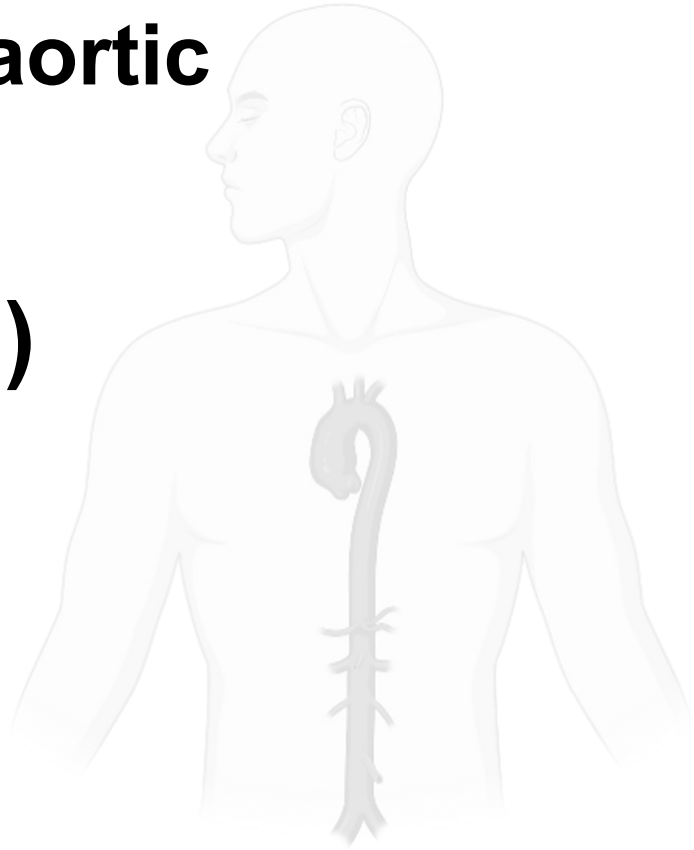
Is fluoroquinolone use associated with the development of aortic aneurysms and aortic dissections?

OHDSI SOS Challenge 2023 (APAC)



Chief investigators:

Jung Ho, Seng Chan You – Republic of Korea

Jack Janetzki, Nicole Pratt – Australia

YONSEI UNIVERSITY

University of South Australia

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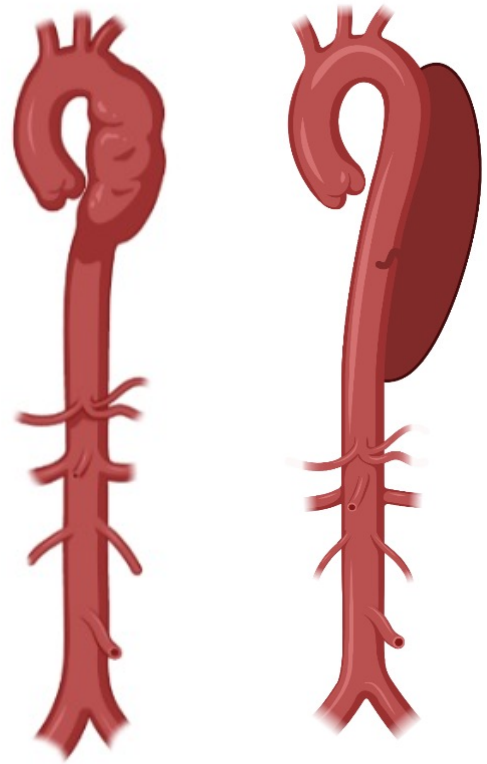
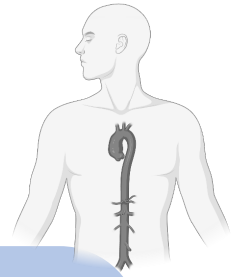
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Background of study:

- Fluoroquinolones – commonly prescribed broad-spectrum antibiotics
- Used to treat variety of infections including **urinary tract infections**
- Post-marketing studies and international regulators identified:
  - ↑ **rare risk of aortic aneurysm or dissection**
    - Pharmacological mechanism not well understood
  - Quality of evidence underpinning the association is <u>moderate</u>:
    - Inconsistencies in study designs (choice of active comparators, follow-up, patient age, inclusion of specific fluoroquinolones)
    - Conflicting results across multiple studies
  - Regulators responded with black box warnings and limitations to prescribing

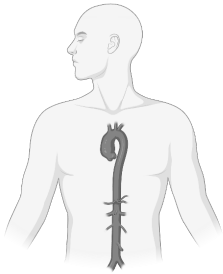




Does exposure to a fluoroquinolone increase the risk of experiencing aortic aneurysm or dissection within a year of starting the medicine?

Characterize the risk of aortic aneurysm or dissection following use of fluoroquinolones

The questions and framework

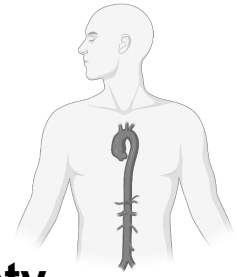


1. **Characterization: incidence and time-to-event of aortic events following quinolone exposure**

- Amongst patients who are new users of fluoroquinolones, *how many* patients experience aortic aneurysms or dissections within 1 year of initiating treatment?

- Amongst patients who are new users of fluoroquinolones, what is the *time-to-event* distribution between exposure and aortic aneurysm or dissection?

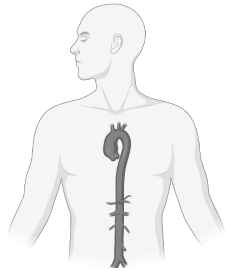
The questions and framework



2. Estimation: comparative safety of fluoroquinolones vs other antibiotics; comparative safety between fluoroquinolones

- Does exposure to FQs ↑ risk of experiencing aortic aneurysm or dissection within 30d, 60d, 90d and 365d of initiating treatment?
- Does exposure to FQs have a different risk of experiencing aortic aneurysm and dissection within 30d, 60d, 90d and 365d of initiating treatment, relative to other antibiotics (trimethoprim +/- sulfamethoxazole or cephalexin)

What happened along the way



SOS Challenge Weekly Tutorial Schedule

Date	Times	Topic
Mar. 28	11 am / 7 pm ET	SOS Week 1 Tutorial: Initiating A Network Study
Apr. 4	11 am / 7 pm ET	SOS Week 2 Tutorial: Data Diagnostics
Apr. 11	11 am / 7 pm ET	SOS Week 3 Tutorial: Phenotype Development
Apr. 18	11 am / 7 pm ET	SOS Week 4 Tutorial: Phenotype Evaluation
Apr. 25	11 am / 7 pm ET	SOS Week 5 Tutorial: Creating Analysis Specifications
May 2	11 am / 7 pm ET	SOS Week 6 Tutorial: Network Execution
May 9	11 am / 7 pm ET	SOS Week 7 Tutorial: Study Diagnostics
May 16	11 am / 7 pm ET	SOS Week 8 Tutorial: Evidence Synthesis
May 23	11 am / 7 pm ET	SOS Week 9 Tutorial: Interpreting The Results

