Observational Health Data Sciences and Informatics (OHDSI)

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Observational Health Data Sciences and Informatics
(OHDSI, as “Odyssey”)

Mission: To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care

A multi-stakeholder, interdisciplinary, international collaborative with a coordinating center at Columbia University

OHDSI's global research community

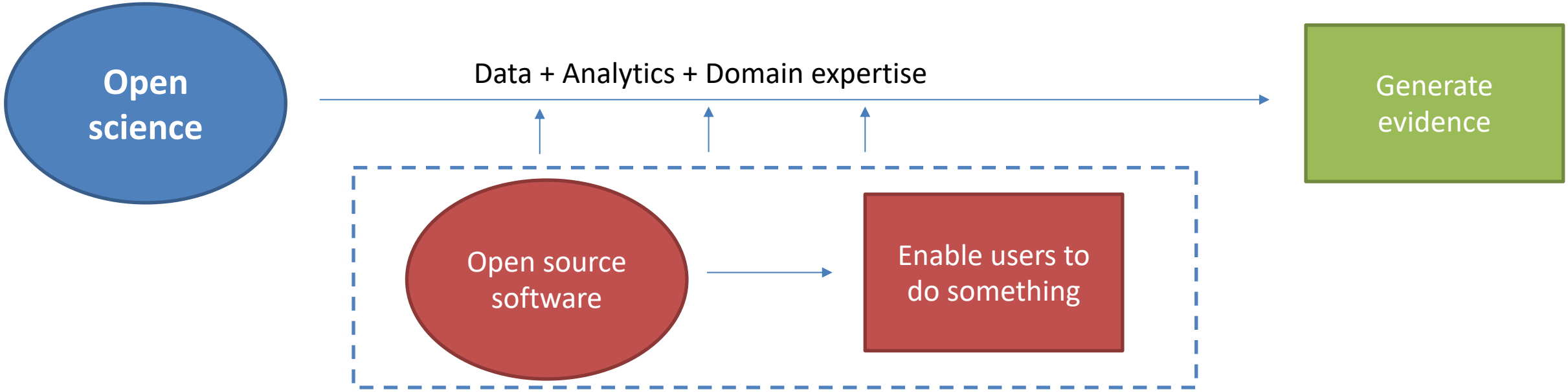
- >200 collaborators from 25 different countries
- Experts in informatics, statistics, epidemiology, clinical sciences
- Active participation from academia, government, industry, providers
- Currently records on about 500 million unique patients in >100 databases

http://ohdsi.org/who-we-are/collaborators/

Evidence OHDSI seeks to generate from observational data

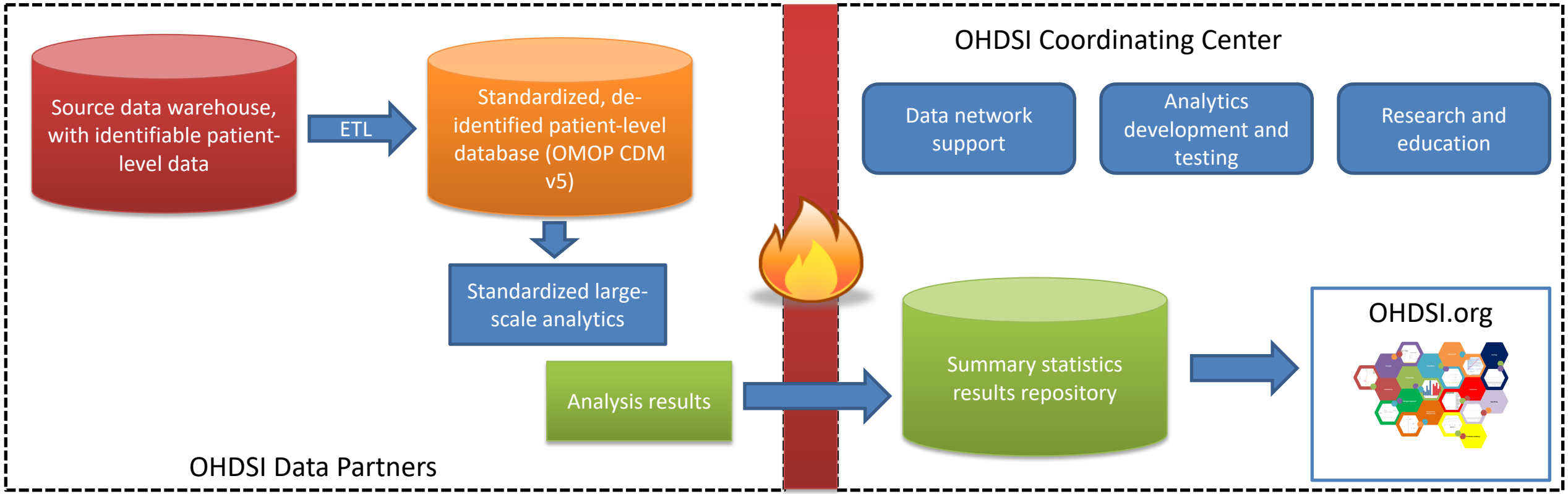
- **Clinical characterization - tally**
  - Natural history: Who has diabetes, and who takes metformin?
  - Quality improvement: What proportion of patients with diabetes experience complications?
- **Population-level estimation - cause**
  - Safety surveillance: Does metformin cause lactic acidosis?
  - Comparative effectiveness: Does metformin cause lactic acidosis more than glyburide?
- **Patient-level prediction - predict**
  - Precision medicine: Given everything you know about me, if I take metformin, what is the chance I will get lactic acidosis?
  - Disease interception: Given everything you know about me, what is the chance I will develop diabetes?

