Scalable Phenotyping for Safety Outcomes Using Electronic Health Record Data

Brian D. Williamson, PhD
Kaiser Permanente Washington Health Research Institute

17—18 November, 2022

Disclaimer

The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

Acknowledgments

Sentinel Advanced Phenotyping Framework and Scalable Natural Language Processing (NLP) Teams

FDA

- Adebola Ajao
- Robert Ball
- Steven Bird
- Sara Karami
- Yong Ma
- Michael Nguyen
- Danijela Stojanovic
- Sanrat Wittayanukorn
- Mingfeng Zhang
- Yueqin Zhao

Harvard Pilgrim

Health Care Institute

- Adee Kennedy
- Judy Maro
- Elizabeth Messenger-Jones
- Kathleen Shattuck
- Mayura Shinde
- Darren Toh

Kaiser Washington

- Maralyssa Bann
- Will Bowers
- David Carrell
- David Cronkite
- James Floyd
- Monica Fujii
- Vina Graham
- Kara Haugen
- Eric Johnson
- Ron Johnson
- Ann Kelley
- Linda Kiel
- Jennifer Nelson
- Arvind Ramaprasan
- Mary Shea
- Brian Williamson
- Jing Zhou

Univ. of Washington

- Patrick Heagerty

Kaiser Northwest

- Andrew Felcher
- Brian Hazlehurst
- Denis Nyongesa
- Daniel Sapp
- Matthew Slaughter

Putnam Data Sciences

- Susan Gruber

Vanderbilt University

- Cosmin (Adi) Bejan
- Michael Matheny
- Joshua Osmanski
- Daniel Park
- Joshua Smith
- Dax Westerman
- Robert Winter

Univ. of Michigan

- Xu Shi

HealthCore

- Kevin Haynes

Duke University

- Keith Marsolo

Brigham and Women’s Hospital, Harvard

- Rishi Desai
- William Feldman
- Shamika More
- Shirley Wang

Univ. of Pennsylvania

- Kevin Johnson

Indiana University

- David Aronoff

Motivation

- Goal: improve safety surveillance using observational data
- Active Risk Identification and Analysis (ARIA) system:

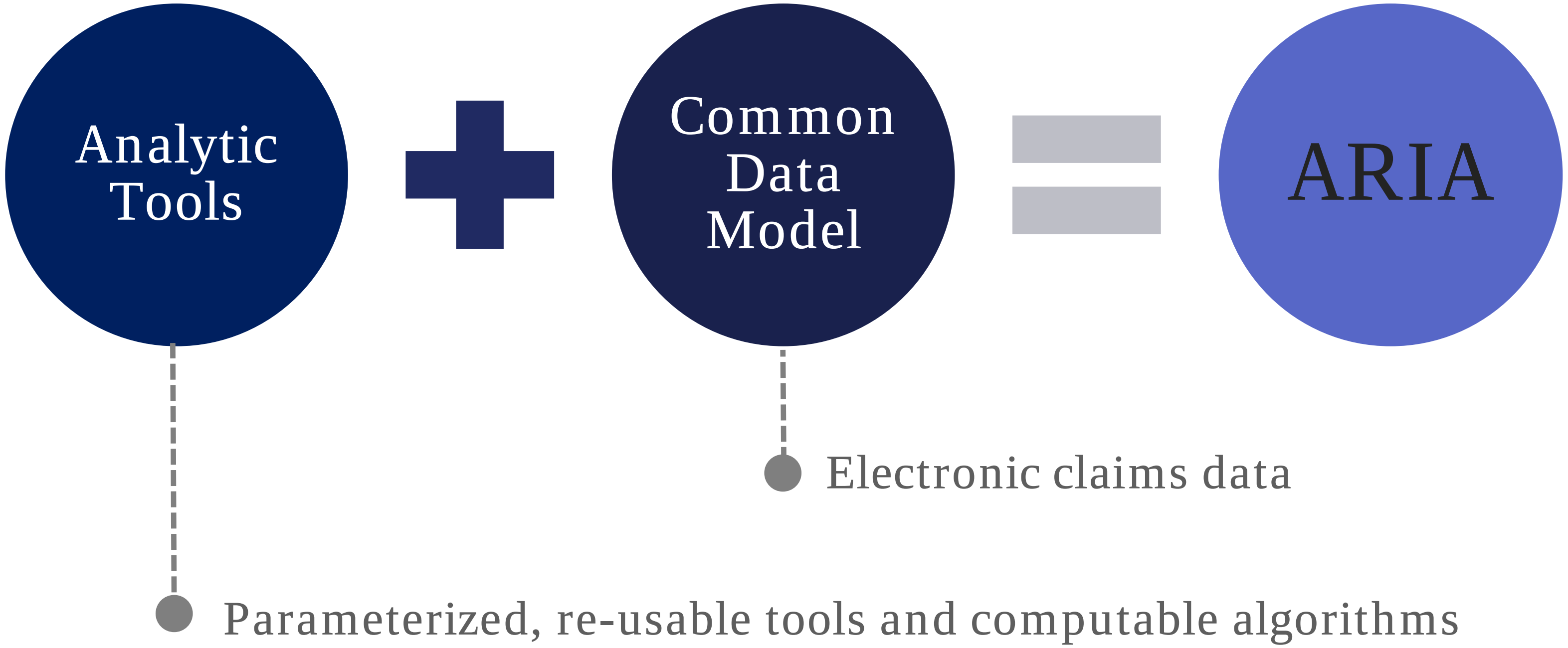
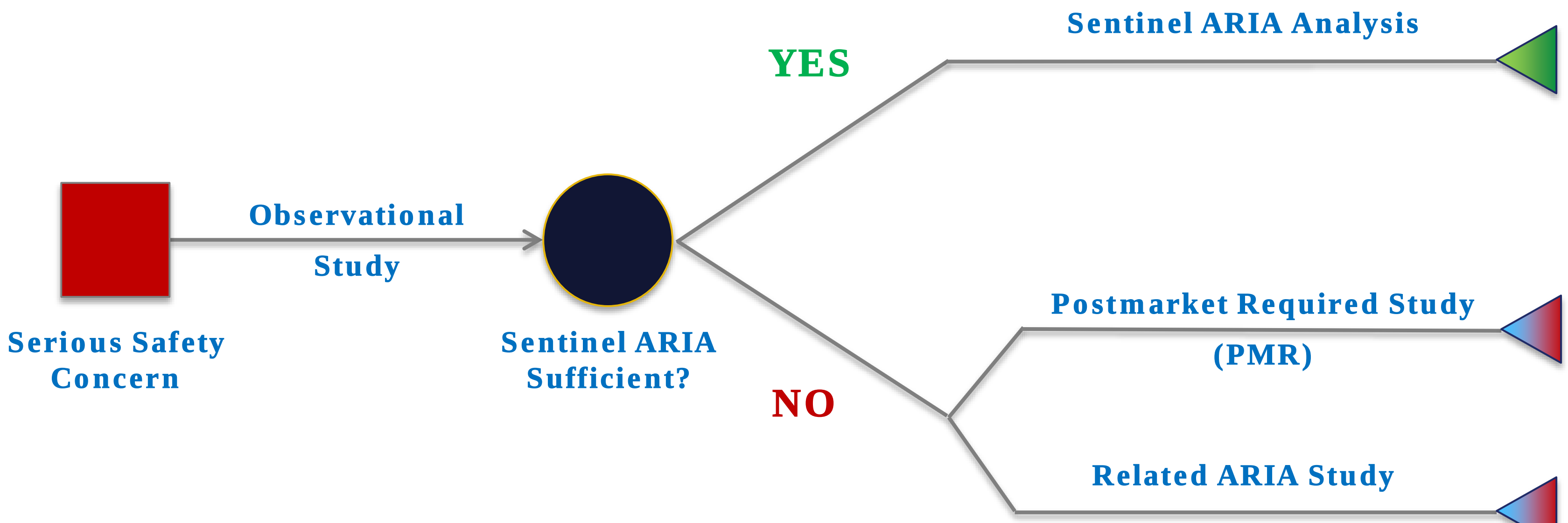


Image courtesy of Michael Nguyen

Motivation

When is the ARIA Process Needed?