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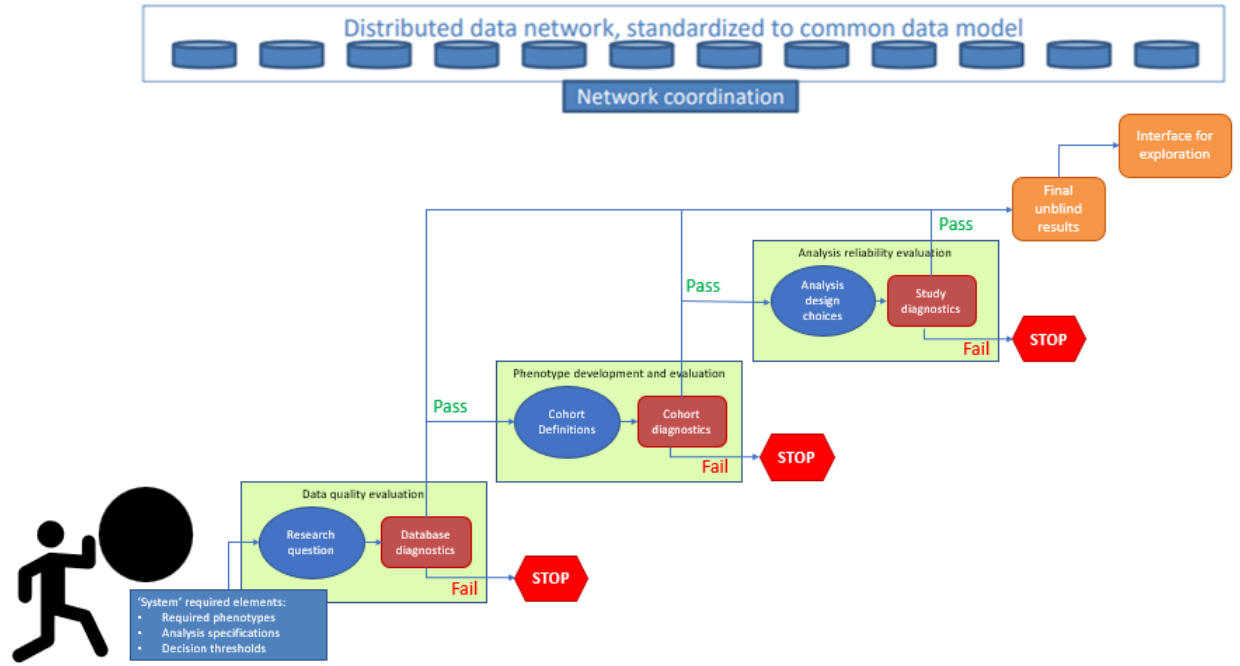

Employed OHDSI's diagnostics to generate reliable results

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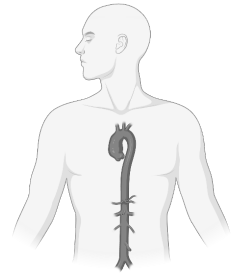
What did we find?



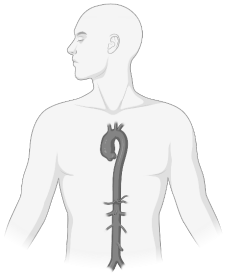
- 13.5 million people included in study
- 14 databases from 5 different countries

SAFE

SAFE

SAFE

Results shared worldwide!



- Code: https://github.com/ohdsi-studies/FluoroquinoloneAorticAneurysm
- ShinyApp of results available at: https://data.ohdsi.org/FluoroquinoloneAorticAneurysm/

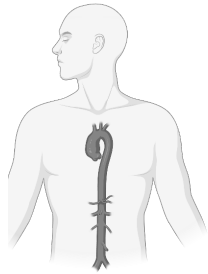
Presentations:
- OHDSI APAC 2023
- OHDSI Global Symposium 2023
- ISPE 2024
- University of South Australia Clinical and Health Sciences 2023
- Medicines Intelligence Centre for Research Excellence symposium (Australia) 2023
- Medicines Intelligence Centre for Research Excellence symposium (Australia) 2024
- OHDSI APAC 2024

Publication:
- Primary publication currently under review in eClinicalMedicine

Thank you OHDSI for hosting the 2023 SOS challenge!

Jung Ho and I are immensely grateful for the opportunities that OHDSI has granted us and we look forward to giving back to the community.

You've taught us about reproducible, reliable and calibrated evidence which are only possible through robust diagnostics and a community that is so open and welcoming. We truly value each collaboration.

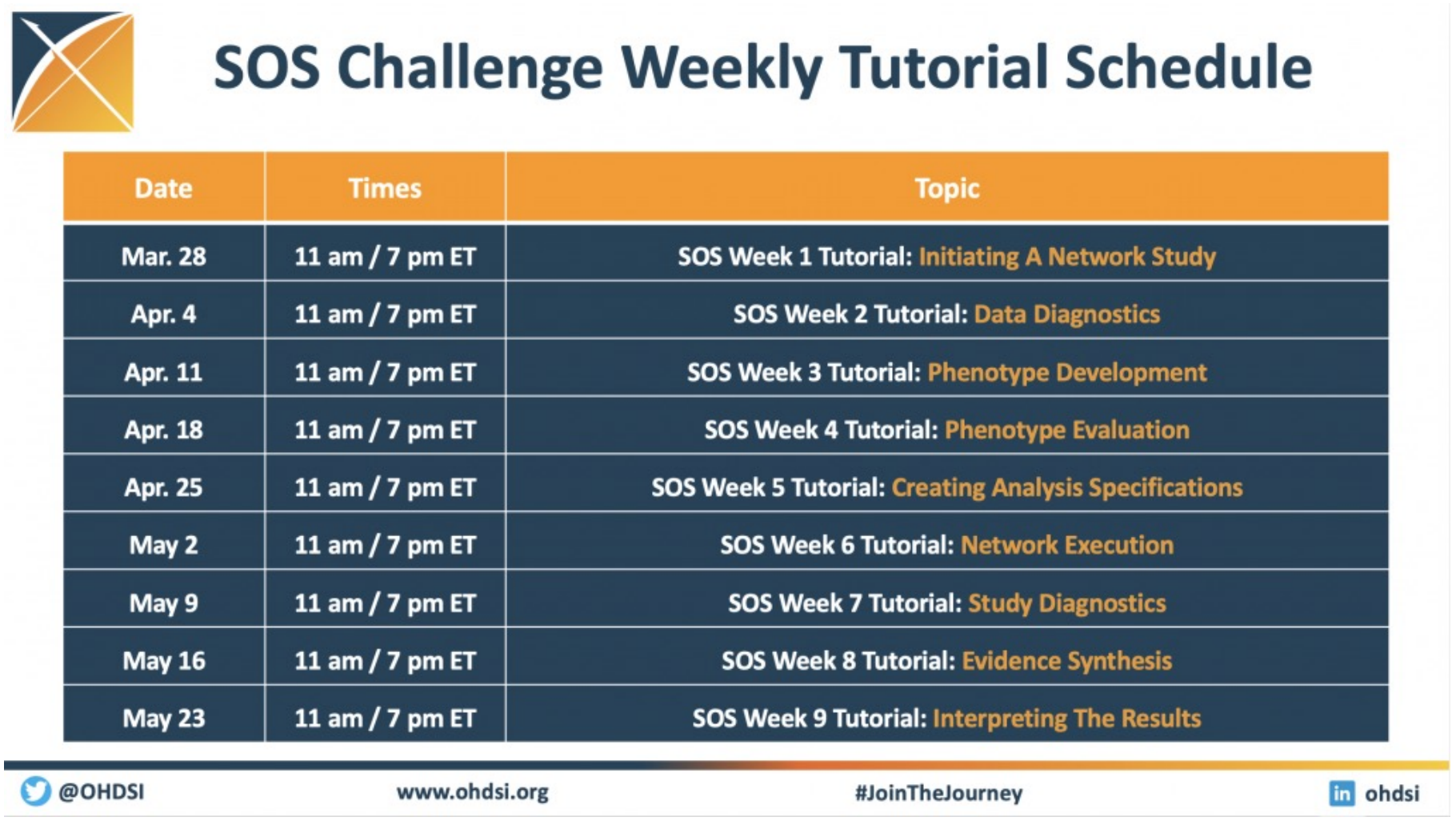


Cindy X. Cai, MD MS

- Retina specialist
- Clinician-scientist
- Assistant Professor of Ophthalmology at Johns Hopkins University
- Assistant Professor of Medicine (Biomedical Informatics and Data Science)