Open Science

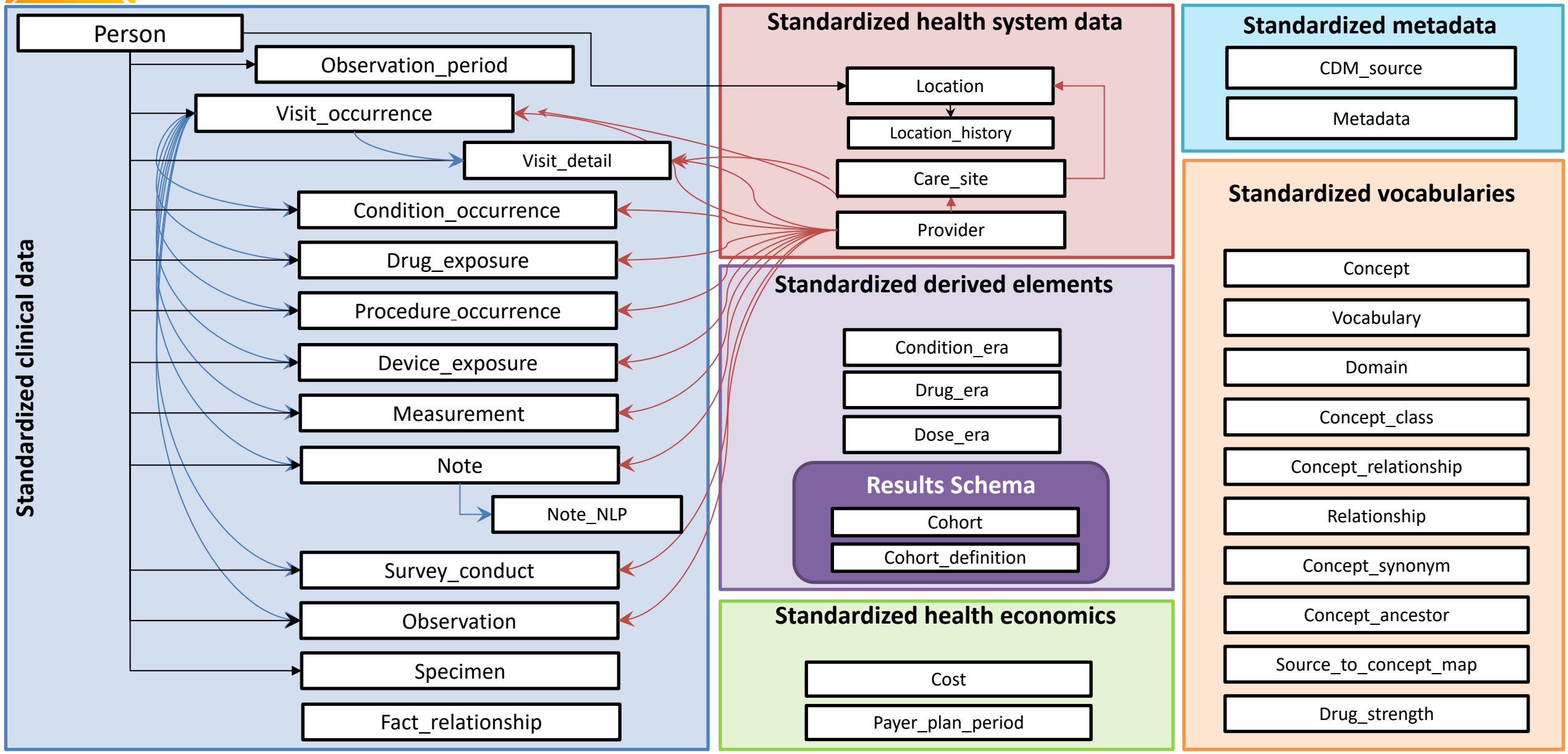


Standardized, transparent workflows

How OHDSI Works

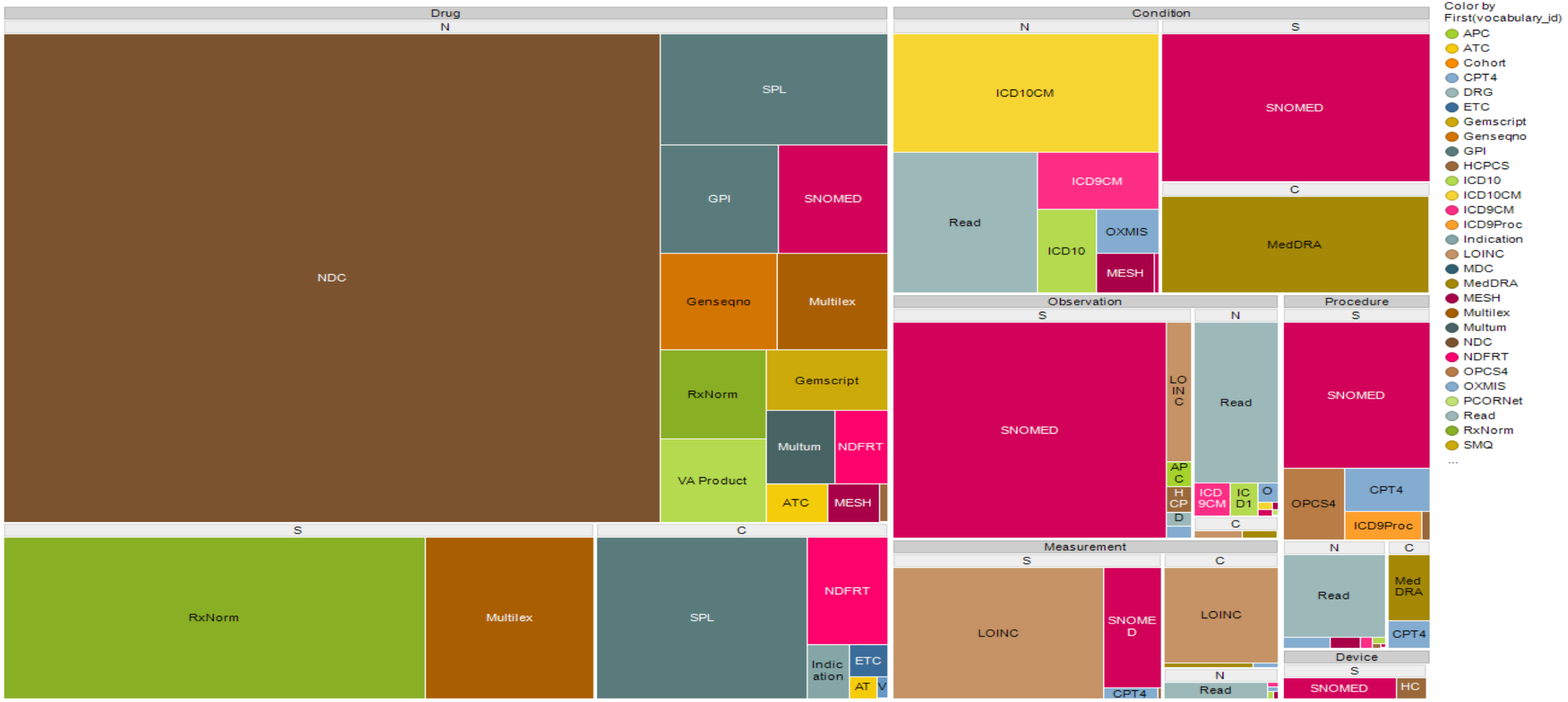


Deep information model
OMOP CDM Version 6



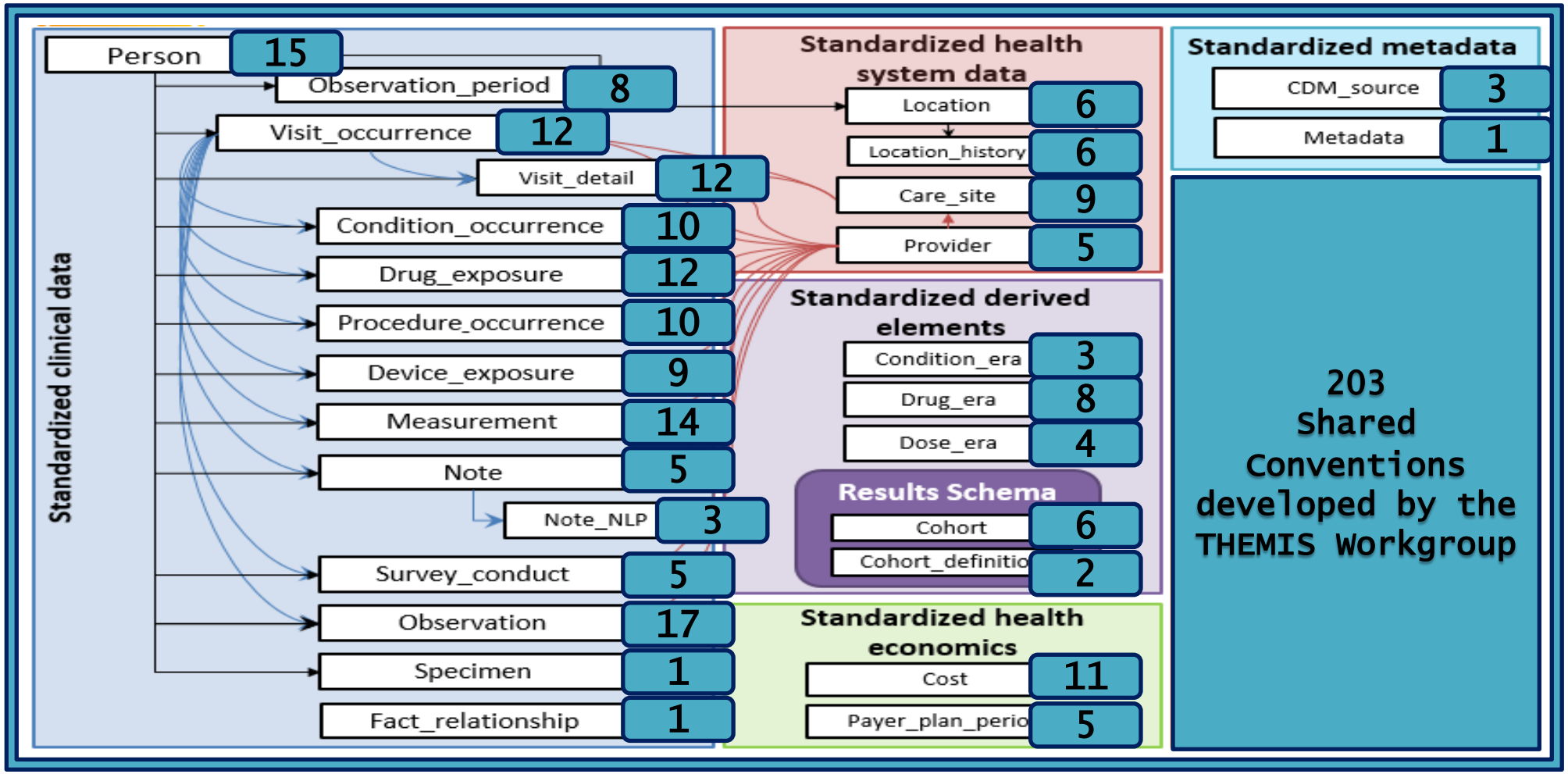
Extensive vocabularies

Breakdown of OHDSI concepts by domain, standard class, and vocabulary

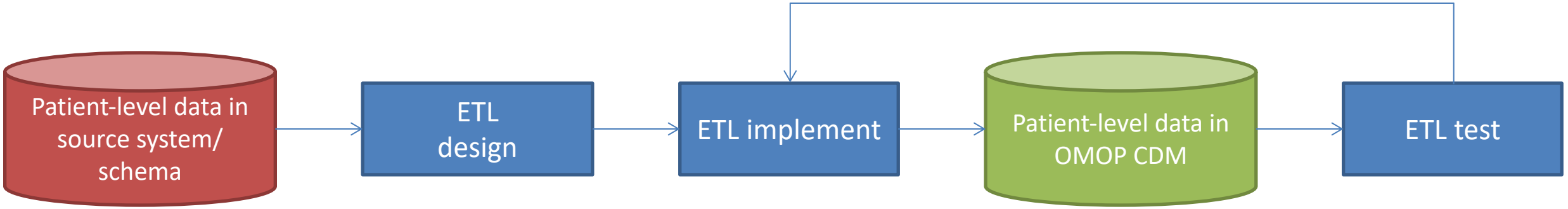


Standardized conventions

OHDSI adjusting to experience



Preparing your data for analysis



OHDSI tools built to help

WhiteRabbit: profile your source data

RabbitInAHat: map your source structure to CDM tables and fields

ATHENA: standardized vocabularies for all CDM domains

Usagi: map your source codes to CDM vocabulary

CDM: DDL, index, constraints for Oracle, SQL Server, PostgresQL; Vocabulary tables with loading scripts

ACHILLES: profile your CDM data; review data quality assessment; explore population-level summaries

OHDSI Forums: Public discussions for OMOP CDM Implementers/developers

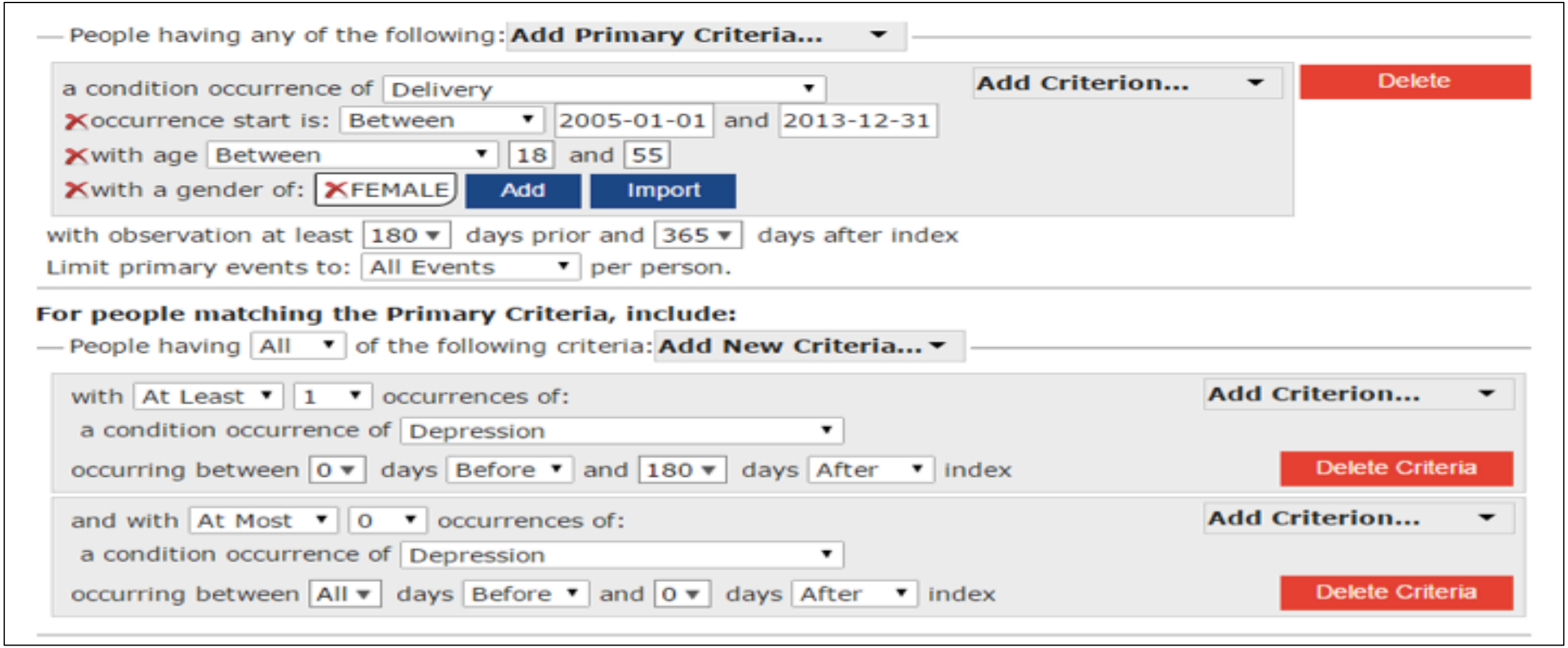
ACHILLES Heel Data Curation

Data Quality Messages

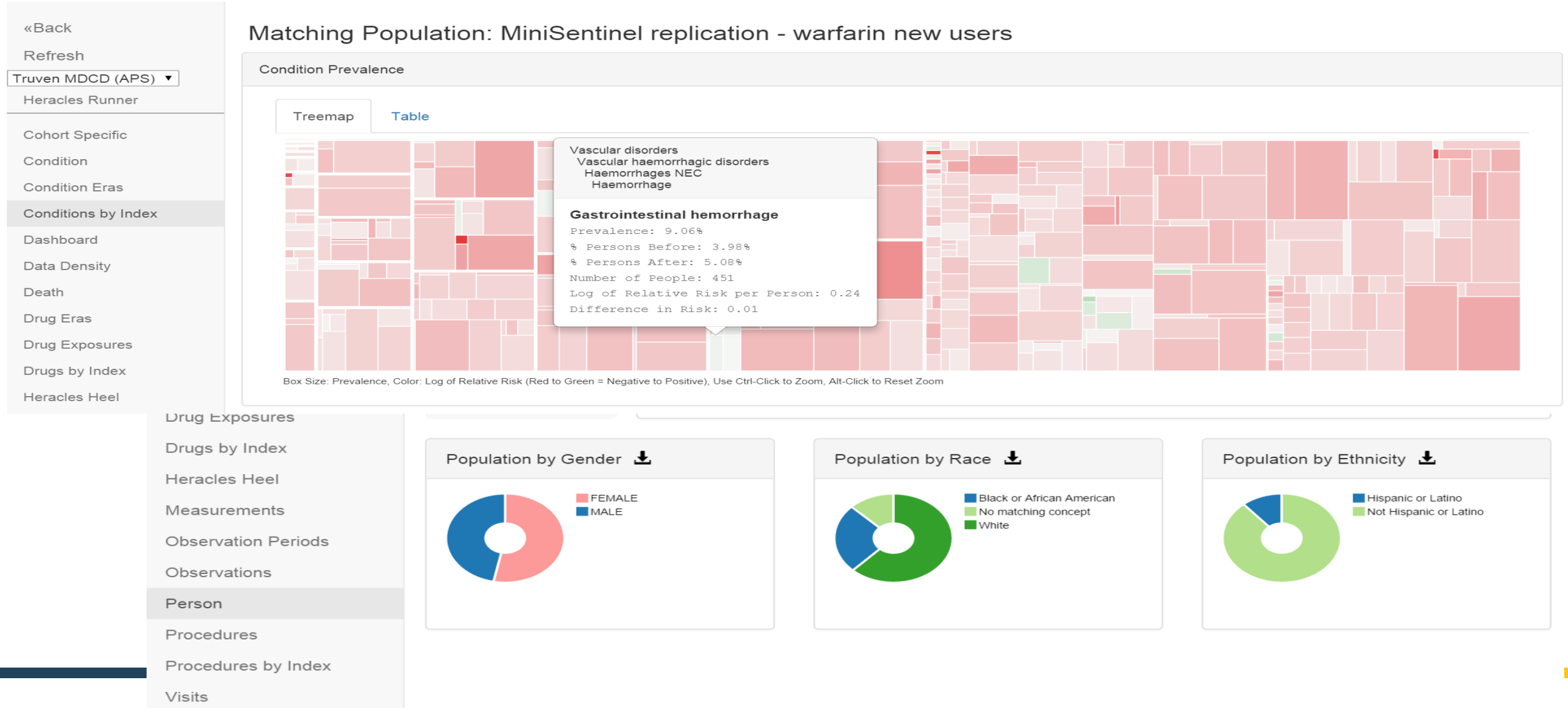
Search: Show / hide columns

Message Type	Message
ERROR	101-Number of persons by age, with age at first observation period; should not have age < 0, (n=848)
ERROR	103 - Distribution of age at first observation period (count = 1); min value should not be negative
ERROR	114-Number of persons with observation period before year-of-birth; count (n=851) should not be > 0
ERROR	206 - Distribution of age by visit_concept_id (count = 7); min value should not be negative
ERROR	301-Number of providers by specialty concept_id; 224 concepts in data are not in correct vocabulary (Specialty)
ERROR	400-Number of persons with at least one condition occurrence, by condition_concept_id; 115 concepts in data are not in correct vocabulary (SNOMED)
ERROR	406 - Distribution of age by condition_concept_id (count = 753); min value should not be negative

