerig

ZOLOFT®
(sertraline hydrochloride)
Tablets and Oral Concentrate

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZOLOFT or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZOLOFT is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

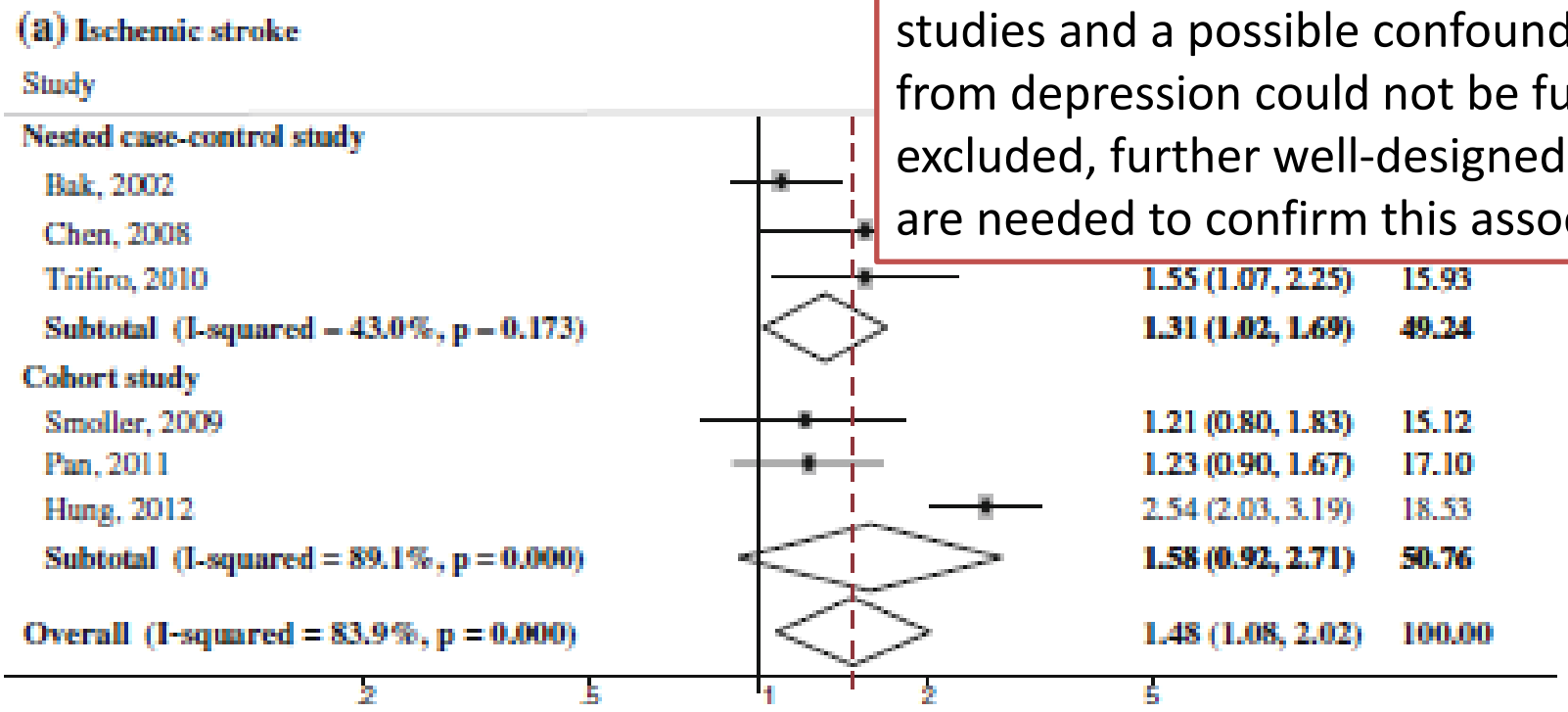
How does observational data currently contribute to the evidence?