OHDSI Journey

- NIH K grant: vision loss and diabetes
  - Develop EHR models, incorporate SDoH, predict lapses in diabetic retinopathy (DR) care, share model across institutions
  - Paul Nagy
  - OMOP CDM
  - Classes, OMOP, OHDSI tools, OHDSI Global Symposium



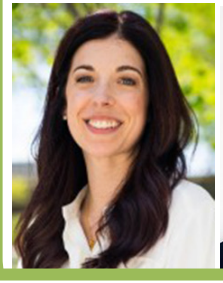
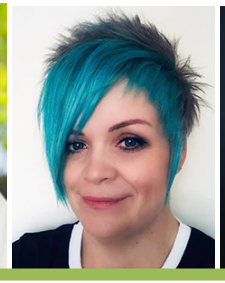
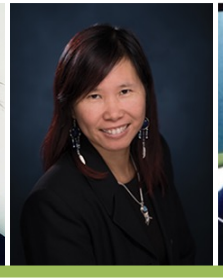
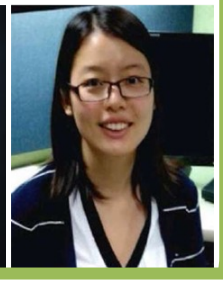
Is the risk of **kidney failure** associated with **intravitreal anti-VEGF** exposure in patients with blinding diseases (DR/DME, AMD, VO) different among patients who receive **ranibizumab, aflibercept, and bevacizumab**?

tems that build trust into the
on and dissemination process

standardized to common data model

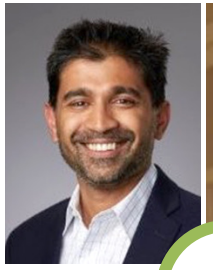
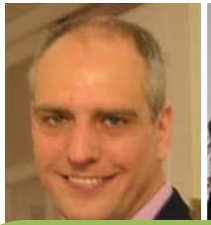
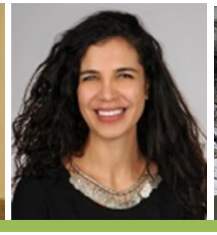
Week 1: Study initiation

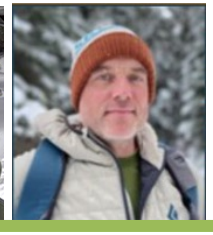
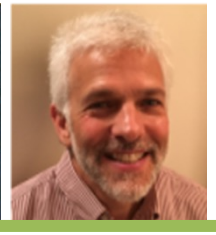

Week 2: Data diagnostics

Week 3-4: Phenotype development and evaluation



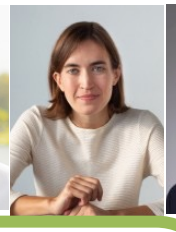



Only possible because of standardized analytics developed across our community







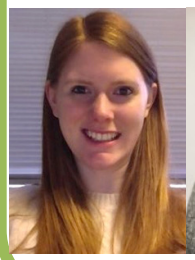




Week 5: Analysis design

unblinded results

Interface for exploration

Week 6-8: Analysis execution, study diagnostics, evidence synthesis











Ophthalmology Retina
AMERICAN ACADEMY OF OPHTHALMOLOGY®

Similar Risk of Kidney Failure among Patients with Blinding Diseases Who Receive Ranibizumab, Aflibercept, and Bevacizumab

An Observational Health Data Sciences and Informatics Network Study

Cindy X. Cai, MD, MS,[1] Akihiko Nishimura, PhD,[2] Mary G. Bowring, MPH,[3] Erik Westlund, PhD,[2] Diep Tran, MSc,[1] Jia H. Ng, MD, MSCE,[4] Paul Nagy, PhD,[5] Michael Cook, BS,[6] Jody-Ann McLeggon, MPH,[7] Scott L. DuVall, PhD,[8,9] Michael E. Matheny, MD, MPH,[10,11] Asieh Golozar, PhD,[12,13] Anna Ostropolets, MD, PhD,[12] Evan Minty, MD, MSc,[14] Priya Desai, MS,[15] Fan Bu, PhD,[16] Brian Toy, MD,[17] Michelle Hribar, PhD,[18,19] Thomas Falconer, MS,[7] Linying Zhang, PhD,[7] Laurence Lawrence-Archer, MSc,[12,13] Michael V. Boland, MD, PhD,[20] Kerry Goetz, MS,[18] Nathan Hall, MS,[21] Azza Shoaibi, PhD,[21] Jenna Reps, PhD,[21] Anthony G. Sena, BA,[21,22] Clair Blacketer, MPH,[21] Joel Swerdel, PhD, MPH,[21] Kenar D. Jhaveri, MD,[23] Edward Lee, BS,[17] Zachary Gilbert, BS,[17] Scott L. Zeger, PhD,[2] Deidra C. Crews, MD, ScM,[24] Marc A. Suchard, MD, PhD,[8,16] George Hripcsak, MD, MS,[7] Patrick B. Ryan, PhD[21]

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Editorial

Intravitreal Anti-VEGF Pharmacotherapy and Kidney Failure: Protecting Vision with an Eye on Renal Safety

Andrew J. Barkmeier, MD - *Rochester, Minnesota*

Intravitreal anti-VEGF pharmacotherapy has preserved vision for millions of patients with sight-threatening retinal and choroidal vascular disease worldwide. Intravitreal injections can be safely performed in the clinic setting and their benefits are widely accessible. Patients with the most common indications for these treatments (diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration) are at increased risk of vascular complications, myocardial infarction, stroke, and kidney disease. In the context of the well-defined thromboembolic and renal risk of intravenous anti-VEGF medications for patients with solid tumors, and the known systemic exposure after intravitreal injection of these agents, it is imperative to elucidate any systemic risks associated with these ocular therapies. This process, however, is not straightforward because there are significant challenges in studying rare but important systemic outcomes, particularly in patients whose ocular treatment indications are inherently associated with elevated systemic risk.

In this issue of *Ophthalmology Retina*, Cai et al[1] (p. 733) report the incidence of kidney failure in patients receiving anti-VEGF pharmacotherapy and compare the relative rates of adverse renal events between patients treated with different anti-VEGF agents: ranibizumab, bevacizumab, and aflibercept. A network of standardized international health care databases was used to identify and analyze outcomes of

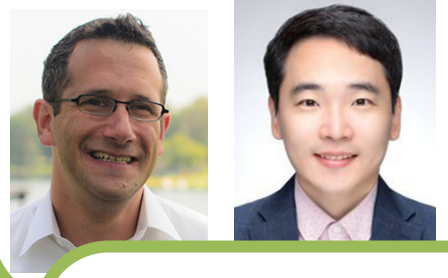
mg/kg treatment arm that was ultimately more efficacious for delaying cancer progression.[2] Looking through a systemic lens, the eye serves as a sustained-release depot for anti-VEGF medication that is gradually released into circulation after intravitreal injection. Although the intraocular dose may only represent 1/200th to 1/1000th of a typical intravenous bolus, these agents enter the systemic circulation at levels capable of decreasing plasma VEGF, which could represent a plausible pathophysiologic mechanism for inducing kidney injury.[3,4] The evidence supporting this concern, however, remains limited to uncontrolled case series and analyses lacking active controls that are susceptible to confounding by indication bias.[5,6] A meta-analysis of 13 clinical trials reporting acute kidney injury outcomes found no increased renal risk in patients randomized to intravitreal aflibercept or ranibizumab versus controls randomized to no anti-VEGF exposure (odds ratio, 1.00; 95% CI, 0.49−2.04).[7] Although indication bias is avoided in this meta-analysis through randomization, the modest sample size limits its power to identify potentially relevant differences in low-frequency kidney events.