ATLAS to build, visualize, and analyze cohorts



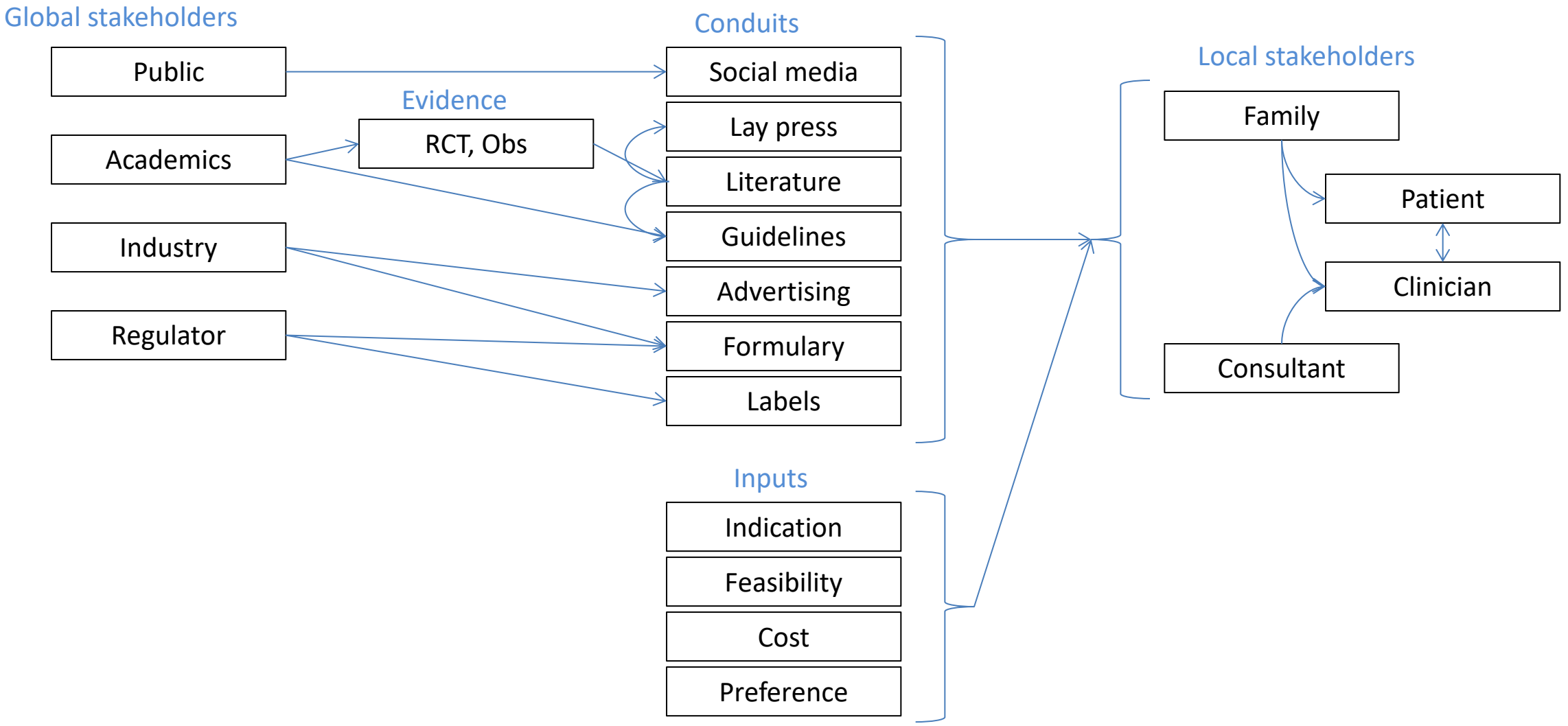
Characterize the cohorts of interest



OHDSI in Action

- Characterization

Treatment Pathways



OHDSI in action:
Chronic disease treatment pathways

- Conceived at AMIA 15Nov2014
- Protocol written, code written and tested at 2 sites 30Nov2014
- Analysis submitted to OHDSI network 2Dec2014
- Results submitted for 7 databases 5Dec2014

OHDSI participating data partners

Abbre-viation	Name	Description	Population, millions
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

Proceedings of the National Academy of Sciences, 2016

PNAS

COLLOQUIUM PAPER

Characterizing treatment pathways at scale using the OHDSI network

George Hripcsak[a,b,c,1], Patrick B. Ryan[c,d], Jon D. Duke[c,e], Nigam H. Shah[c,f], Rae Woong Park[c,g], Vojtech Huser[c,h], Marc A. Suchard[c,i,j,k], Martijn J. Schuemie[c,d], Frank J. DeFalco[c,d], Adler Perotte[a,c], Juan M. Banda[c,f], Christian G. Reich[c,l], Lisa M. Schilling[c,m], Michael E. Matheny[c,n,o], Daniella Meeker[c,p,q], Nicole Pratt[c,r], and David Madigan[c,s]

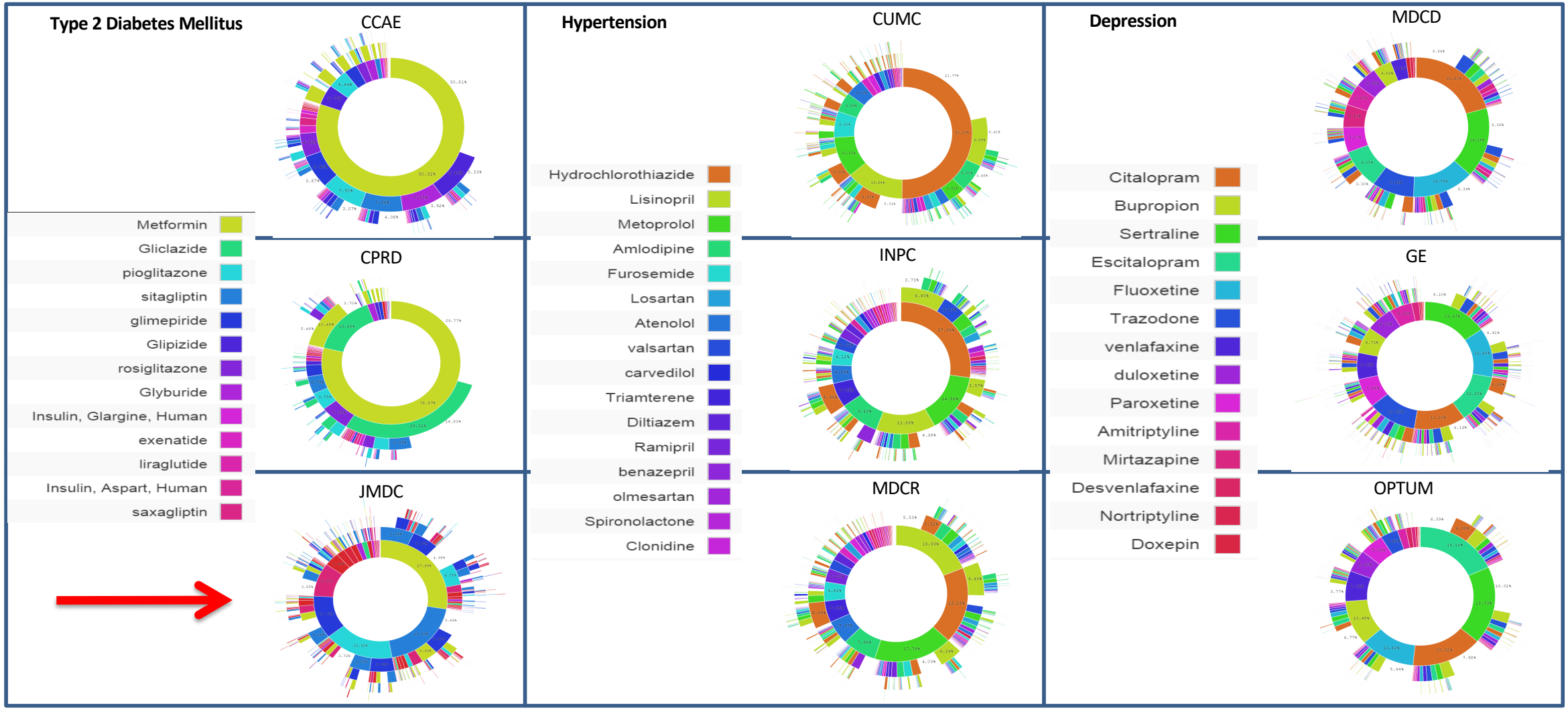
[a]Department of Biomedical Informatics, Columbia University Medical Center, New York, NY 10032; [b]Medical Informatics Services, NewYork-Presbyterian Hospital, New York, NY 10032; [c]Observational Health Data Sciences and Informatics, New York, NY 10032; [d]Epidemiology Analytics, Janssen Research and Development, Titusville, NJ 08560; [e]Center for Biomedical Informatics, Regenstrief Institute, Indianapolis, IN 46205; [f]Center for Biomedical Informatics Research, Stanford University, CA 94305; [g]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, South Korea, 443-380; [h]Lister Hill National Center for Biomedical Communications (National Library of Medicine), National Institutes of Health, Bethesda, MD 20894; [i]Department of Biomathematics, University of California, Los Angeles, CA 90095; [j]Department of Biostatistics, University of California, Los Angeles, CA 90095; [k]Department of Human Genetics, University of California, Los Angeles, CA 90095; [l]Real World Evidence Solutions, IMS Health, Burlington, MA 01809; [m]Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045; [n]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN 37212; [o]Geriatric Research, Education and Clinical Center, VA Tennessee Valley Healthcare System, Nashville, TN 37212; [p]Department of Preventive Medicine, University of Southern California, Los Angeles, CA 90089; [q]Department of Pediatrics, University of Southern California, Los Angeles, CA 90089; [r]Division of Health Sciences, University of South Australia, Adelaide, SA, Australia 5001; and [s]Department of Statistics, Columbia University, New York, NY 10027

Edited by Richard M. Shiffrin, Indiana University, Bloomington, IN, and approved April 5, 2016 (received for review June 14, 2015)

Observational research promises to complement experimental research by providing large, diverse populations that would be infeasible for an experiment. Observational research can test its own clinical hypotheses, and observational studies also can contribute to the design of experiments and inform the generalizability of experimental research. Understanding the diversity of populations

Without sufficiently broad databases available in the first stage, randomized trials are designed without explicit knowledge of actual disease status and treatment practice. Literature reviews are restricted to the population choices of previous investigations, and pilot studies usually are limited in scope. By exploiting the ClinicalTrials.gov national trial registry (9) and electronic health