J Neurol (2014) 261:686–695
DOI 10.1007/s00415-014-7251-9

ORIGINAL COMMUNICATION

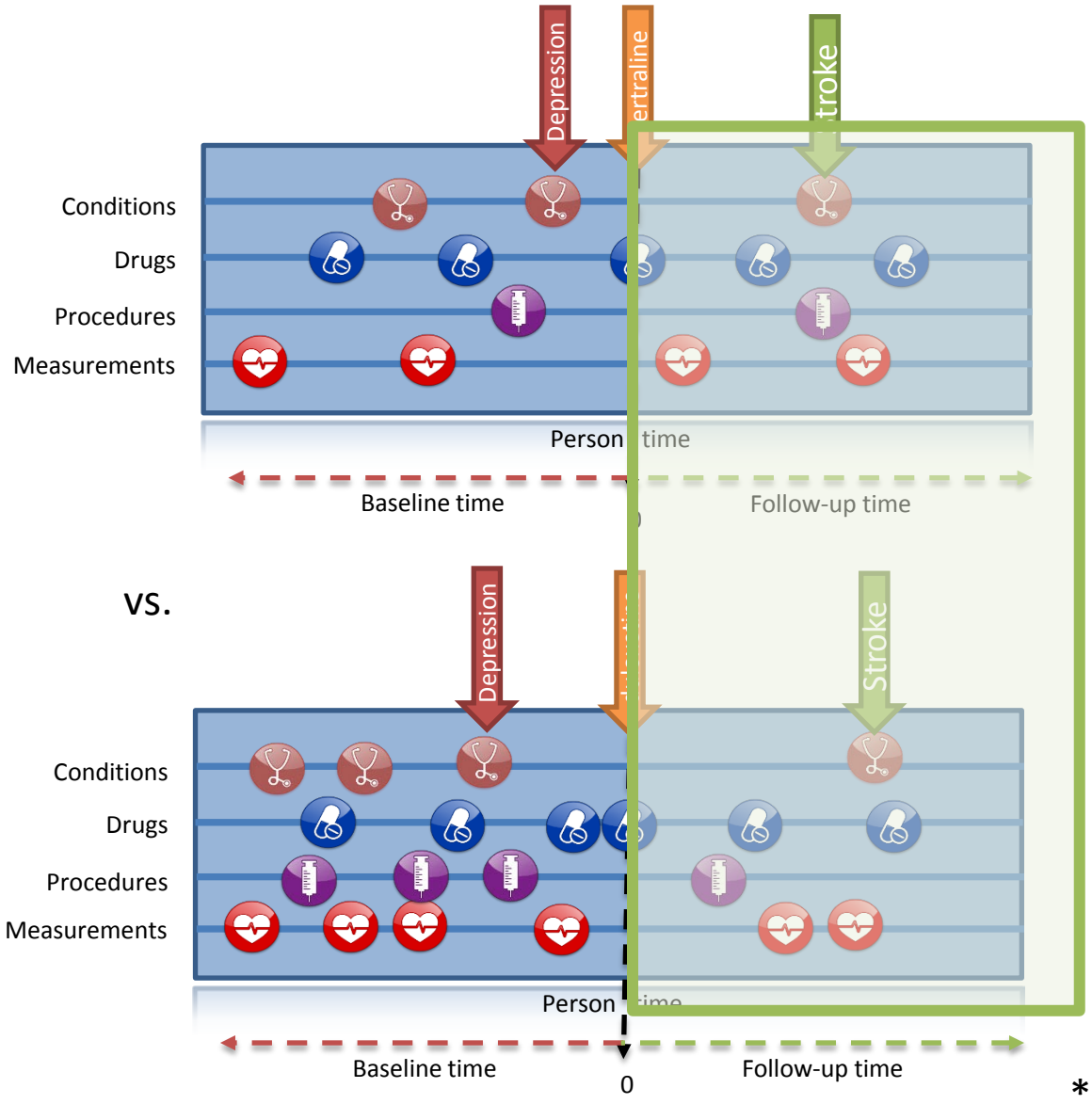
Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis

Doosup Shin · Yun Hwan Oh · Chun-Sick Eom ·



Conclusion by Shin et al.:
"Since there was heterogeneity among studies and a possible confounding effect from depression could not be fully excluded, further well-designed studies are needed to confirm this association."