ARIA must be considered before a sponsor PMR can be issued

Slide courtesy of Michael Nguyen

ARIA Sufficiency

- ARIA is sufficient when:
  - Outcome & exposure of interest, covariates can be identified from data
  - Methods can assess exposure-related risk *with satisfactory precision*
- 2016—2018: ARIA insufficient for 45 of 89 drug/outcome pairs
  - Inadequate identification of outcome: 38 pairs

Example ARIA sufficient* outcomes:

- GI bleeding
- Heart failure
- Lymphoma
- Major adverse cardiac events (MACE)
- Myocardial infarction
- Multiple sclerosis relapse
- Non-melanoma skin cancer
- Seizure
- Stroke

Example ARIA insufficient* outcomes:

- Acute pancreatitis
- Anaphylaxis
- Drug-induced liver injury
- Fatal MACE
- Malignancies (several)
- Nerve injury
- Suicide or suicidal ideation

*Sufficiency is highly dependent on the scientific question and regulatory context

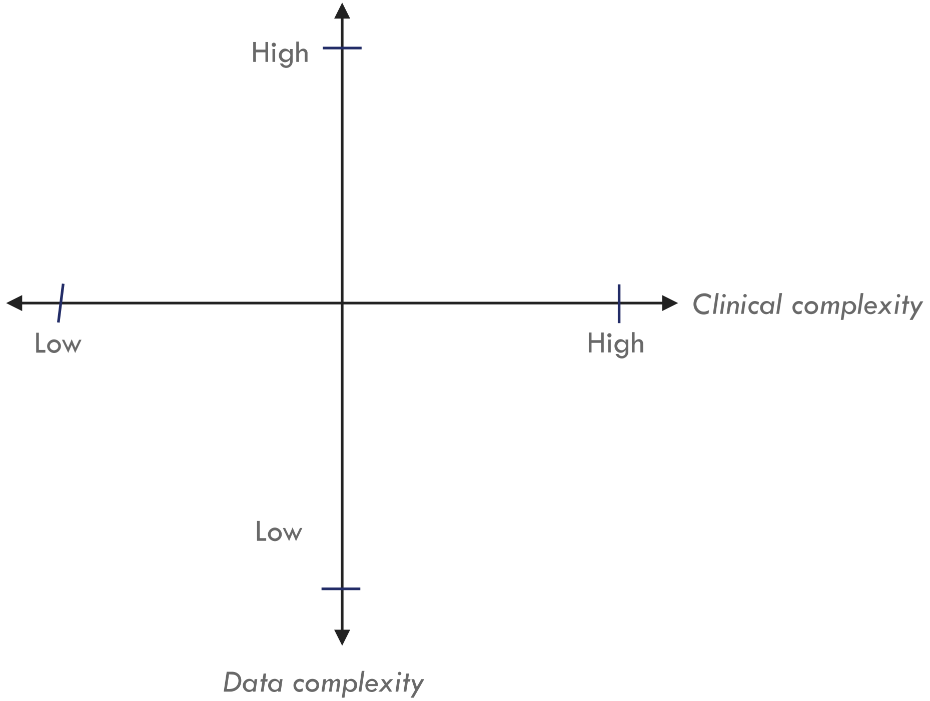
Improving ARIA Sufficiency

- Our focus: outcome identification (phenotyping)
- Key considerations:
  - Gold-standard data creation
  - Feature engineering
  - Model development
  - Model evaluation
- Challenge: traditional chart review expensive (in time and resources)
- Approach: a general framework for scalable phenotyping algorithms
- Case studies: acute pancreatitis, anaphylaxis, severe COVID-19