Population-level heterogeneity across systems, and patient-level heterogeneity within systems



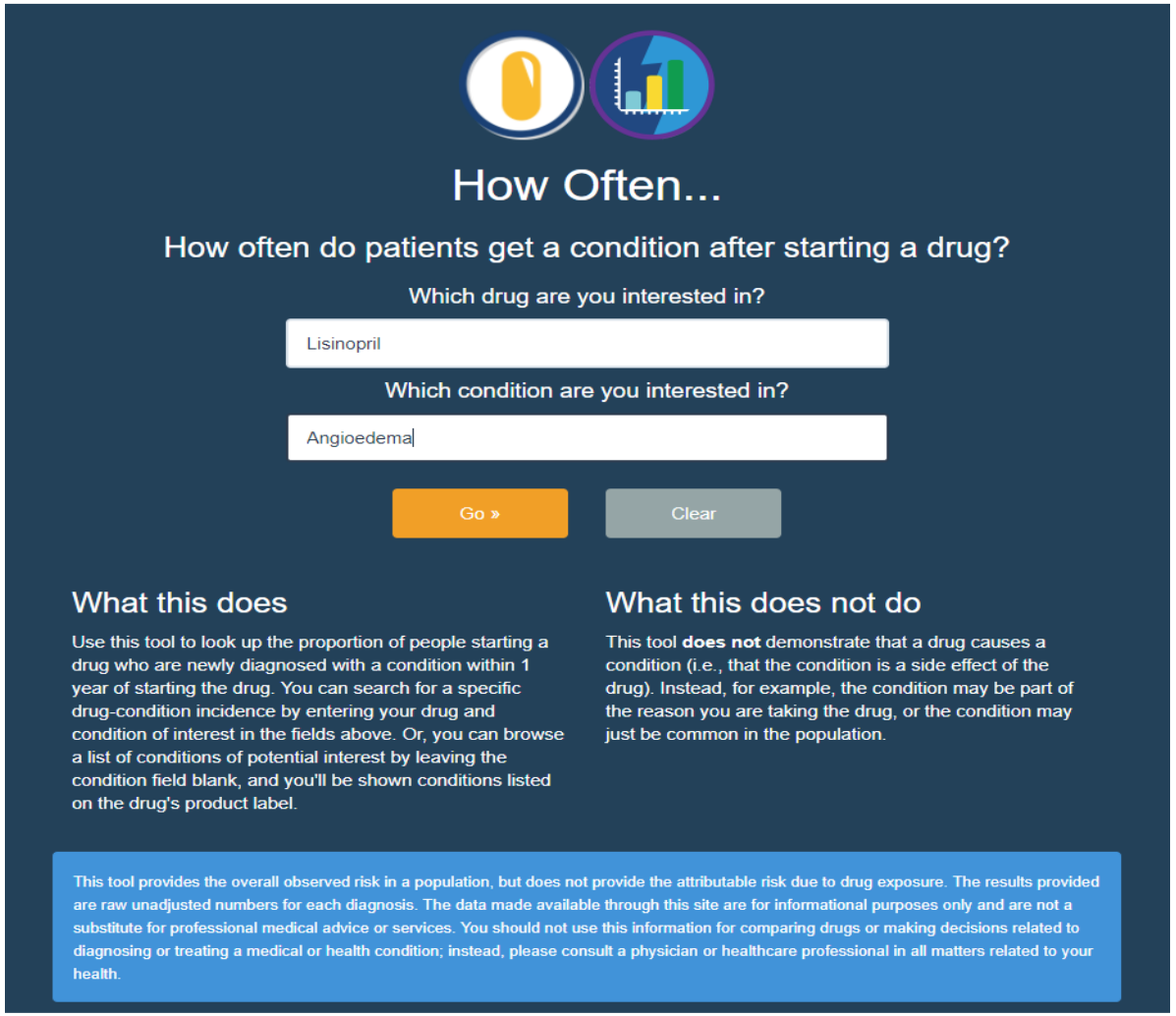
Conclusions: Network research

- It is feasible to encode the world population in a single data model

- Generating evidence is feasible
- Stakeholders willing to share results
- Able to accommodate vast differences in privacy and research regulation

howoften.org

- Incidence of side effects
- Any drug on the world market
- Any condition
- Absolute risk
  - Not causal (Characterization)
- On the Internet



OHDSI in Action

OHDSI is not just a data model

→ Methods development

What is the quality of the current evidence from observational analyses?

ORIGINAL CONTRIBUTION

JAMA®

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

August2010: "Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer"

BMJ

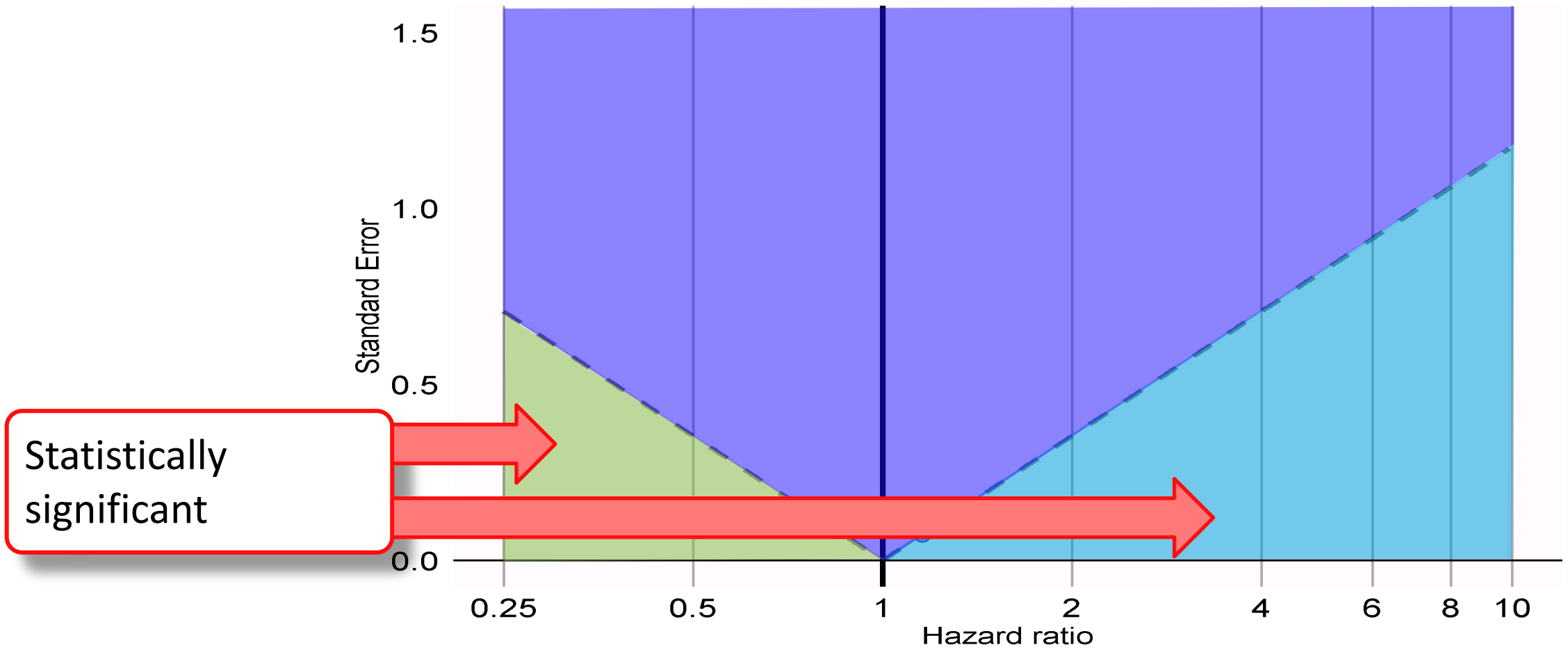
RESEARCH

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

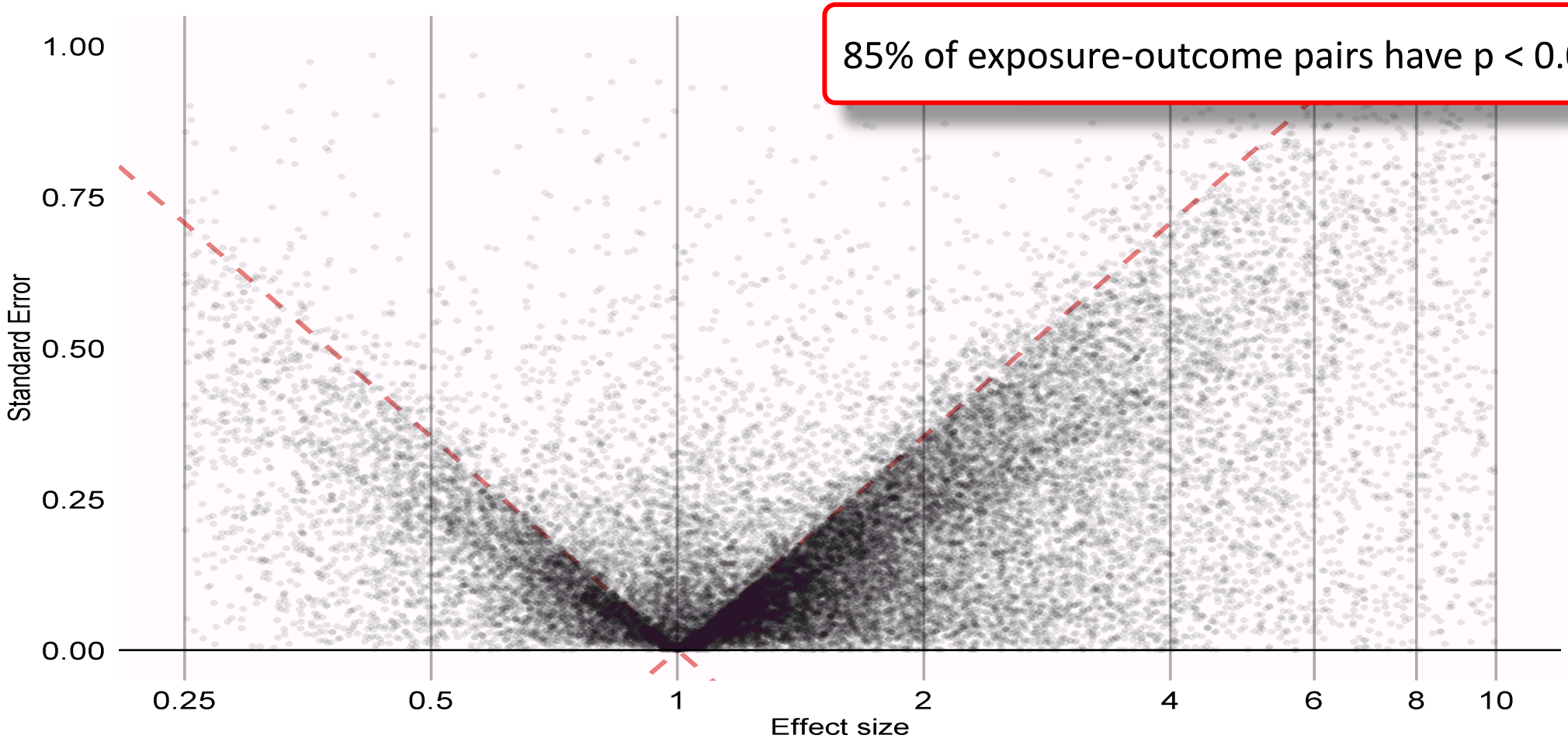
Sept2010: "In this large nested case-control study within a UK cohort [General Practice Research Database], we found a significantly increased risk of oesophageal cancer in people with previous prescriptions for oral bisphosphonates"

Standard error vs effect size



Observational research results in literature

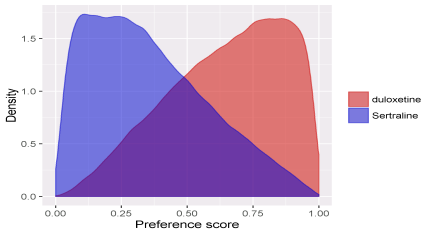
85% of exposure-outcome pairs have p < 0.05