Cai et al[1] report an elevated incidence of kidney failure among patients receiving intravitreal anti-VEGF injections in routine clinical practice (678 per 100 000) compared with the general population. This finding is to be expected. In addition to the higher prevalence of risk factors for development of

"This question has **high-clinical relevance** because of known interagent differences in systemic exposure, and the clinician's ability to preferentially select a more favorable agent, if indicated."

"Cai et al make a **valuable contribution** to understanding the relative renal impact of available intravitreal anti-VEGF medications, and their conclusion that choice of intravitreal medications need not be routinely considered out of concern for precipitating kidney failure should be reassuring to patients, ophthalmologists, and clinicians managing renal health."

Week 1: Study initiation



Week 2: Data diagnostics

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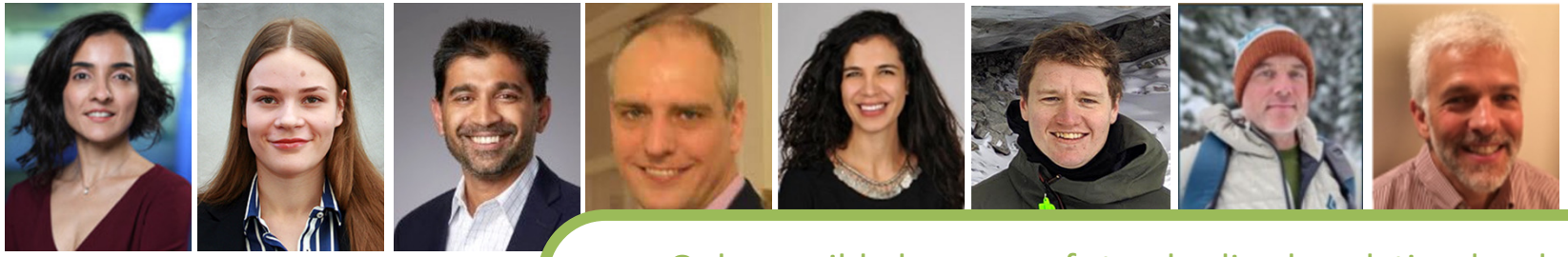
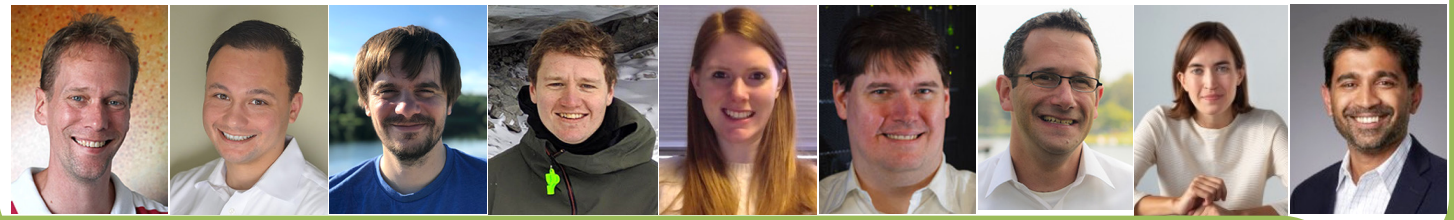
Week 3-4: Phenotype development and evaluation



Only possible because of standardized analytics developed across our community



Week 5: Analysis design

Week 6-8: Analysis execution, study diagnostics, evidence synthesis

Titan Award for Methodology Research 2024

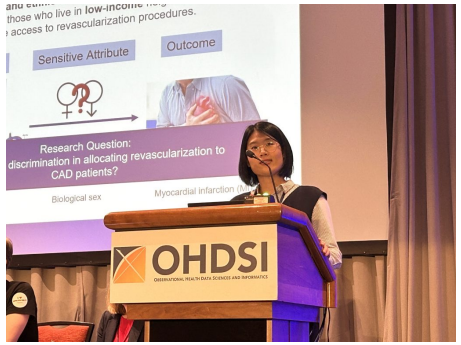
Linying Zhang

11/5/2024 OHDSI Community Call

My OHDSI journey…

- 2018-2023: PhD student at Columbia University DBMI.
- Part of my dissertation is about advancing OHDSI methods. Won the AMIA Shortliffe Dissertation Award 2024
- 2023-now: Assistant Professor at WashU, researching methods and building local OHDSI team

Jan 2021, Columbia DBMI terrace



Lightening talk at 2022 OHDSI Global Symposium

Tutorial team at 2024 OHDSI Global Symposium

My methods research journey…

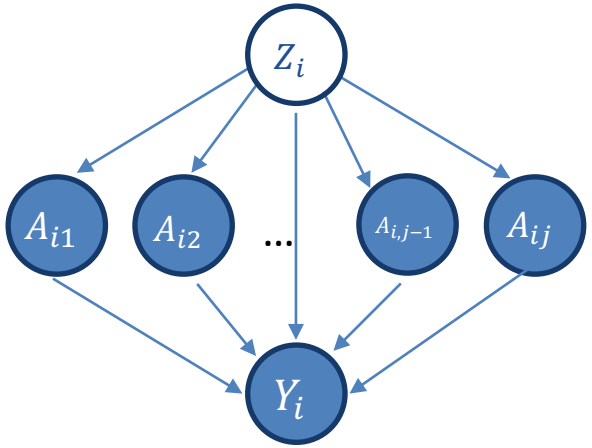
- Causal machine learning for reliable real-world evidence generation in healthcare
- This dissertation aims to provide **theoretical foundations** and **empirical characterization** of causal inference methods in addressing **unmeasured confounding** from electronic health records data, with two areas of application: (1) **estimation of medication effects** in multi-medication setting and comparative setting, and (2) **fairness assessment of treatment allocation** in clinical practice.

Started with a “big” dream …

- Let’s estimate effects of multiple treatments in one model.
- The multiplicity of treatments helps us construct latent variables that contains unmeasured confounders.
- Innovative method but challenging to apply because of study design.

	Drug 1	Drug 2	Drug 3	Drug 4	…	Blood sugar level
	1	1	0	0	…	120
	0	1	1	0	…	130
	0	1	1	1	…	200
…	…	…	…	…	…	

Example data.



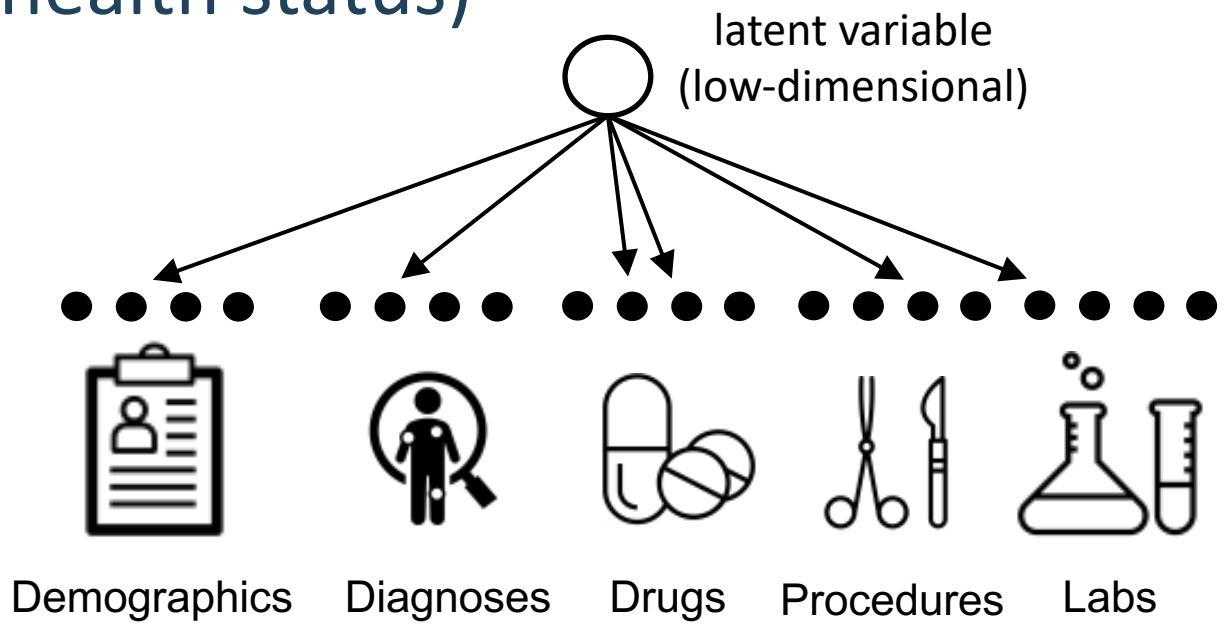
For the *i*-th patient,
A_i: causes
Y_i : outcome
Z_i : unmeasured confounder

Causal diagram for multiple treatments setting.