Assessing Fitness for Purpose

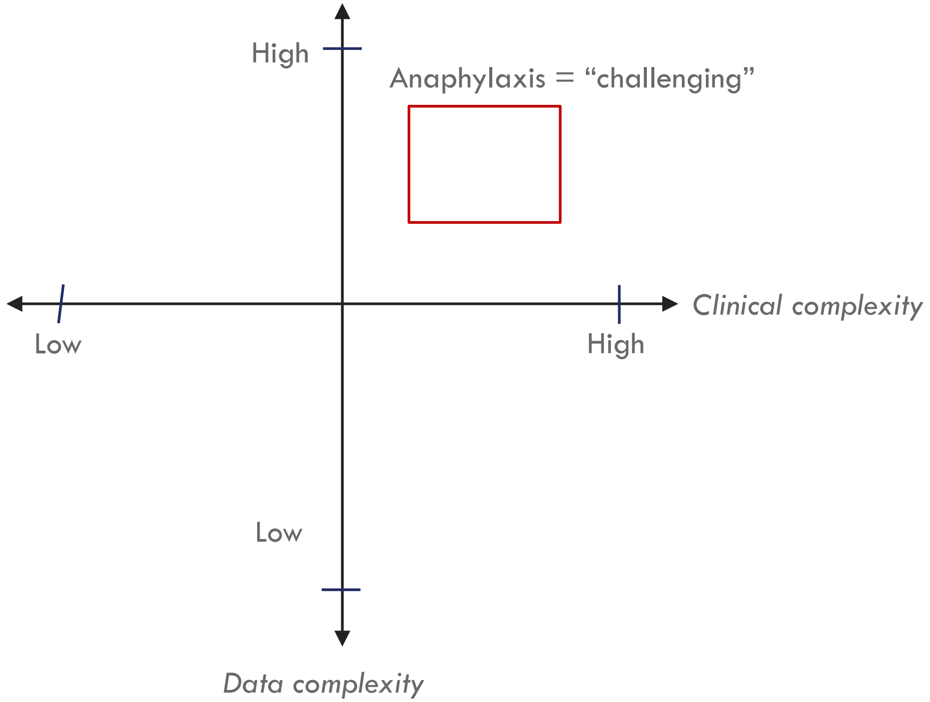
Can a phenotyping effort succeed for the outcome of interest?

- Key considerations:
  - Downstream use of the predicted outcome
  - Ambiguity of the clinical condition (*clinical complexity*)
  - Ambiguity arising from healthcare data *(data complexity)*



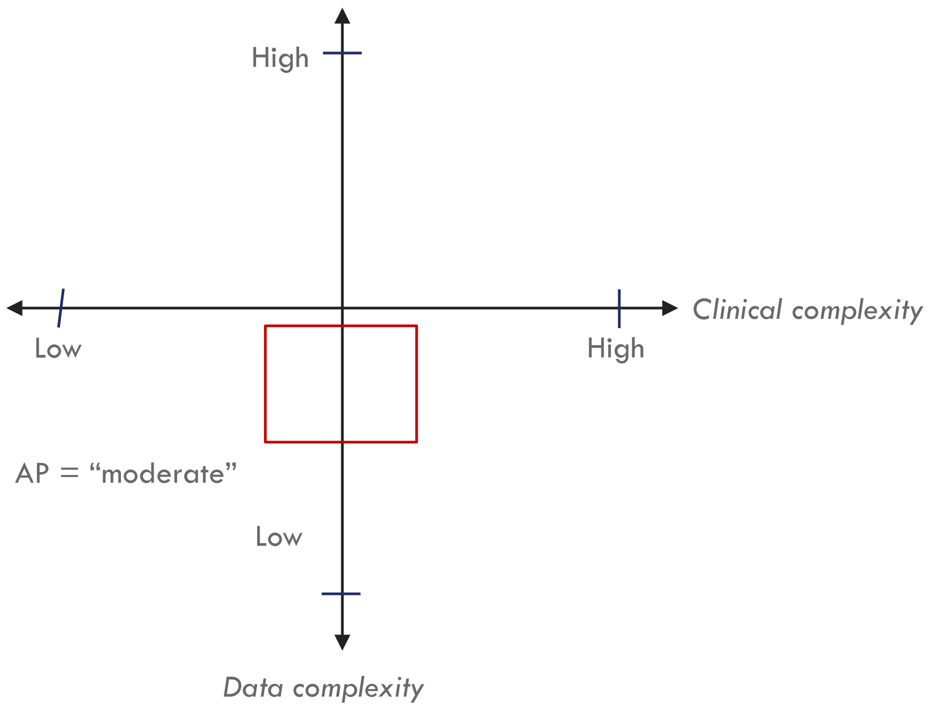
Clinical and Data Complexity: Anaphylaxis