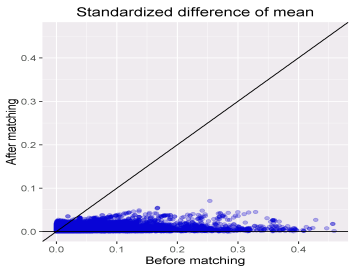


29,982 estimates
11,758 papers

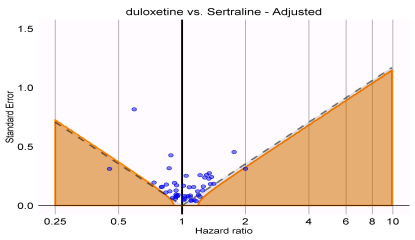
Addressing reproducibility

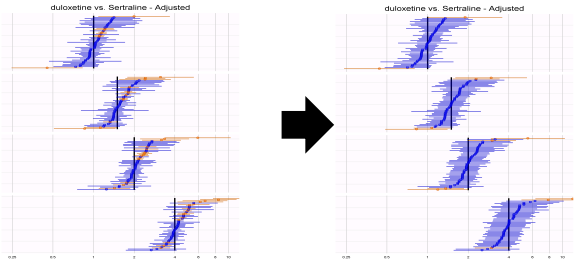
1. **Propensity stratification with *systematic* variable selection: measured confounding**





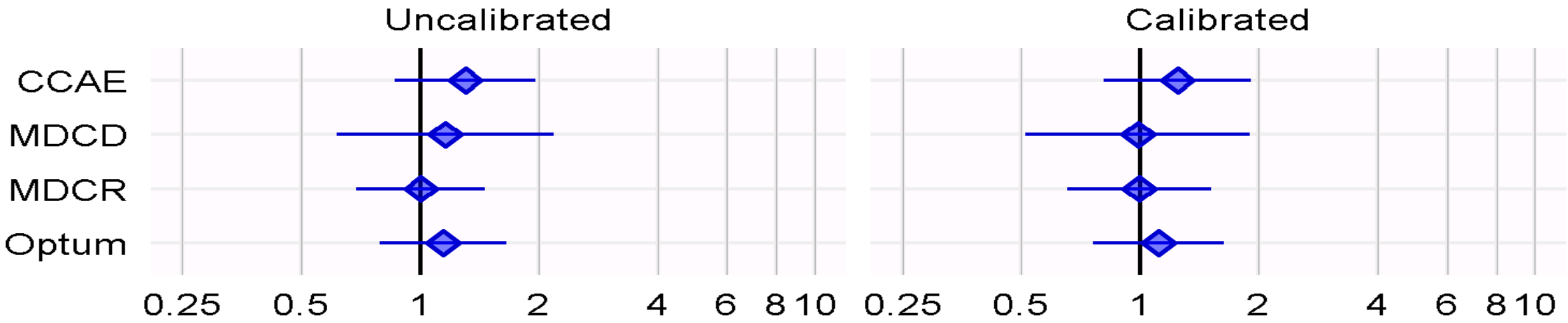
2. Confidence interval calibration using negative controls: unmeasured confounding





Addressing reproducibility

3. Multiple databases, locations, practice types



4. Publish all hypotheses, code, parameters, runs

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□RL←1000
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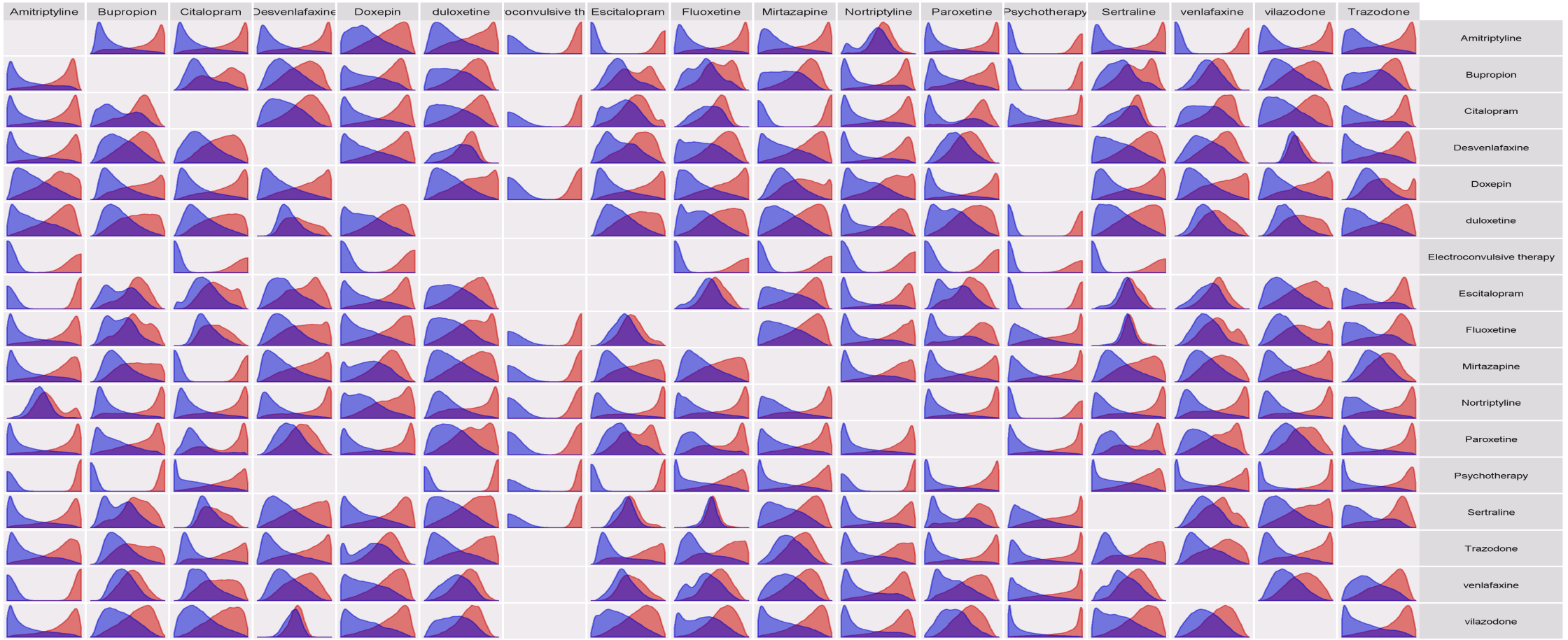
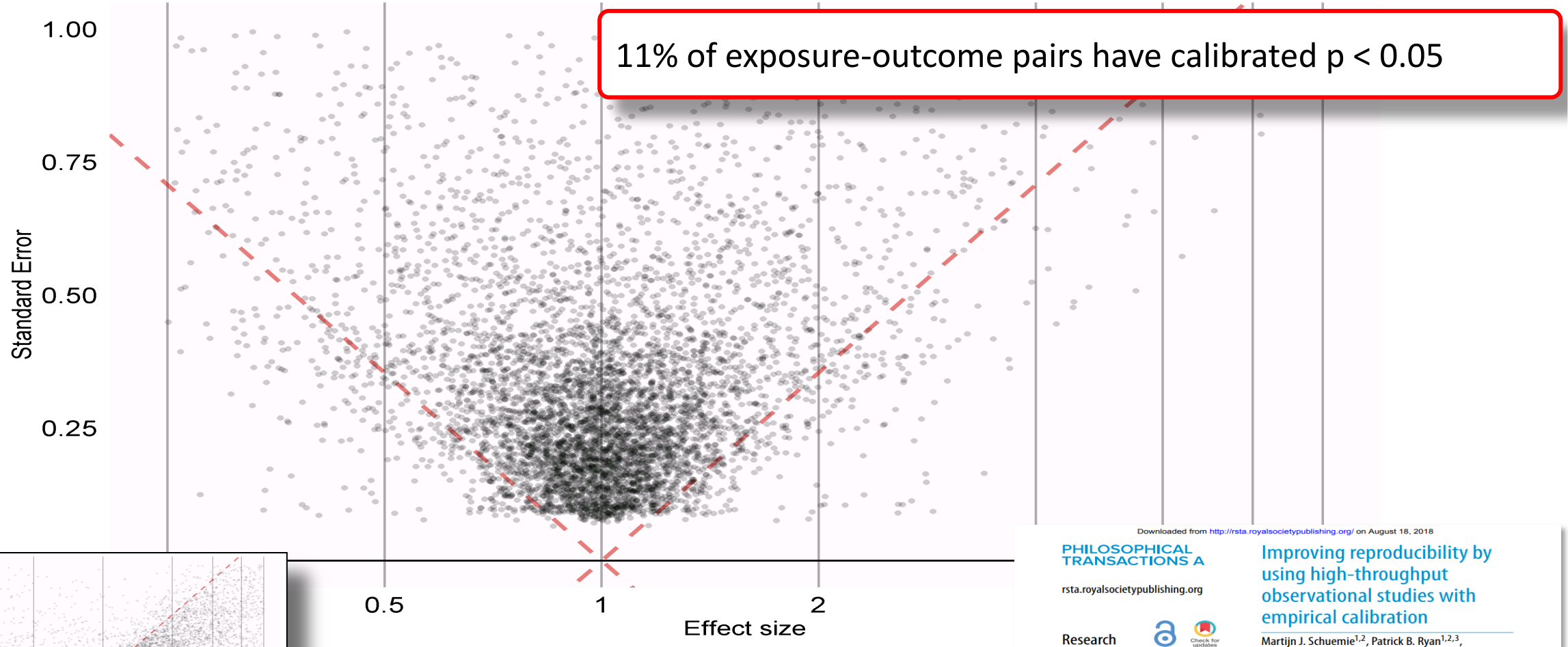
Addressing reproducibility

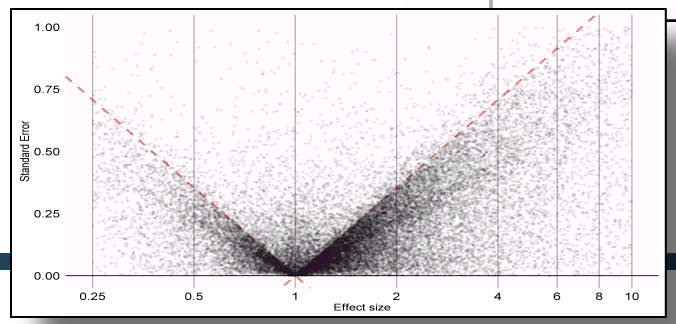
5. Carry out on aligned hypotheses at scale



Estimates are in line with expectations

11% of exposure-outcome pairs have calibrated p < 0.05





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PHILOSOPHICAL TRANSACTIONS A

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Research

Cite this article: Schuemie MJ, Ryan PB, Hripcsak G, Madigan D, Suchard MA. 2018 Improving reproducibility by using high-throughput observational studies with empirical calibration. *Phil. Trans. R. Soc. A* **376**: 20170356.
http://dx.doi.org/10.1098/rsta.2017.0356

Accepted: 8 May 2018

Improving reproducibility by using high-throughput observational studies with empirical calibration

Martijn J. Schuemie[1,2], Patrick B. Ryan[1,2,3], George Hripcsak[1,3,4], David Madigan[1,5] and Marc A. Suchard[1,6,7,8]