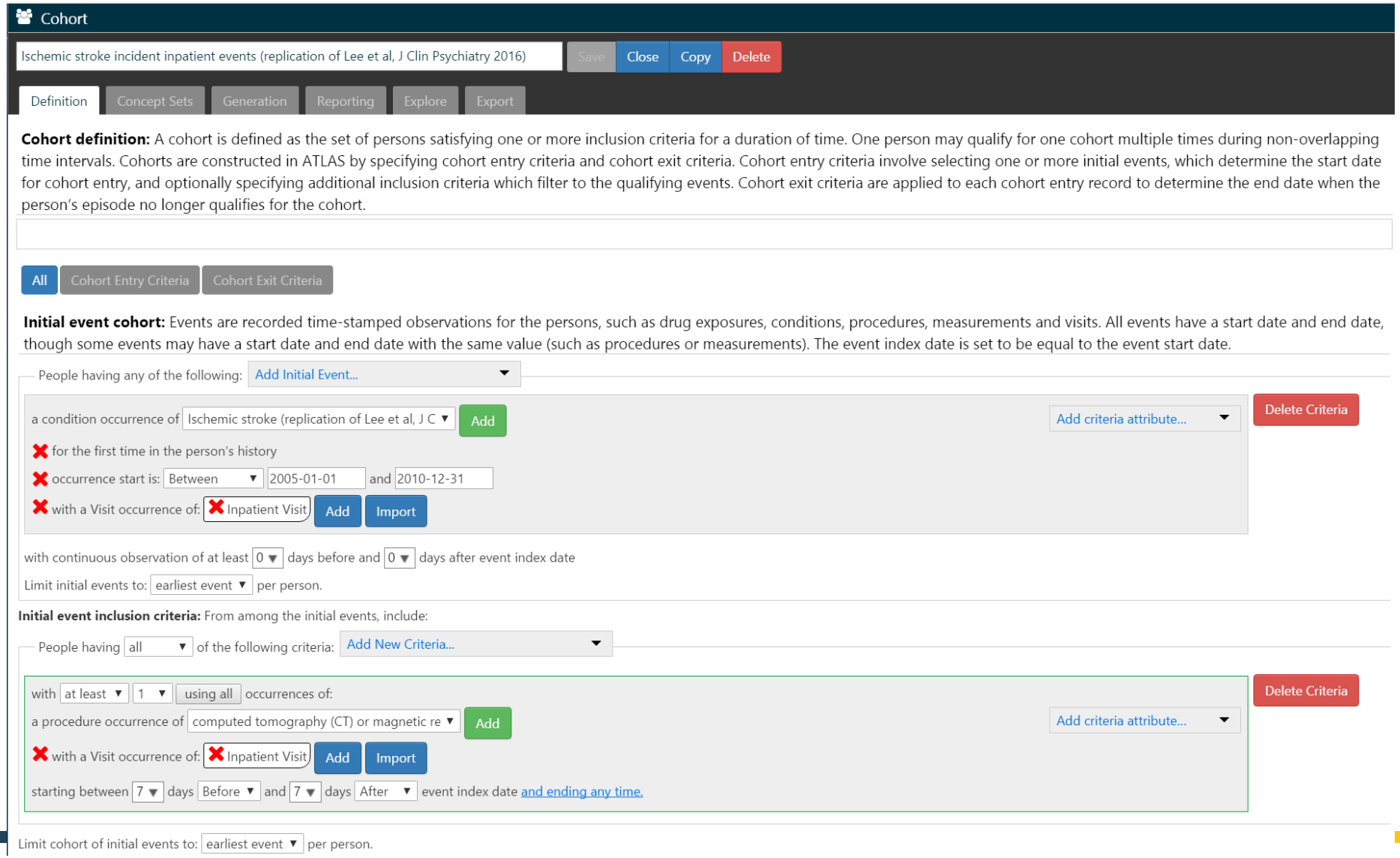
How many patients experienced the outcome after treatment?



- Create cohorts for all outcomes of interest
- Summarize incidence of outcomes within each treatment group
- Systematically explore risk differences in subpopulations of interest

*check out posters by Chandran, Cho

Standardized cohort construction



Standardizing the evaluation of cohort definitions

Focus on Geriatric P

Comparison of Norepinephrin Serotonin Reu Events

Yen-Chieh Lee, MD[a], Lu, MSc[c]; Chia-Hsuir

ABSTRACT

Background: Use of selective serotonin reuptake inhibitors (S has been associated with an inc risk of intracranial hemorrhage

Outcome Ascertainment and Follow-Up

The outcome of interest was defined by the first hospitalization diagnosis for ischemic stroke (*ICD-9-CM* code 433, 434, 436) or

We know these definitions are different, but we don't know tradeoff of sensitivity vs. specificity or the impact in the validity of our analysis results.

suggested that algorithms to evaluate the presence of ischemic stroke and intracranial hemorrhage had high positive predictive values

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD;

Outcome	ICD-9 Codes	Position	Setting
AMI	410 (all)	1st or 2nd	IP only
Ischemic stroke	433.x1, 434.x (except subcode: x0), 436	1st	IP only

Proposed strategies for evaluation

- Create standardized definition and explore large-scale characterization of baseline characteristics
  - See ATLAS demo by Chris Knoll
- Review patient profiles
  - See CHRONOS poster by Sigfried Gold
- Compare alternative definitions in the literature
  - Check out Vocabularies tutorial by Reich/Hripcsak/DeFalco
- Compare with probabilistic-based definition
  - Check out Cohort definition tutorial by Duke/Shah/Knoll

MORE RESEARCH NEEDED….JOIN THE JOURNEY!