- Clinical complexity:
  - Diagnosis complex, relies on subjective assessment of signs and symptoms
  - 20% of charts at KPWA identified as “difficult” or discordant across two MD reviewers
  - Event often does not occur under direct observation
- Data complexity:
  - Relevant information captured in chart notes



Clinical and Data Complexity: Acute Pancreatitis

- Clinical complexity:
  - Established events criteria include pain, imaging results
- Data complexity:
  - Relevant information captured in ICD-10 diagnosis code and serum lipase laboratory value*



*Floyd et al. (2022). Validation of acute pancreatitis among adults in an integrated healthcare system. *Epidemiology*.

Gold-standard Data Creation

- Goal: identify true cases and controls for algorithm training
- Challenge: limited resources (time, personnel)
- Best practices:
  - Chart abstraction guidelines reflect clinical diagnostic criteria
  - Clinician oversight of chart abstractors
  - Dual review of samples to assess replicability
  - Use K-fold cross-validation
- Future work:
  - Can NLP-assisted methods reduce review time?
  - Can surrogate outcomes be incorporated in model training?

Feature Engineering

- Goal: identify useful features from the EHR
- Challenges:
  - Limited resources (time, personnel)
  - Local vocabulary reduces generalizability
- Best practices:
  - Incorporate clinical and domain knowledge
  - Engineer many features
  - Consider manual and automated approaches
- Future work:
  - Can automated approaches capture all relevant relationships?
  - Automated approaches with acute outcomes?