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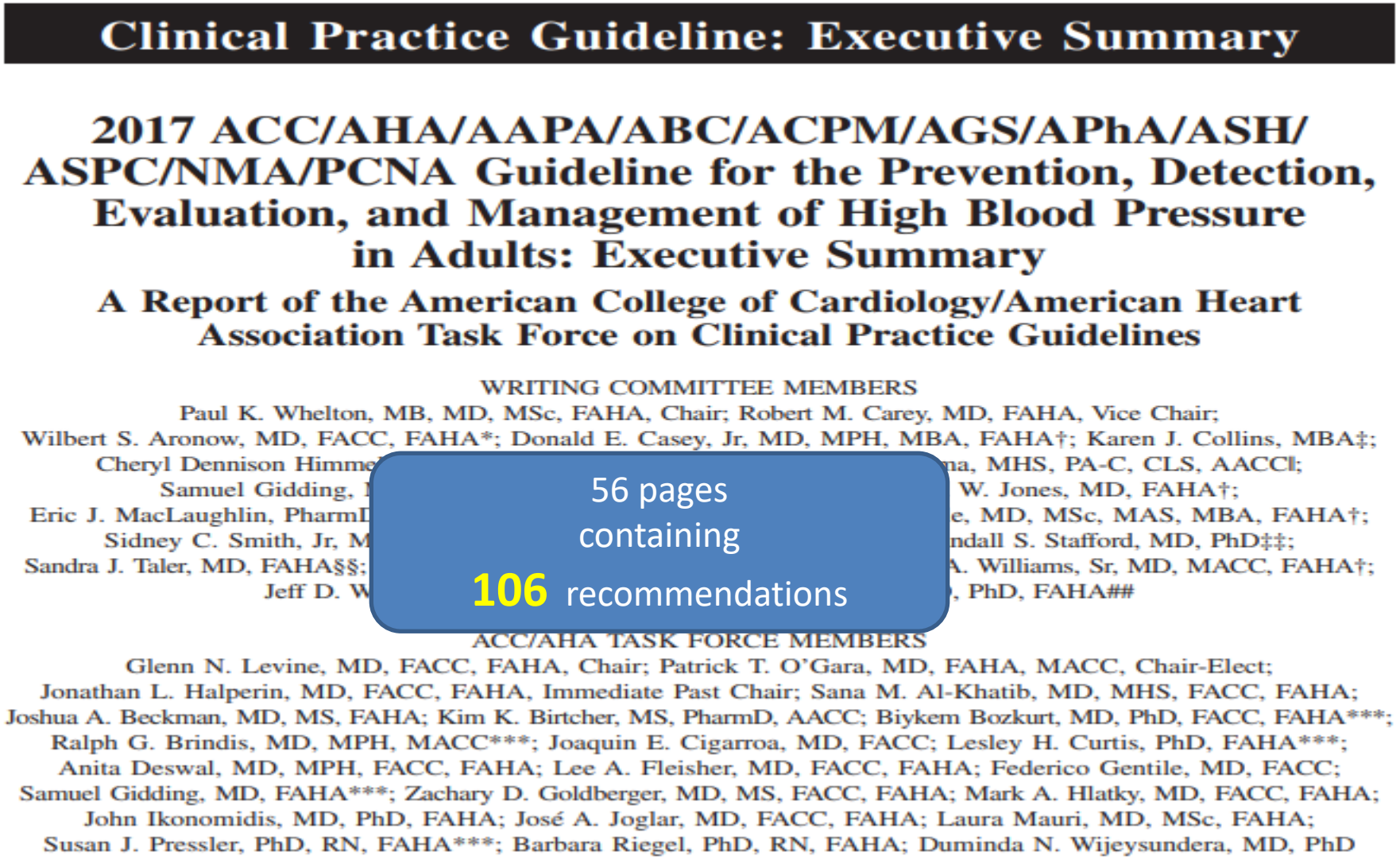
OHDSI LEGEND Hypertension Study

OHDSI is not just a data model

Not just methods development

→ Evidence generation

What's in a guideline?



Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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56 pages containing **106** recommendations

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8.1.6. Choice of Initial Medication

Recommendation for Choice of Initial Medication References that support the recommendation are summarized in Online Data Supplement 27 and Systematic Review Report.		
COR	**LOE**	**Recommendation**
I	A^{SR}	1. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.[S8.1.6-1,S8.1.6-2]

SR indicates systematic review.

Table 18. Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5–25	1	• Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid–lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–10	1	
ACE inhibitors	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ACE inhibitors. • Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
	Trandolapril	1–4	1	
ARBs	Azilsartan	40–80	1	• Do not use in combination with ACE inhibitor or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in those on K^+ supplements or K^+-sparing diuretics. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB 36 hours or 7 days after ACE inhibitor is discontinued. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines	Amlodipine	2.5–10	1	• Avoid use in patients with HF*r*EF; amlodipine or felodipine may be used if required. • They are associated with dose-related edema which is more common in women.
	Felodipine	5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
	Nisoldipine	30–90	1	
CCB—nondihydropyridines	Diltiazem SR	180–360	2	• Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. • Do not use in patients with HF*r*EF. • There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).
	Diltiazem ER	120–480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100–480	1 (in the evening)	

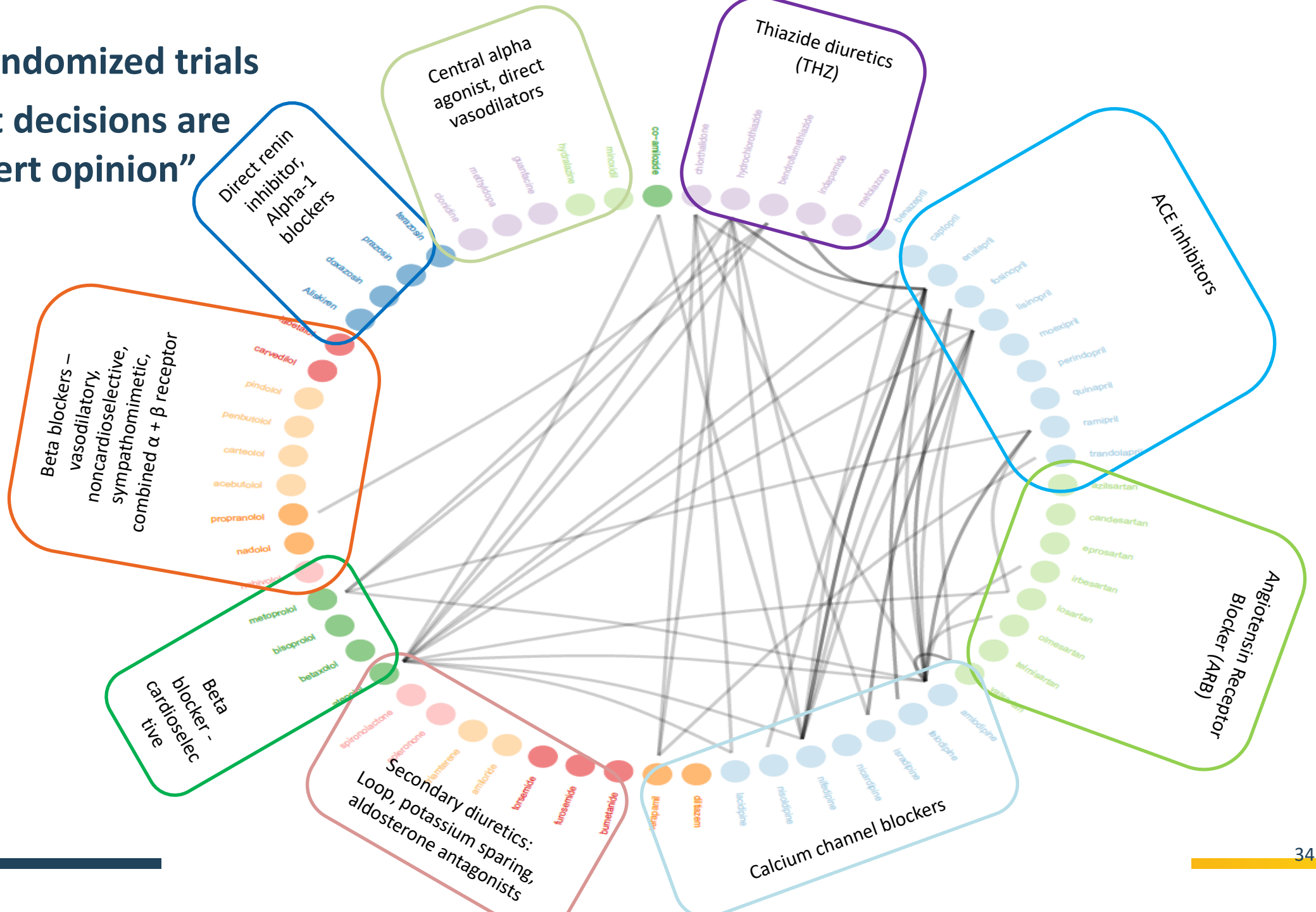
Only **29** different drugs in **5** different classes to choose from!

Distinguished from **28** drugs in **12** other classes that are classified as potential secondary agents **(including Beta Blockers)**

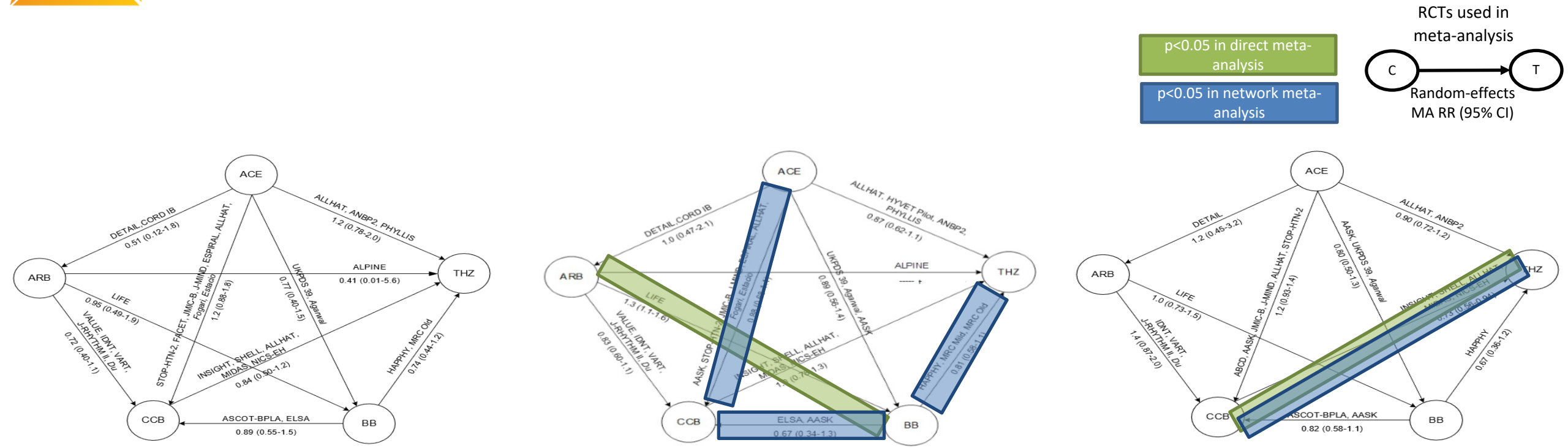
Hypertension

Whelton et al., Hypertension 2018

- **40 randomized trials**
- **Most decisions are “expert opinion”**



RCT evidence about comparative effectiveness for cardiovascular outcomes



Myocardial infarction

- 8/10 DMA comparisons cannot rule out possibility of 2x risk

Stroke

- 1/10 DMA comparisons cannot rule out possibility of 2x risk

Heart failure

- 4/10 DMA comparisons cannot rule out possibility of 2x risk

Reboussin et al., Hypertension 2018

58 outcomes of interest

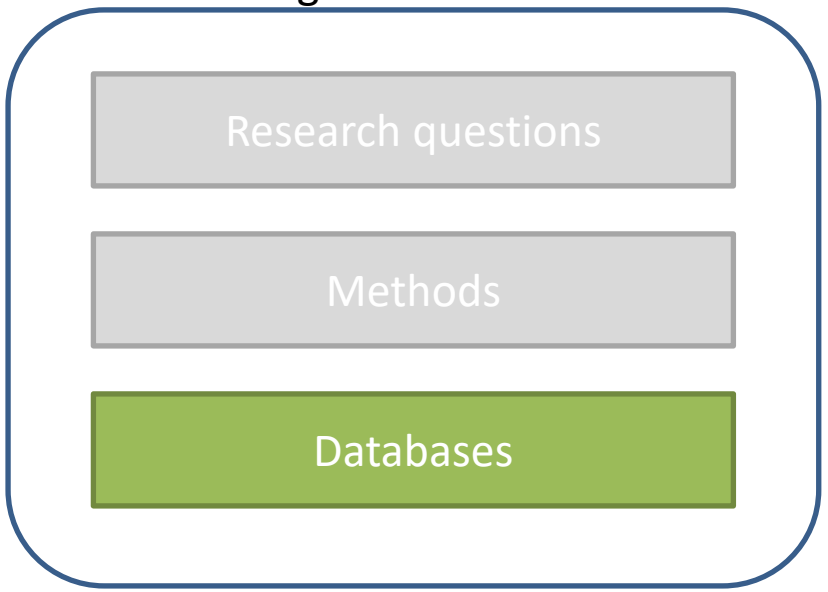
Abdominal pain
Abnormal weight gain
Abnormal weight loss
Acute myocardial infarction
Acute pancreatitis
Acute renal failure
All-cause mortality
Anaphylactoid reaction
Anemia
Angioedema
Anxiety
Bradycardia
Cardiac arrhythmia
Cardiovascular disease
Cardiovascular-related mortality
Chest pain or angina
Chronic kidney disease
Coronary heart disease
Cough
Decreased libido
Dementia
Depression
Diarrhea
Edema
End stage renal disease
Fall
Gastrointestinal bleeding
Gout
Headache
Heart failure
Hemorrhagic stroke
Hepatic failure
Hospitalization with heart failure
Hospitalization with preinfarction syndrome
Hyperkalemia
Hypokalemia
Hypomagnesemia
Hyponatremia
Hypotension
Impotence
Ischemic stroke
Kidney disease
Malignant neoplasm
Measured renal dysfunction
Nausea
Neutropenia or agranulocytosis
Rash
Rhabdomyolysis
Stroke
Sudden cardiac death
Syncope
Thrombocytopenia
Transient ischemic attack
Type 2 diabetes mellitus
Vasculitis
Venous thromboembolic events
Vertigo
Vomiting