Linying Zhang, Yixin Wang, Anna Ostropolets, Jami J. Mulgrave, David M. Blei, George Hripcsak. *Proceedings of the 4th Machine Learning for Healthcare Conference*, PMLR 106:490-512, 2019.

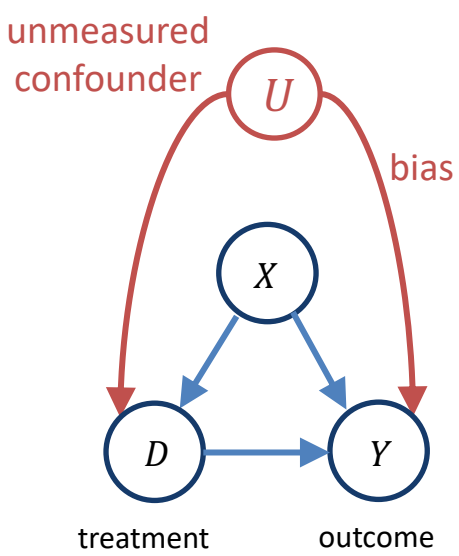
Worked on down-to-earth approaches…

- Large-scale propensity score (LSPS)
- An unmeasured confounder is likely correlated with other measured covariates through shared latent variables (e.g., underlying health status)



Large-scale propensity score (LSPS) and pinpointing

- LSPS adjusts for unmeasured confounder under pinpointability.

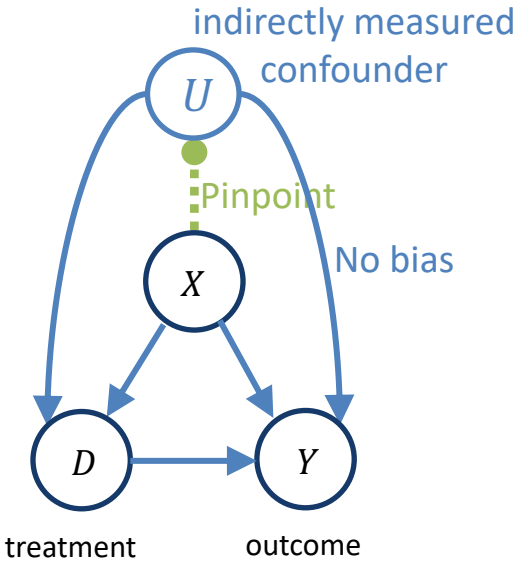


$p(d \mid \boldsymbol{x}) \neq p(d \mid \boldsymbol{x}, u)$

Pinpointability

$p(u \mid x) = \delta(f(x))$

where $\delta()$ is a point mass

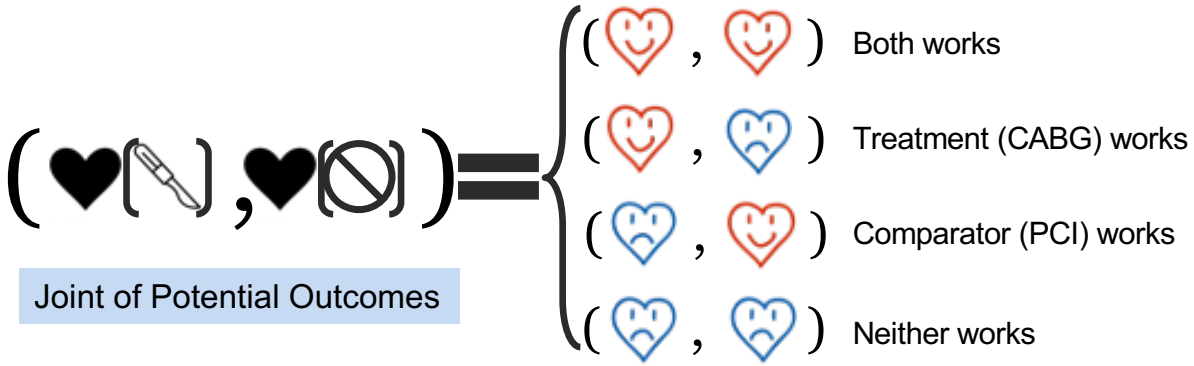


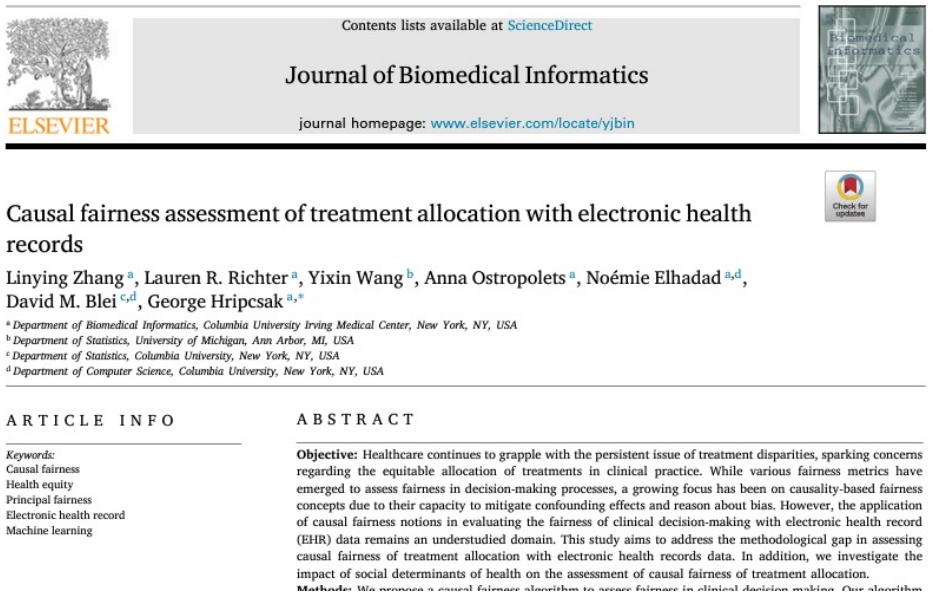
$p(d \mid \boldsymbol{x}) = p(d \mid \boldsymbol{x}, u)$

Zhang L, Wang Y, Schuemie MJ, Blei DM, Hripcsak G. Adjusting for indirectly measured confounding using large-scale propensity score. *J Biomed Inform*. 2022.

