Defining/developing CDEs for use in AI/ML Applications for Clinical Research with Electronic Health Record Data

Advancing the Use and Development of Common Data Elements in Research Workshop

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Outline

- Example project w/ artificial intelligence (AI)/machine learning (ML) for clinical research
    - Treatment response in rheumatoid arthritis (RA)
- Application of common data elements (CDE)
    - Challenges
    - Potential solutions
    - Future directions

Rheumatoid arthritis (RA)

- Most common autoimmune inflammatory joint disease
- Numerous potent immunomodulatory treatments available
- Treatment in 2024 remains a trial-and-error approach
  - Joint destruction & disability
  - Side effects from ineffective therapies

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RA

Source: ACP Medicine © 2004 WebMD Inc.

AI/ML to study treatment response in RA

- RA randomized controlled trials (RCTs)
  - Gold standard for treatment effectiveness
- RCTs powered to answer specific set of clinical question(s)
  - Not powered for subgroup analyses
- Observational data w/ large population → potential to study RCT subgroup findings
  - Limited by confounding

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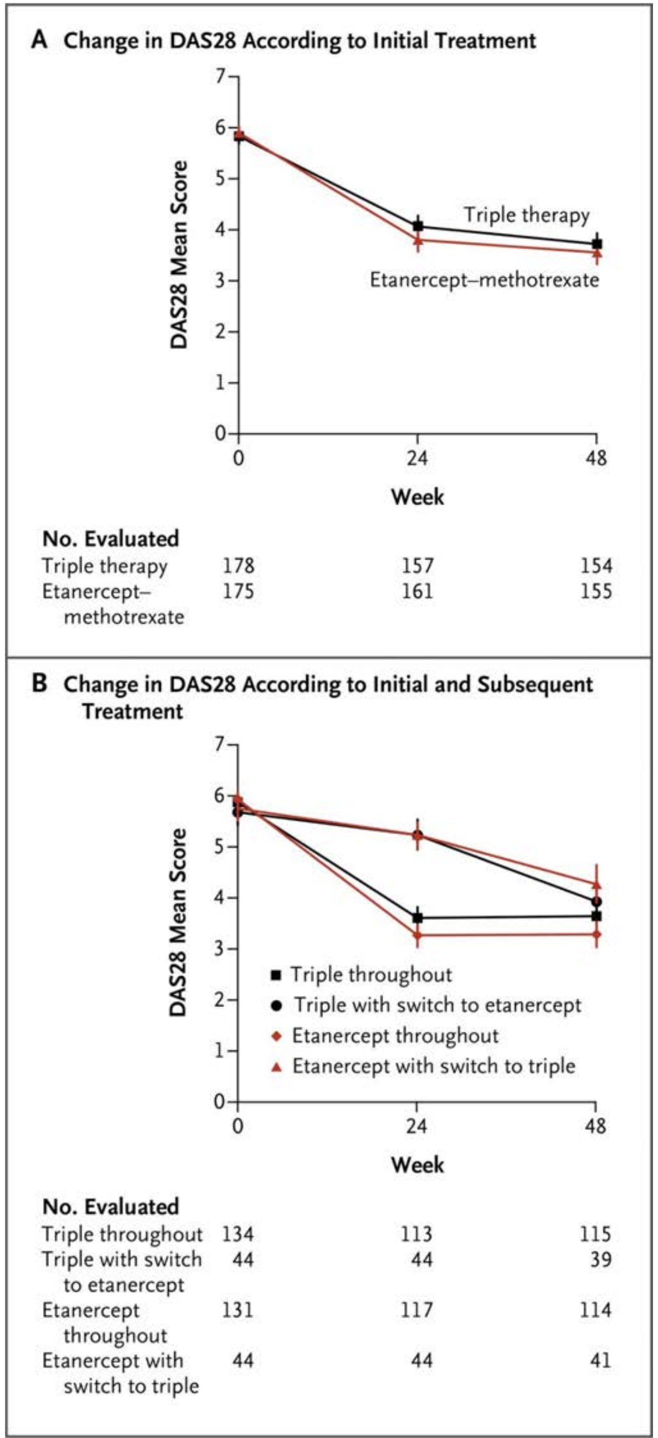
Therapies for active RA after methotrexate failure trial (RACAT)