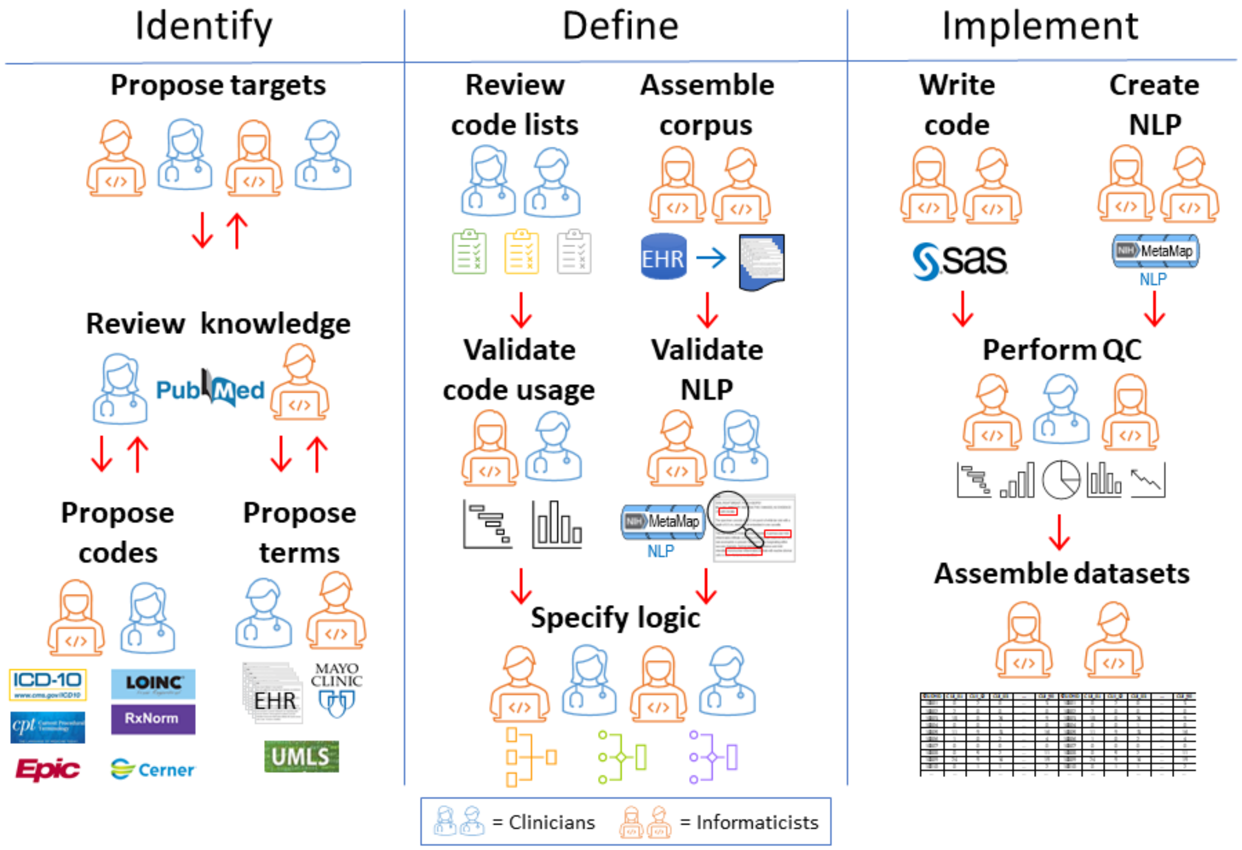


Image courtesy of David Carrell

Model Development and Evaluation

- Goal: construct a useful prediction model
- Challenges:
  - Performance constrained by clinical and data complexity
  - Evaluation requires gold-standard outcomes
- Best practices:
  - Incorporate domain knowledge
  - Consider a large, diverse set of candidate prediction algorithms (including machine learning)
  - Evaluate performance using K-fold cross-validation
  - Consider many performance metrics
  - Final algorithm choice guided by downstream performance, replicability, generalizability
- Future work:
  - Under what conditions can models be transported to new settings without additional gold-standard evaluation?