Extend causality to health equity

- Principle fairness for assessing treatment allocation equity





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Journal of Biomedical Informatics

journal homepage: www.elsevier.com/locate/yjbin

Causal fairness assessment of treatment allocation with electronic health records

Linying Zhang [a], Lauren R. Richter [a], Yixin Wang [b], Anna Ostropolets [a], Noémie Elhadad [a,d], David M. Blei [c,d], George Hripcsak [a,*]

[a] Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, NY, USA
[b] Department of Statistics, University of Michigan, Ann Arbor, MI, USA
[c] Department of Statistics, Columbia University, New York, NY, USA
[d] Department of Computer Science, Columbia University, New York, NY, USA

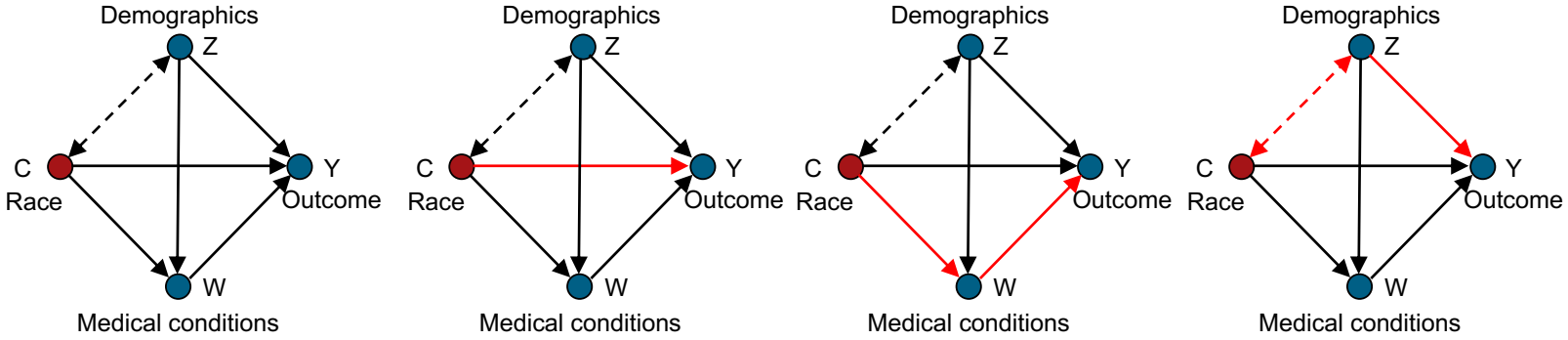
ARTICLE INFO

Keywords:
Causal fairness
Health equity
Principal fairness
Electronic health record
Machine learning

ABSTRACT

Objective: Healthcare continues to grapple with the persistent issue of treatment disparities, sparking concerns regarding the equitable allocation of treatments in clinical practice. While various fairness metrics have emerged to assess fairness in decision-making processes, a growing focus has been on causality-based fairness concepts due to their capacity to mitigate confounding effects and reason about bias. However, the application of causal fairness notions in evaluating the fairness of clinical decision-making with electronic health record (EHR) data remains an understudied domain. This study aims to address the methodological gap in assessing causal fairness of treatment allocation with electronic health records data. In addition, we investigate the impact of social determinants of health on the assessment of causal fairness of treatment allocation.

- Causal mediation analysis with double machine learning for explaining treatment allocation disparities (ongoing).



(a) Standard fairness model (b) Direct effect (c) Indirect effect (d) Spurious effect

The goal is to integrate causal modeling with machine learning to generate reliable real-world evidence and to build an equitable healthcare system.

CausAI Lab. Summer 2024.

OHDSI
Observational Health Data Sciences and Informatics

Mahidol University
Faculty of Medicine
Siriraj Hospital

Siriraj Informatics and
Data Innovation Center
SiData

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Standing on the shoulders of giants!

🌏 APAC + Global Collaboration 🤝

OMOP Data ETL ▶ **Research Studies** ▶ **Reliable Evidence**

🇹🇭 Thailand

🇰🇷

🇲🇾 🇸🇬

+ APAC

EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

EHDEN Community Manager

Montse Camprubi

Synapse

EHDEN: Vision and Mission

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Vision

The European Health Data & Evidence Network (EHDEN) aspires to be the trusted observational research ecosystem to enable better health decisions, outcomes and care

Mission

Our mission is to provide a new paradigm for the discovery and analysis of health data in Europe, by building a large-scale, federated network of data sources standardised to a common data model

Universities, public bodies and research organisations

Erasmus MC Universitair Medisch Centrum Rotterdam — Academic coordinator

Uppsala Monitoring Centre

universidade de aveiro

NICE National Institute for Health and Care Excellence

Tartu Ülikool 1632 Universitas Tartuensis

University of Oxford

Small & Mid-sized companies

SYNAPSE Research Management Partners

The Hyve

ODYSSEUS DATA SERVICES INC

Other organisations

EPF European Patients Forum

ICHOM

EFPIA & Associated partners

BAYER

Celgene

Pfizer

Lilly

janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson

abbvie

SERVIER

AstraZeneca

EFPIA Lead

SANOFI

ucb

NOVARTIS

CALL PROCESS OVERVIEW

Data sources

Open calls

Tailored for project objectives and sustainability

Grant awarding

Evaluated via a pre-defined set of criteria by the Data source prioritisation committee