Develop standardize cohort definitions for all outcomes of interest

22 outcomes known to be associated with antidepressants:

Acute liver injury	Hypotension
Acute myocardial infarction	Hypothyroidism
Alopecia	Insomnia
Constipation	Nausea
Decreased libido	Open-angle glaucoma
Delirium	Seizure
Diarrhea	Stroke
Fracture	Suicide and suicidal ideation
Gastrointestinal hemhorrage	Tinnitus
Hyperprolactinemia	Ventricular arrhythmia and sudden cardiac death
Hyponatremia	Vertigo

Large-scale incidence characterization for depression

- 17 **treatments**
- 22 **outcomes**
- 6 **stratification factors**
- 4 **databases** (so far)

- 17*22*6*4 = 8,976 **incidence rates**

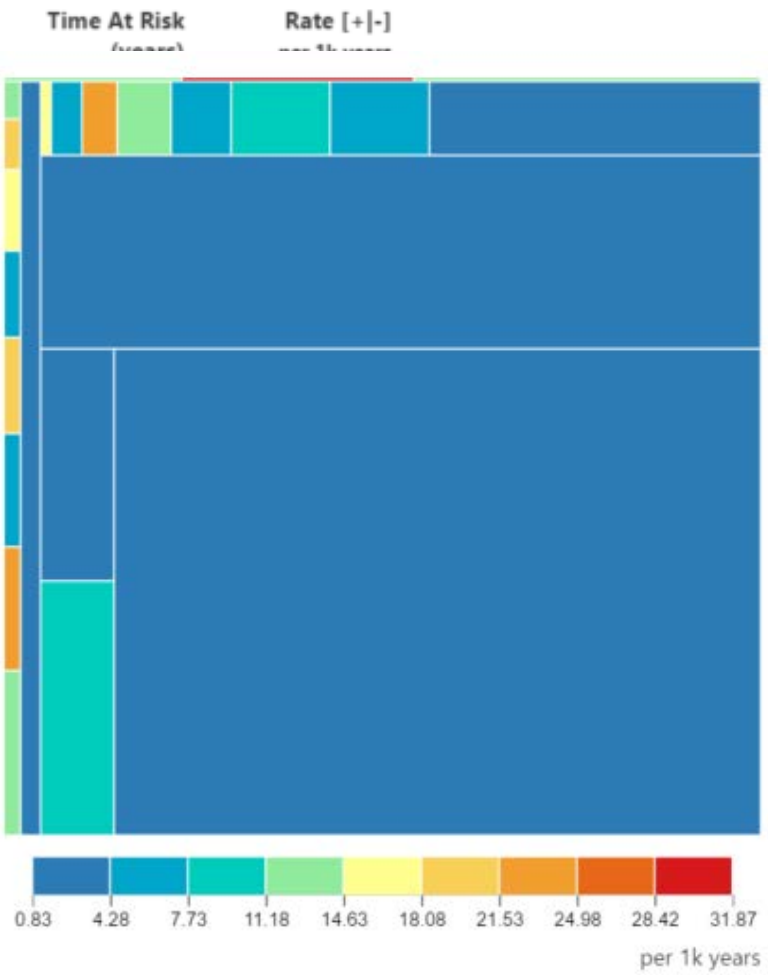
- Large-scale analysis is not ‘data mining’!

What is the incidence of ischemic stroke in patients with SSRI?

	Persons	Cases	Proportion [+|-] per 1k persons	Time At Risk (years)	Rate [+|-] per 1k years
Summary Statistics:	706,797	985	1.39	375,519	2.62

	Stratify Rule	N	Cases	Proportion [+|-] per 1k persons
1.	Gender = Male	222,938	373	1.67
2.	Age <65	616,632	386	0.63
3.	Age 65-74	42,637	180	4.22
4.	Age 75+	47,528	419	8.82
5.	has Type 2 diabetes mellitus	73,876	310	4.20
6.	has heart failure	20,550	188	9.15

Let's see ATLAS in action!