76 negative controls

Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Acute conjunctivitis
Amputated foot
Anal and rectal polyp
Burn of forearm
Calcaneal spur
Cannabis abuse
Cervical somatic dysfunction
Changes in skin texture
Chondromalacia of patella
Cocaine abuse
Colostomy present
Complication due to Crohn's disease
Contact dermatitis
Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Hereditary thrombophilia
Herpes zoster without complication
High risk sexual behavior
Homocystinuria
Human papilloma virus infection
Ileostomy present
Impacted cerumen
Impingement syndrome of shoulder region
Ingrowing nail
Injury of knee
Irregular periods
Kwashiorkor
Late effect of contusion
Late effect of motor vehicle accident
Leukorrhea
Macular drusen
Melena
Nicotine dependence
Noise effects on inner ear
Nonspecific tuberculin test reaction
Non-toxic multinodular goiter
Onychomycosis due to dermatophyte
Opioid abuse
Passing flatus
Postviral fatigue syndrome
Presbyopia
Problem related to lifestyle
Psychalgia
Ptotic breast
Regular astigmatism
Senile hyperkeratosis
Somatic dysfunction of lumbar region
Splinter of face, without major open wound
Sprain of ankle
Strain of rotator cuff capsule
Tear film insufficiency
Tobacco dependence syndrome
Vaginitis and vulvovaginitis
Verruca vulgaris
Wrist joint pain
Wristdrop

Databases

Evidence generation



- US insurance databases
  - IBM® MarketScan® CCAE
  - IBM® MarketScan® MDCD
  - IBM® MarketScan® MDCR
  - Optum© Clinformatics®
- Japanese insurance database
  - Japan Medical Data Center
- Korean national insurance database
  - NHIS-NSC
- US EHR databases
  - Columbia University Medical Center
  - Optum© PANTHER®
- German EHR database
  - QuintilesIMS Disease Analyzer (DA) Germany

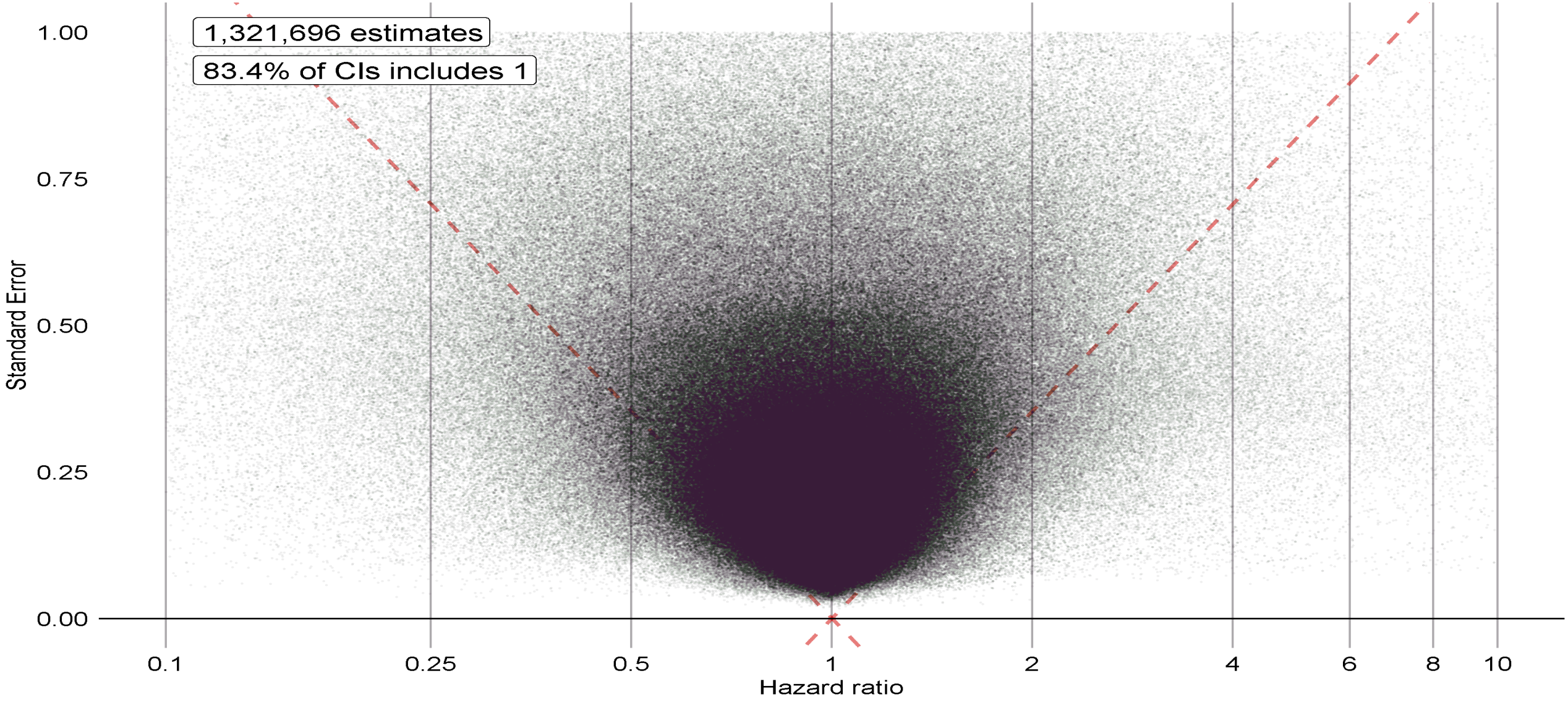
Ajou University

Columbia University

Comparisons of hypertension treatments

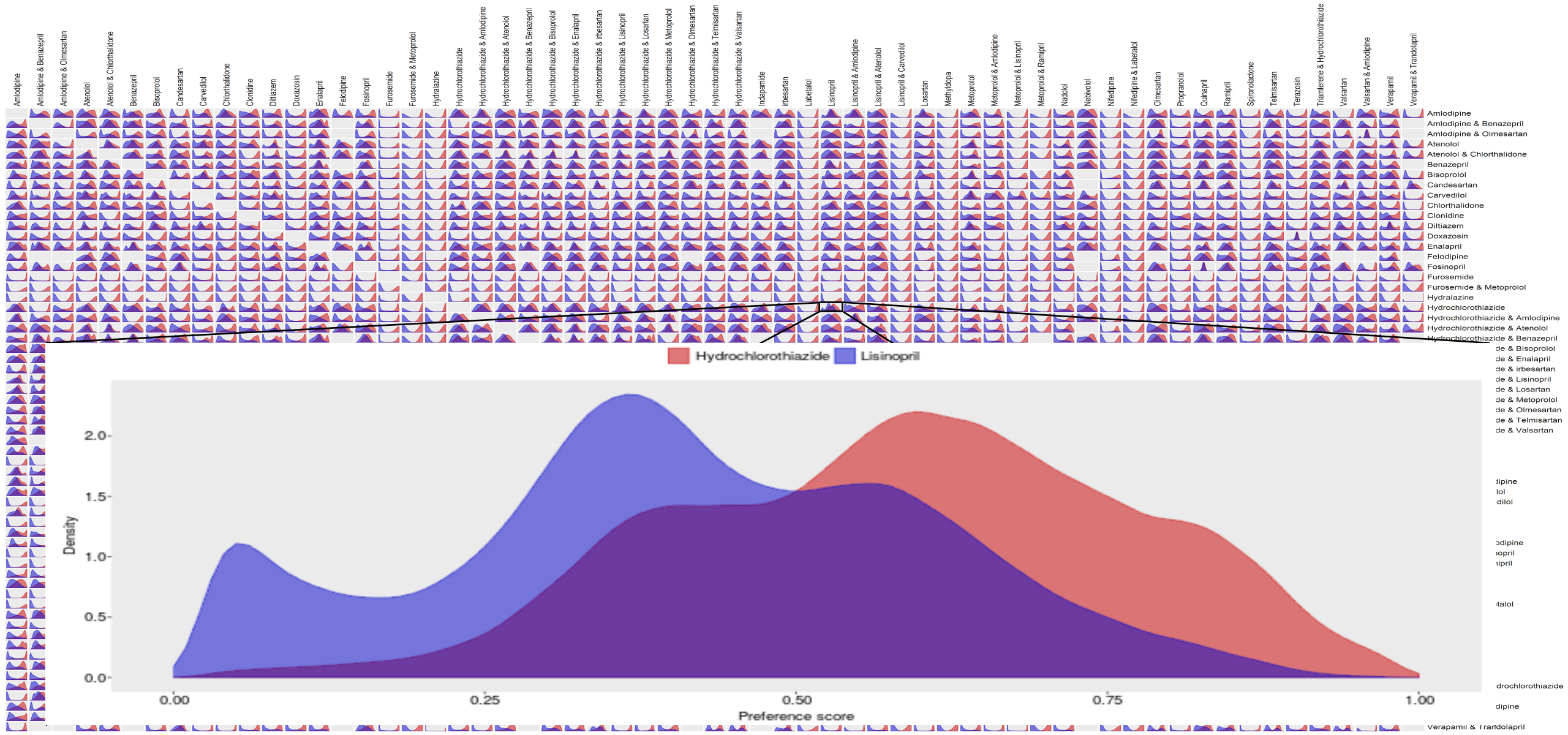
	Theoretical	Observed (n > 2,500)
Single ingredients	58	39
Single ingredient comparisons	58 * 57 = 3,306	1,296
Single drug classes	15	13
Single class comparisons	15 * 14 = 210	156
Dual ingredients	58 * 57 / 2 = 1,653	58
Single vs duo drug comparisons	58 * 1,653 = 95,874	3,810
Dual classes	15 * 14 / 2 = 105	32
Single vs duo class comparisons	15 * 105 = 1,575	832
Duo vs duo drug comparisons	1,653 * 1,652 = 2,730,756	2,784
Duo vs duo class comparisons	105 * 104 = 10,920	992
…	…	…
Total comparisons	2,843,250	10,278
Outcomes of interest	58	58
Target-comparator-outcomes	2,843,250 * 58 = 164,908,500	587,020