Supporting SMEs

Open calls

Focusing on SMEs able to support mapping and sustainability

Training & Certification

SME certification committee prioritises SMEs for training and certification

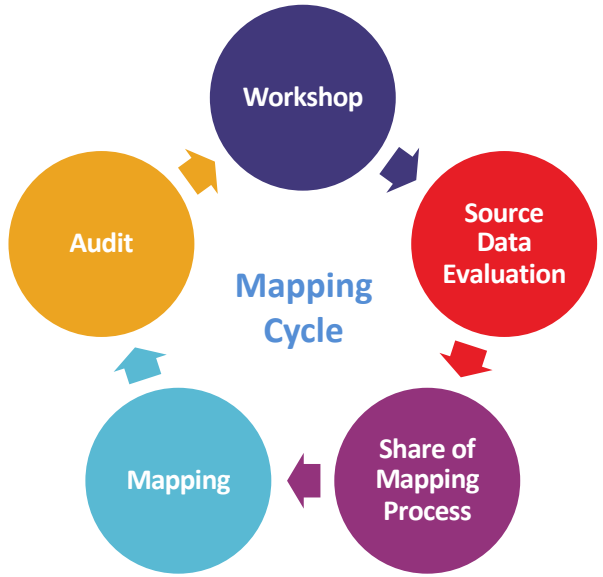
EHDEN Academy

Harmonisation Fund

Data sources can choose the SME from the pool of EHDEN certified SMEs

SMEs are paid via grants from the harmonisation fund

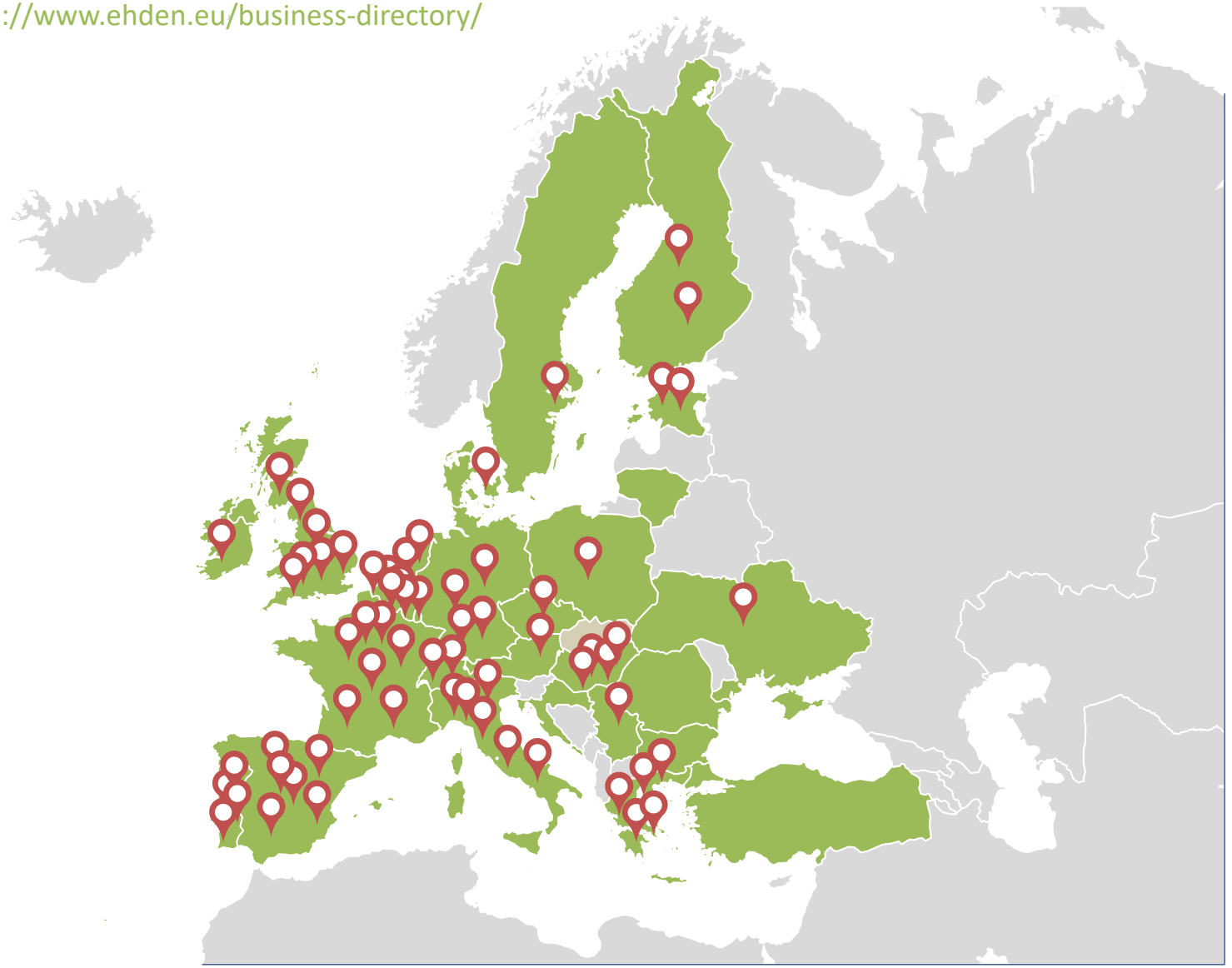
Payments are milestone based



Mapped data sources are encouraged to be active members of the **EHDEN community**, participating in **research studies.**

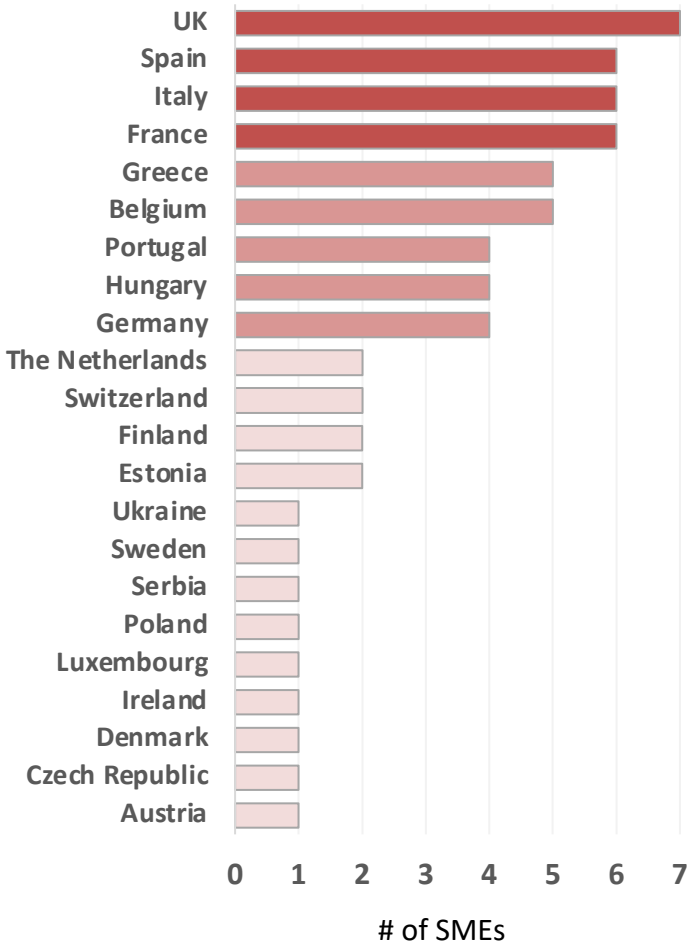
OUR COMMUNITY: SMEs

https://www.ehden.eu/business-directory/



Certified SMEs (n=64)

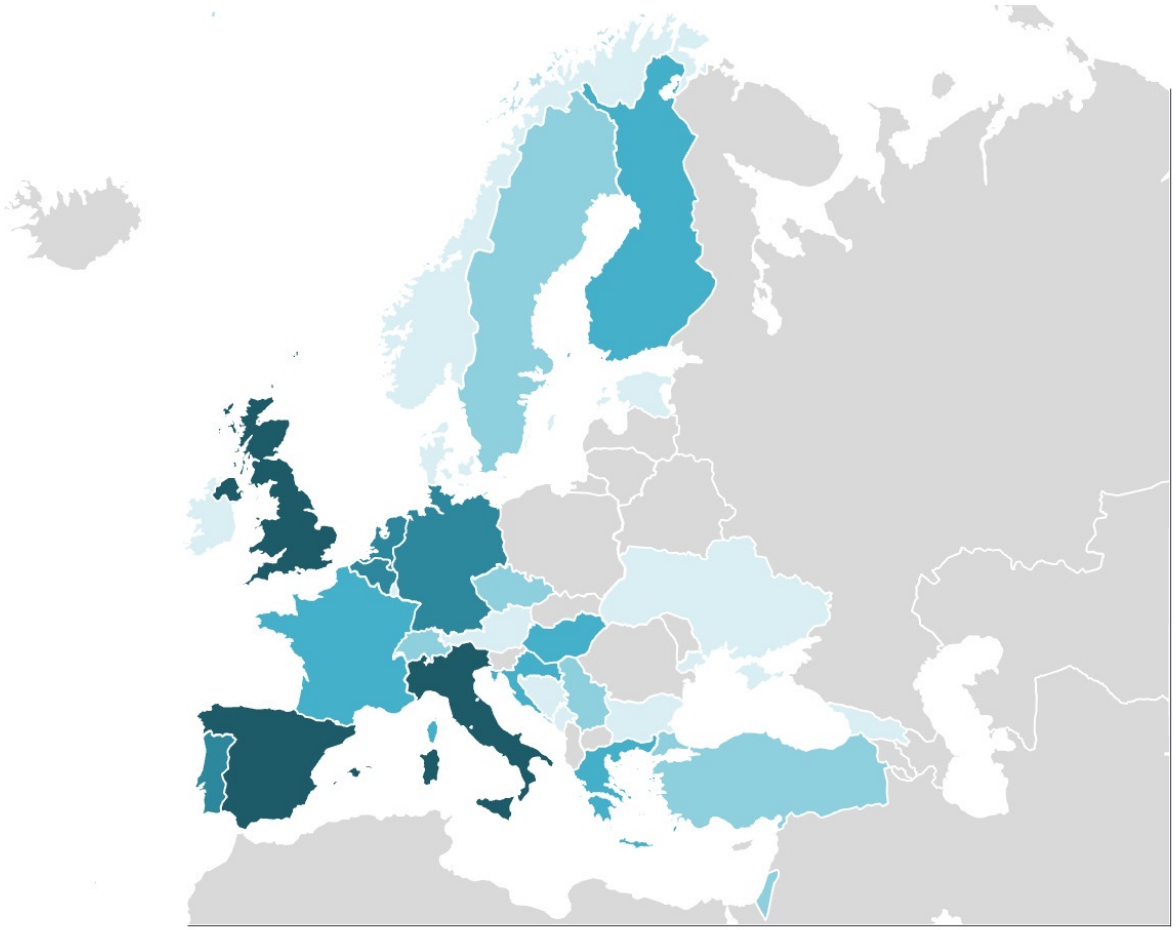
Applications (n=143)