- Findings: Triple therapy non-inferior to tumor necrosis factor (TNFi)

- RA treatment response defined by disease activity, e.g., DAS28

- Subgroup analyses
    - Same % switched at 24 weeks
    - Significant improvement in both groups
    - *Suggests some pts may have benefitted from one or the other therapy at outset*

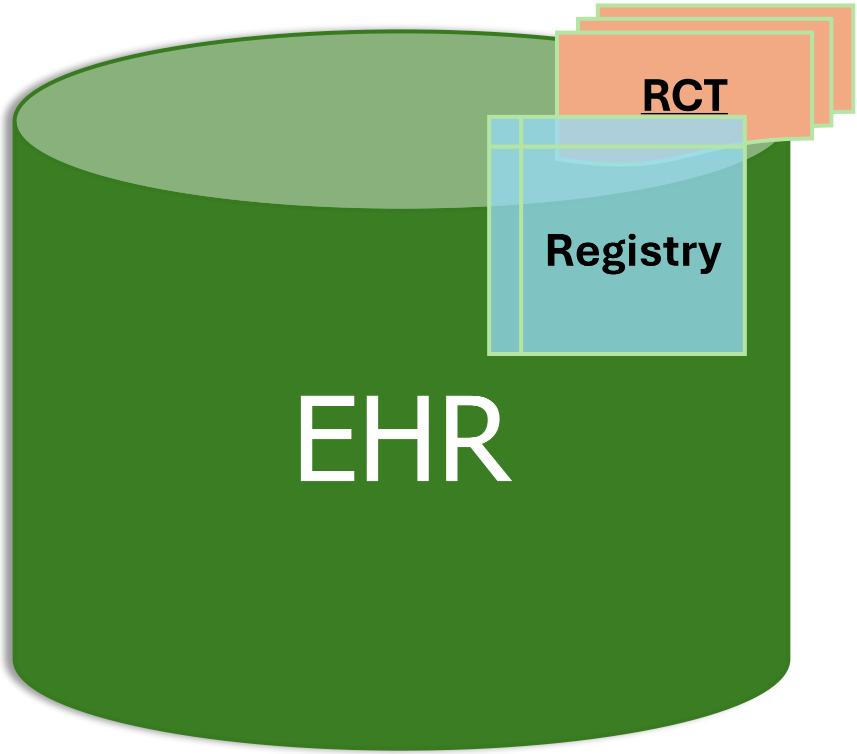


O'Dell et al., NEJM 2013

Data sources, data types, and CDEs

- Test causal inference & machine learning (ML) to leverage observational data to study drug effectiveness using RCTs as the gold standard

- Electronic health records (EHR)
  - Veteran Affairs (VA), ~22 million
  - Mass General Brigham (MGB), ~14 million
- RCT
  - RACAT @ VA
- Registry
  - VARA
  - BRASS