LEGEND results

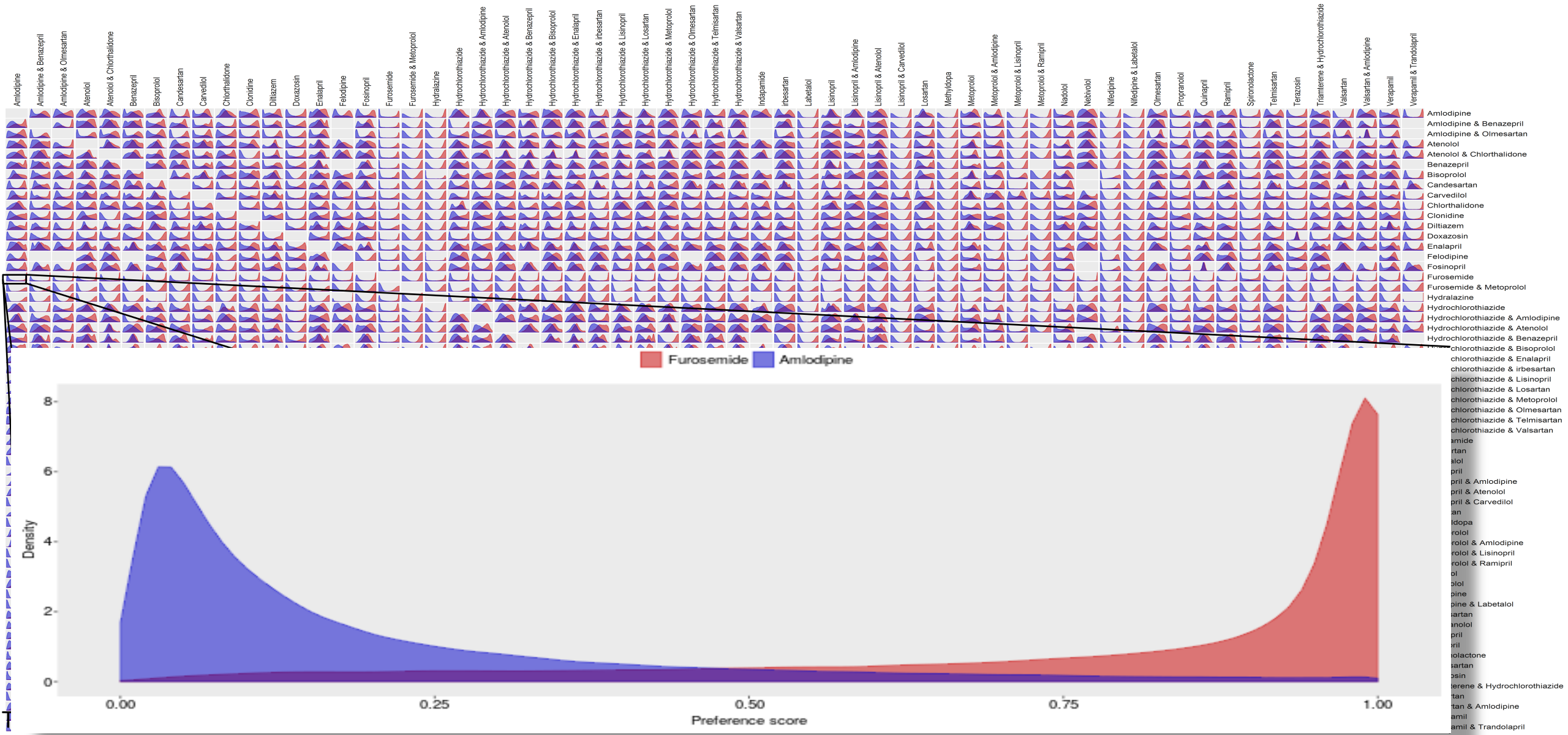


Not all comparisons are valid

Not all comparisons are valid

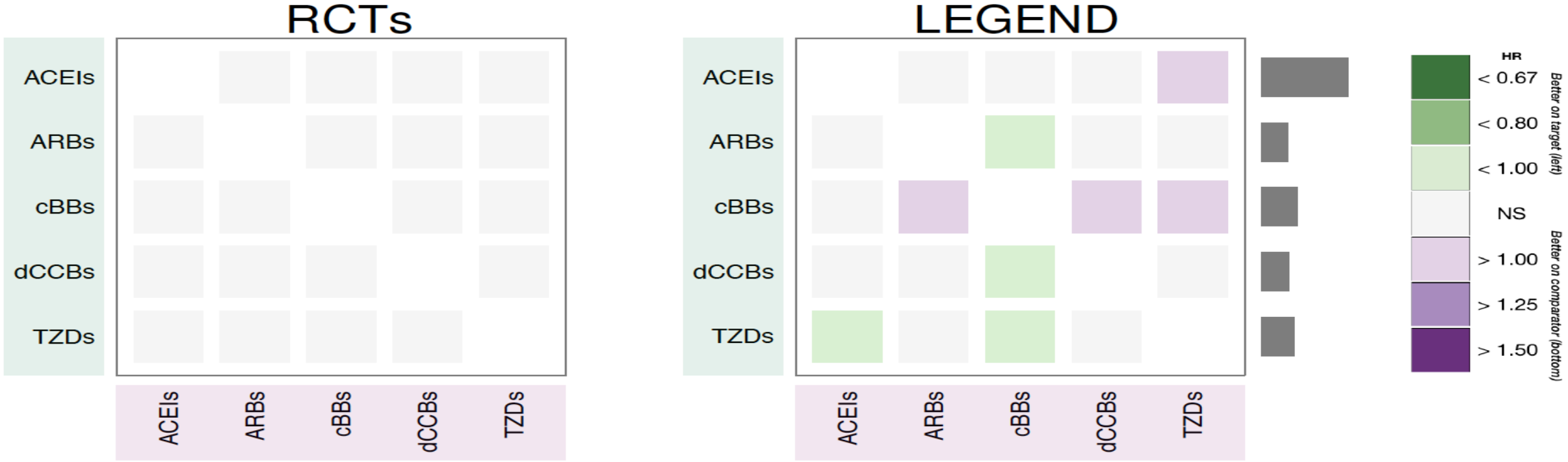


Not all comparisons are valid



First-line agents: comparisons from LEGEND

Efficacy outcome: **myocardial infarction**, heart failure, stroke



Data source: meta-analysis, $\sim 1 - 2$M total patients per study

- Beta blockers underperform alternatives
- Unexpected: TZDs $>$ ACEIs. Reliable?

Cardiovascular efficacy by drug

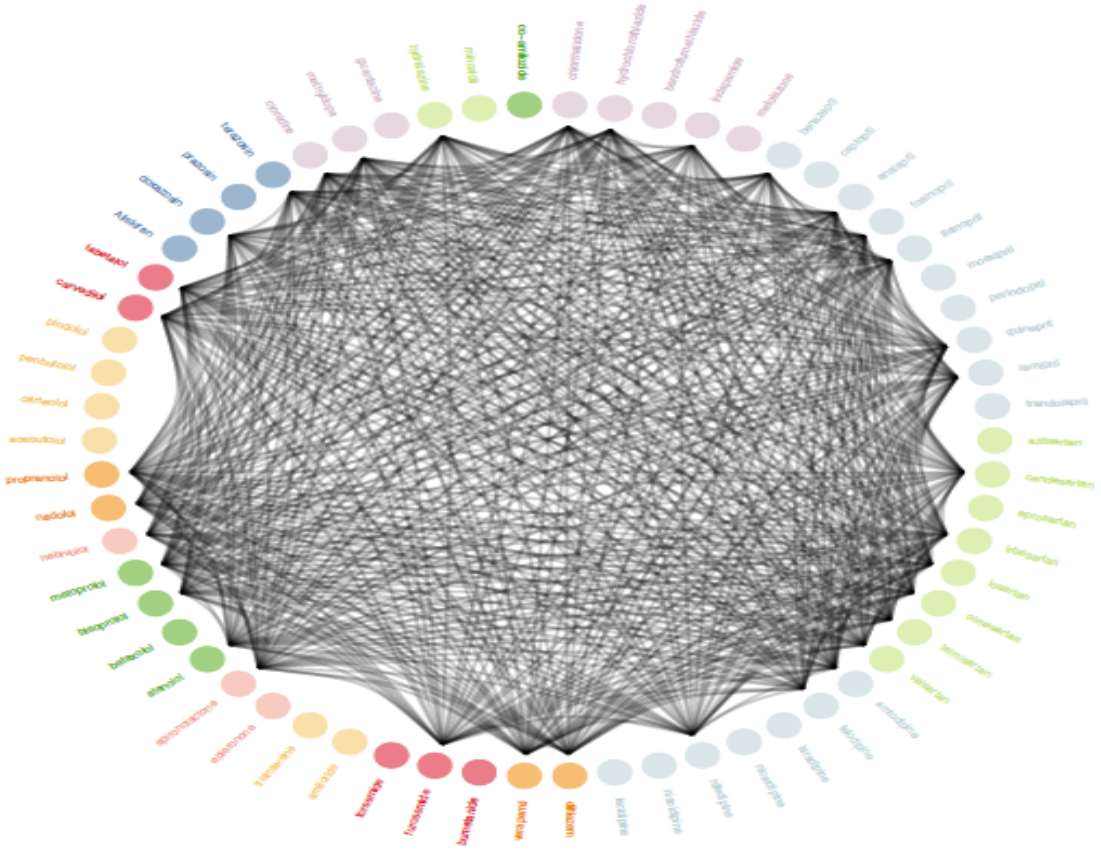
Composite (MI, HF, stroke) outcome in meta-analysis

Prescriptions are not written at the class-level; must choose an individual drug for the patient

- 1st-line > 2nd-line
- Some within-class differences failed diagnostics, e.g. captopril

LEGEND knowledge base for hypertension

Head-to-head HTN drug comparisons



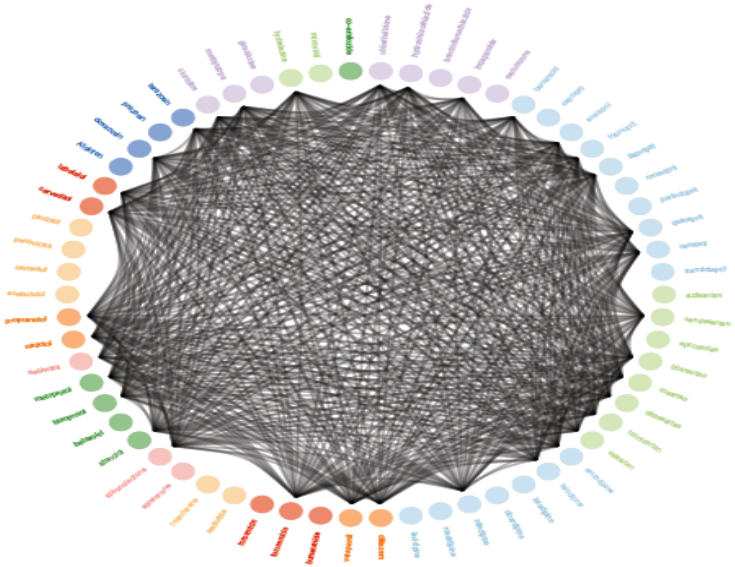
- Trials: 40
- $N = 102 - [1148] - 33K$

- Comparisons: 10,278
- $N = 3502 - [212K] - 1.9M$

Clinical lessons for hypertension

LEGEND evidence is concordant with RCTs:

- Where RCT results exist, but many unanswered questions remains
- More outcomes, comparisons, data sources

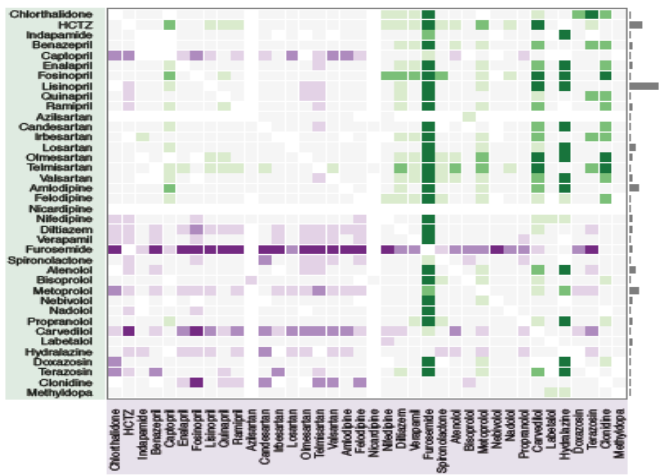


Not all 1st-line agents are equivalent:

- ↓ BBs, TZDs > ACEIs

Combo-therapy initiation:

- ↓ evidence that combo-therapy is better
- Evidence of ↑ safety risk



DCP trial prediction:

- CTD vs. HCTZ – no efficacy difference

Conclusions

- It is feasible to create an enormous international research network
- Sites will volunteer to run studies
- Completely open
  - Data model, methods, tools
- Concrete approach to address the credibility crisis
- OHDSI is supports all part of the evidence generation process and generates evidence

Join the journey

http://ohdsi.org