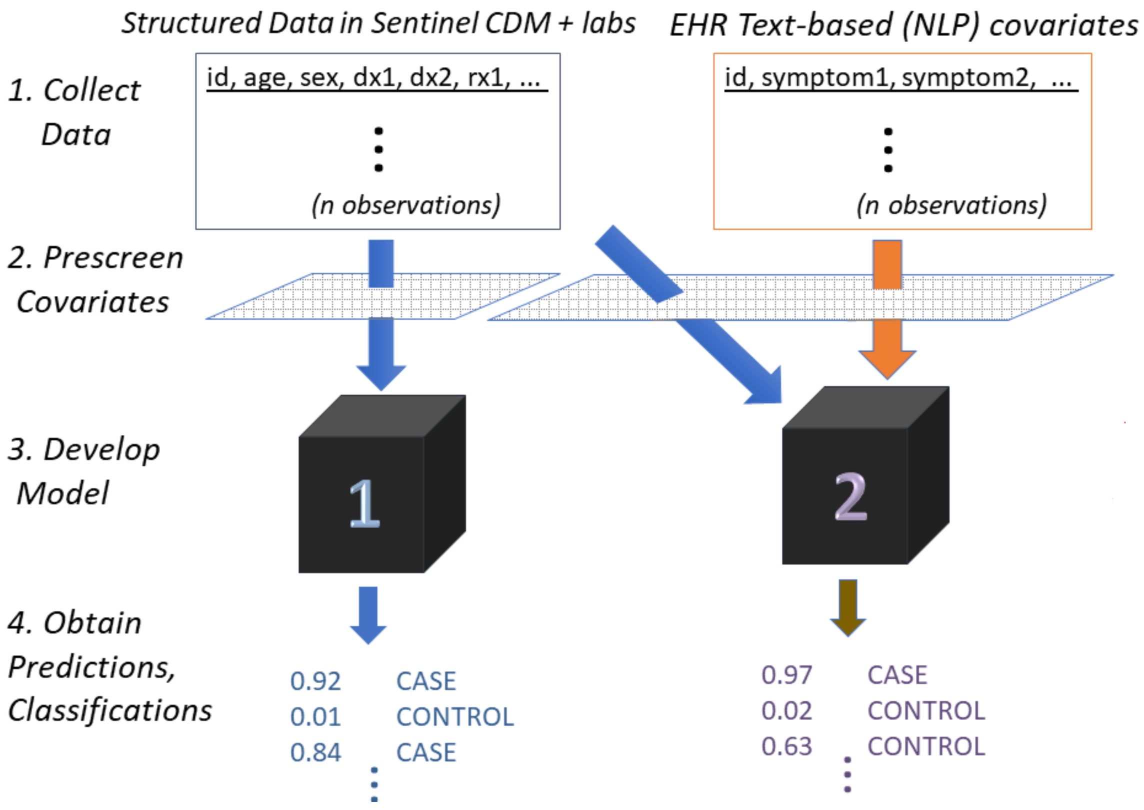
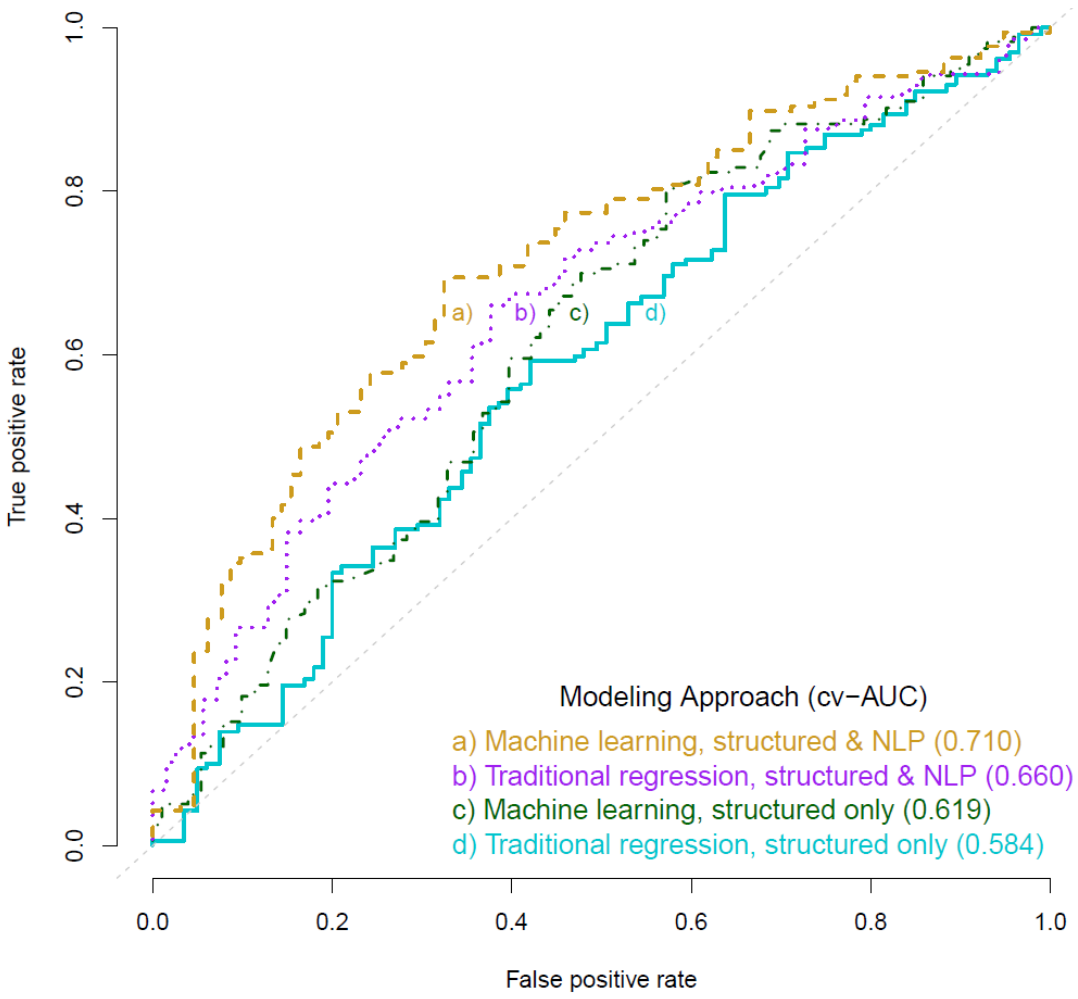