Journey toward reliable evidence

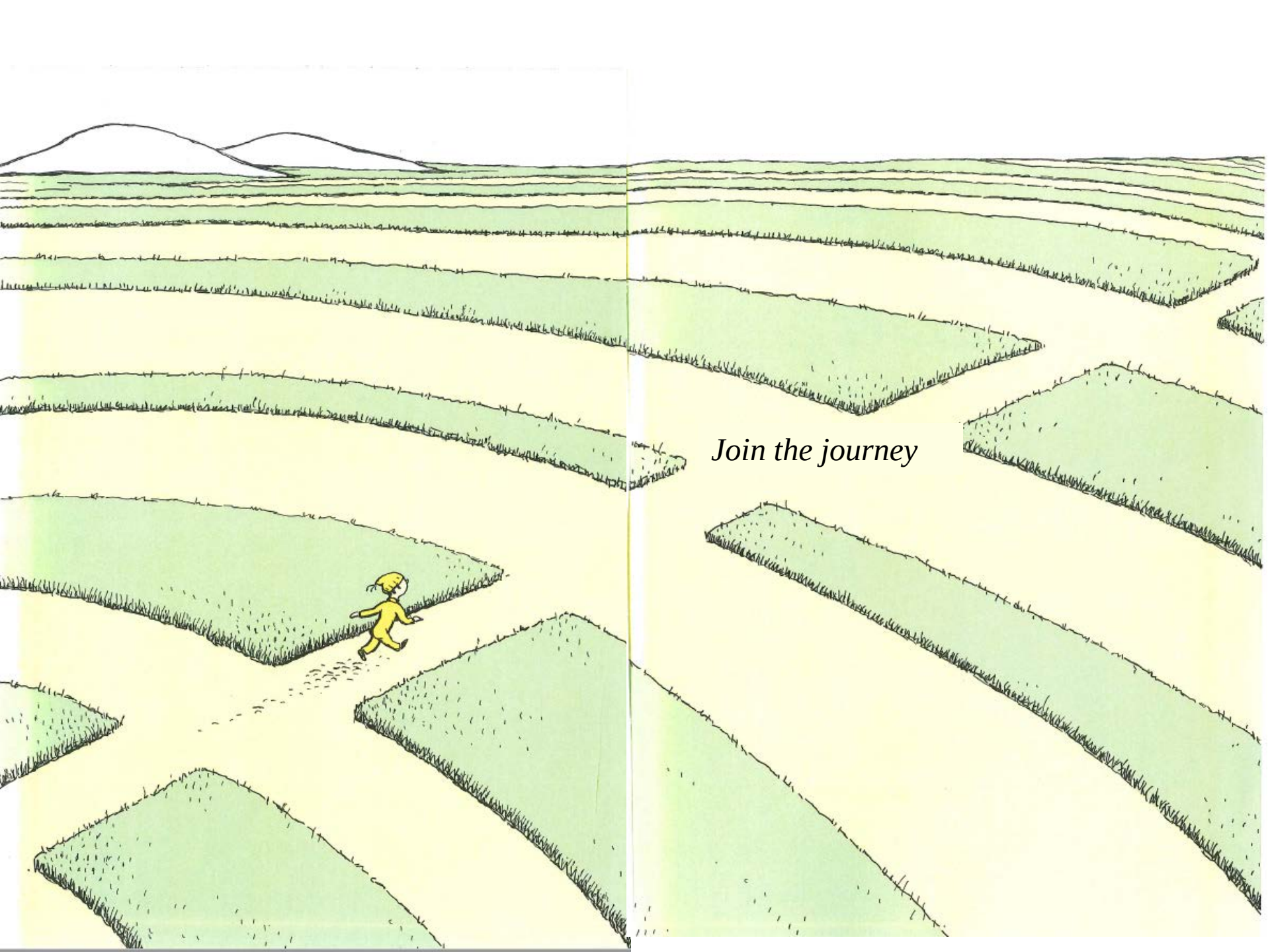
- How to produce evidence from the data?
- How do we know the evidence is reliable?
- How do we share evidence to inform decision making?

Clinical characterization

- Follow a standardized process
- Open source code
- Use validated software
- Analyses should be scalable to many exposures, many outcomes
- Replicate across databases

- Apply tools to explore patient journeys and population characteristics to assess validity of cohort definitions
- Compare across populations to study heterogeneity

- Characterization requires an exploratory framework, not just static reporting
- Characterization results should be a required supplement to any patient-level prediction and population-level estimation


Join the journey