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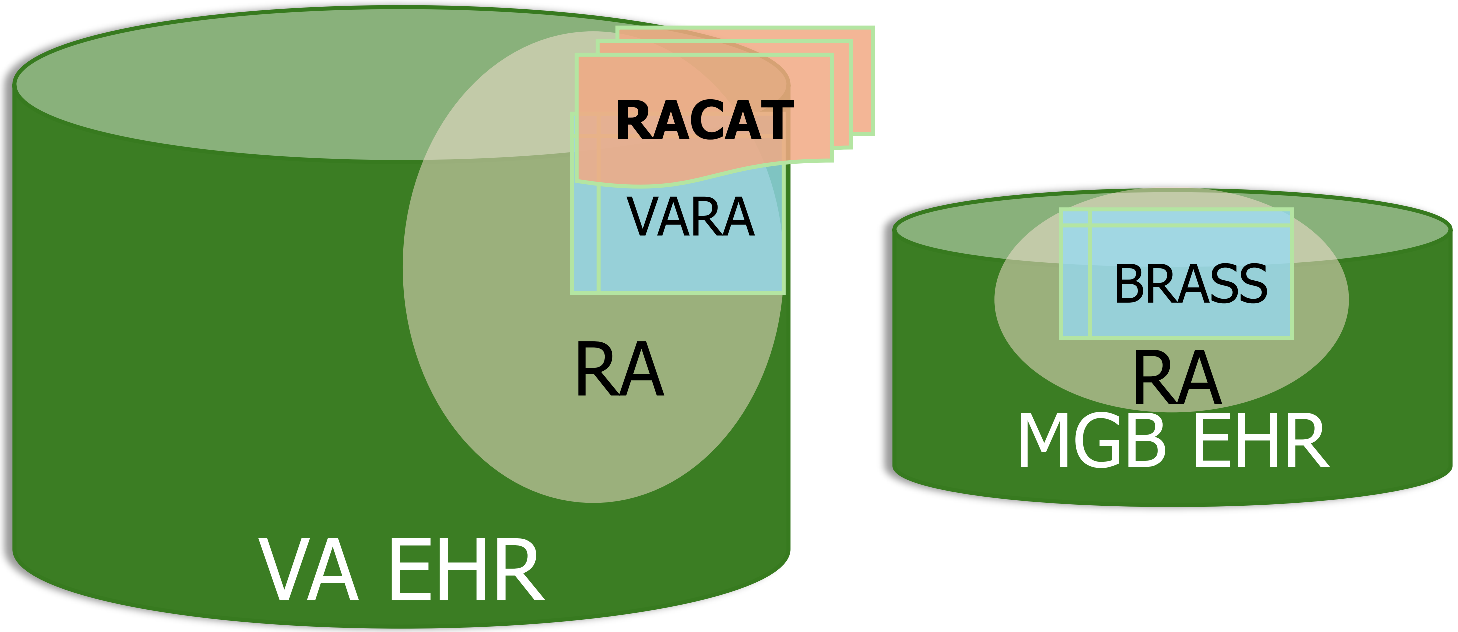
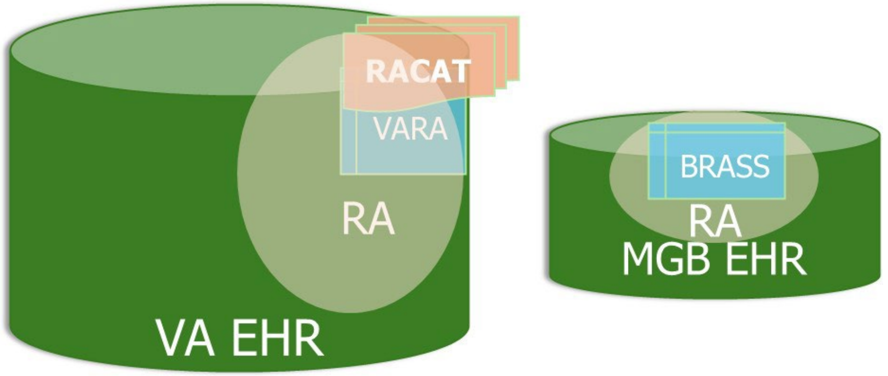
Data sources, data types, and CDEs



BRASS= Brigham Rheumatoid Arthritis Sequential Study
EHR= electronic health record
MGB= Mass General Brigham
VARA= Veteran Affairs Rheumatoid Arthritis registry
VA= Veteran Affairs

CDE related challenges



- Defining RA in two EHRs
  - Positive predictive value of ≥1 RA code 20%
  - Published ML pipeline for phenotyping
  - Mapping equivalent features in two different EHR systems
    - Medications, e.g., TNFi
- Imputing RA disease activity, no code or standard with EHR data
  - Train/co-train, port, validate
  - Harmonizing features
    - "RA" code
    - Map health system specific EHR codes to standardized
    - NLP for disease activity
      - RA-specific, e.g., synovitis