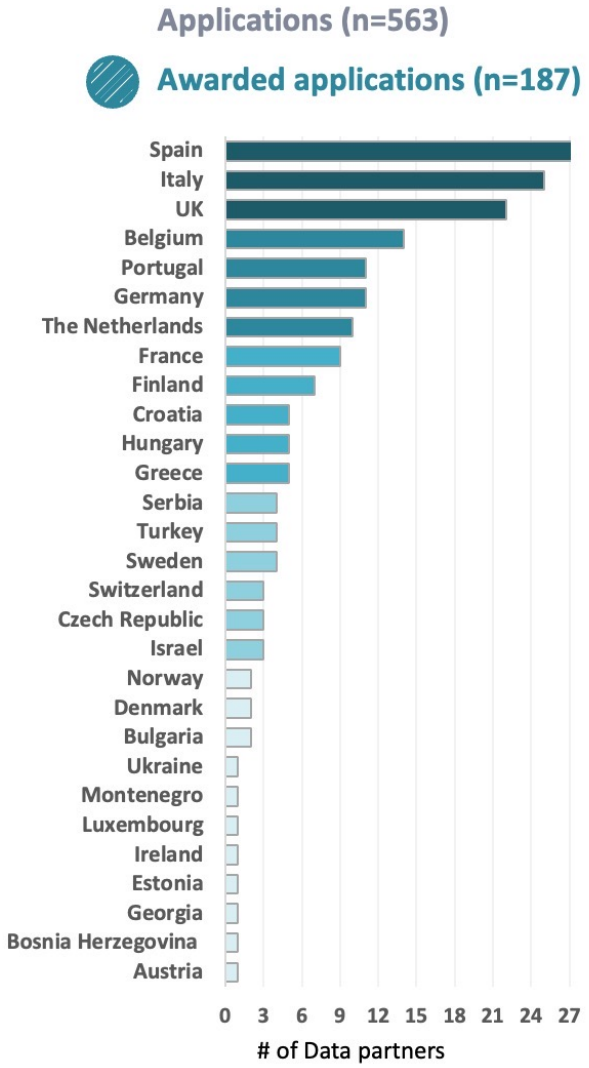
Our Community: SMEs

Our Community: Data Partners

https://www.ehden.eu/datapartners/

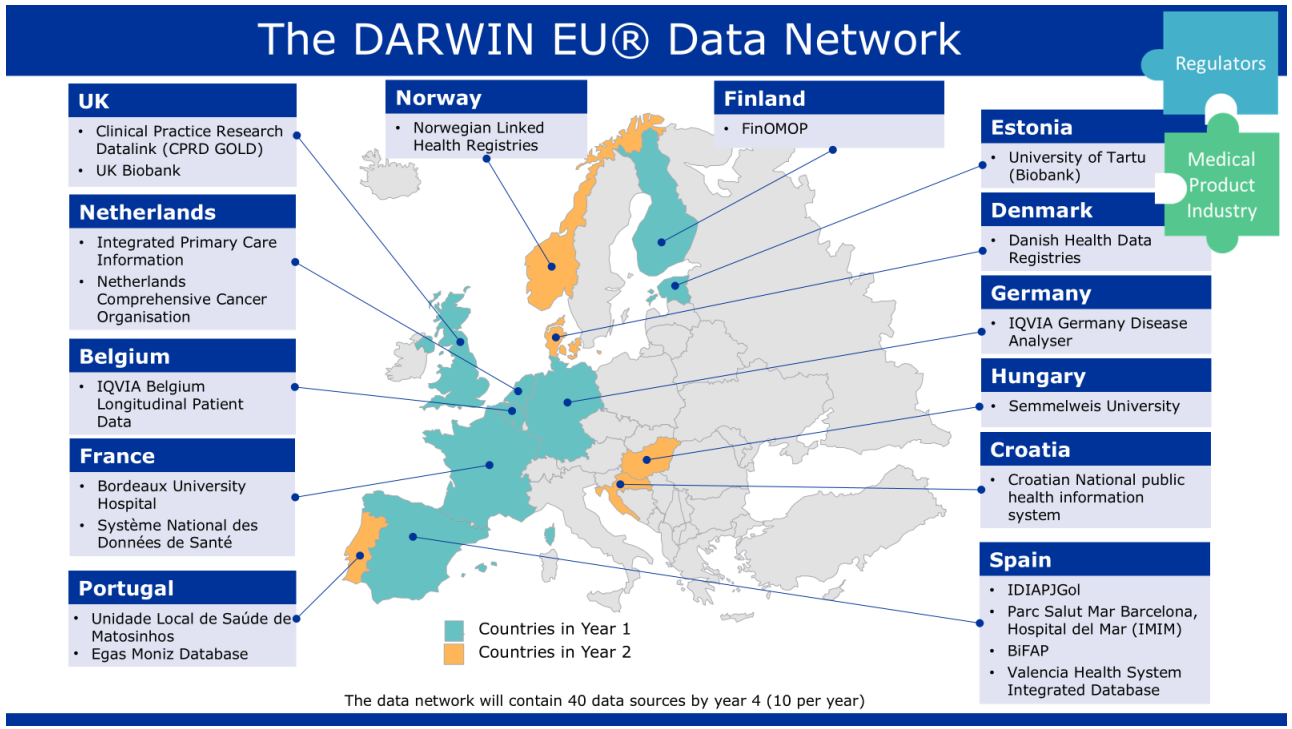


Geographic spread of data partners. The shade of blue indicates the # of data partners in that country (darker = more)



~336 million anonymous records being mapped to OMOP CDM

Our Community: Data Partners Impact



OHDSI National Nodes

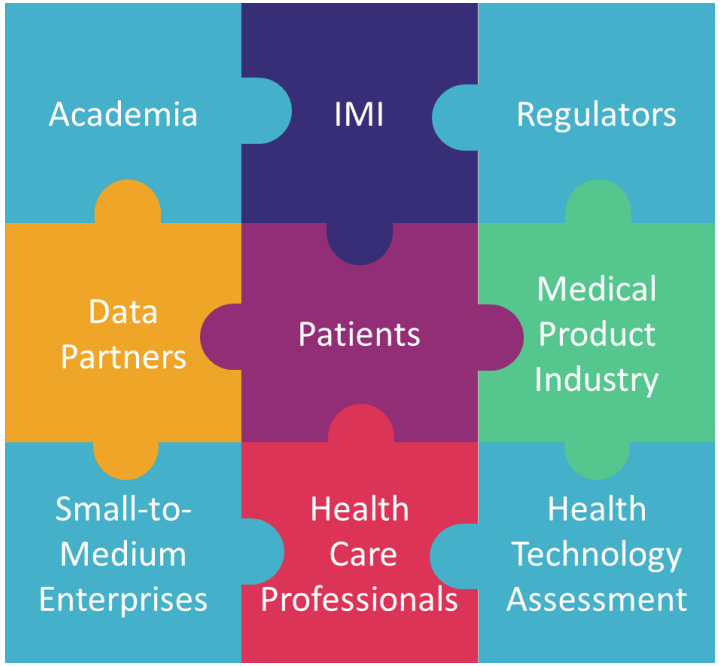
Belgium
Denmark
Estonia
Finland
Germany
Greece
Israel
Italy
Luxembourg
The Netherlands
Norway
Portugal
Spain
United Kingdom

European map representing countries with National OHDSI Nodes

Our Future

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

EHDEN Foundation



THE EHDEN BOOKLET