Image courtesy of Susan Gruber

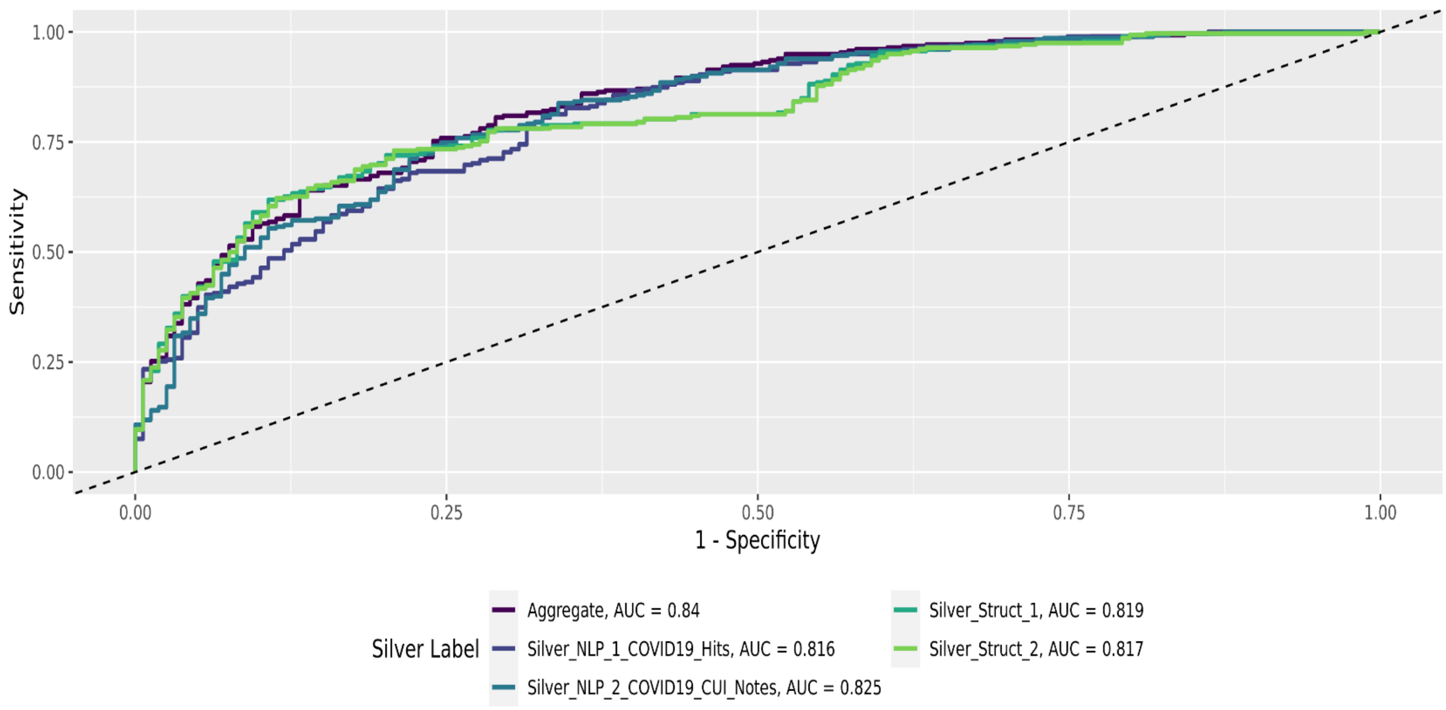
Selected Results

Predicting Anaphylaxis



Carrell et al., *American Journal of Epidemiology (accepted)*

Predicting Symptomatic COVID-19



Closing Thoughts

All aspects of phenotyping can be improved by

- Considering data and clinical complexity
- Incorporating domain knowledge
- Using a wide variety of tools (including machine learning), with proper evaluation

Our framework provides guidelines for fully incorporating EHR data into phenotyping analyses

Sentinel

Thank You

Brian Williamson

Assistant Investigator, Biostatistics Division

Kaiser Permanente Washington Health Research Institute

Contact: brian.d.williamson@kp.org