Liao et al., Arth Care & Res 2010;
Carroll et al., JAMIA 2012

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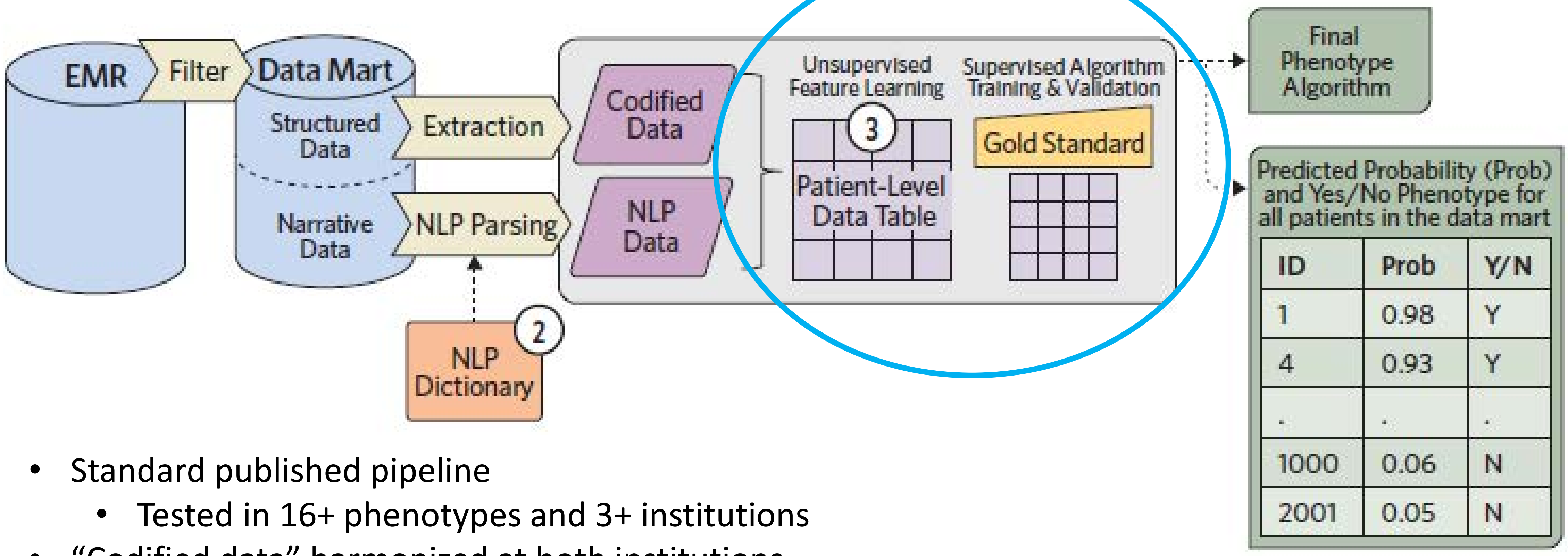
Defining RA in 2 EHRs

Semi-supervised phenotyping



- Standard published pipeline
  - Tested in 16+ phenotypes and 3+ institutions
- “Codified data” harmonized at both institutions
- NLP data mapped to Unified Medical Language System (UMLS) concepts, NIH NLM

Zhang, Cai, Yu, et al., Nat Protocol 2019

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Common CDE building blocks

- "Proto-CDEs" to find equivalent features across EHRs
  - Data extracted w/ NLP → UMLS, concept unique identifiers (CUIs)
  - Structured ICD EHR data → PheWAS Code (Phecode)
    - Starting definition for "RA code"
    - Modification use Phecode as reference
  - Medications
    - RxNorm, UMLS
    - National Drug Code (NDC), US FDA
- Challenge: who was prescribed a TNFi?
  - RxNorm + National Drug Code (NDC) for all 5 TNFi's
    - Roll-up both codes to create a "TNFi" category
    - Subcategory: generic + trade name by biologic

Denny et al., Nat Biotech 2013

Algorithm to impute RA disease activity

- Challenge: Identify relevant features for disease activity
  - Features available in VA and MGB EHRs
  - No codes for RA disease activity

- Create a knowledge network/graph
  - Identify entities, e.g., "phenotypes" defined by groups of ICD codes (Phecodes)
  - Quantify relationship of entities to each other, i.e., embedding vectors
  - Apply large language models (LLMs)
  - Co-trained with EHR data from MGB & VA
    - Performed in collaboration with Dept of Energy

Hong et al., NPG Digit Med 2021;
Mikolov, et al. arxiv 2013,

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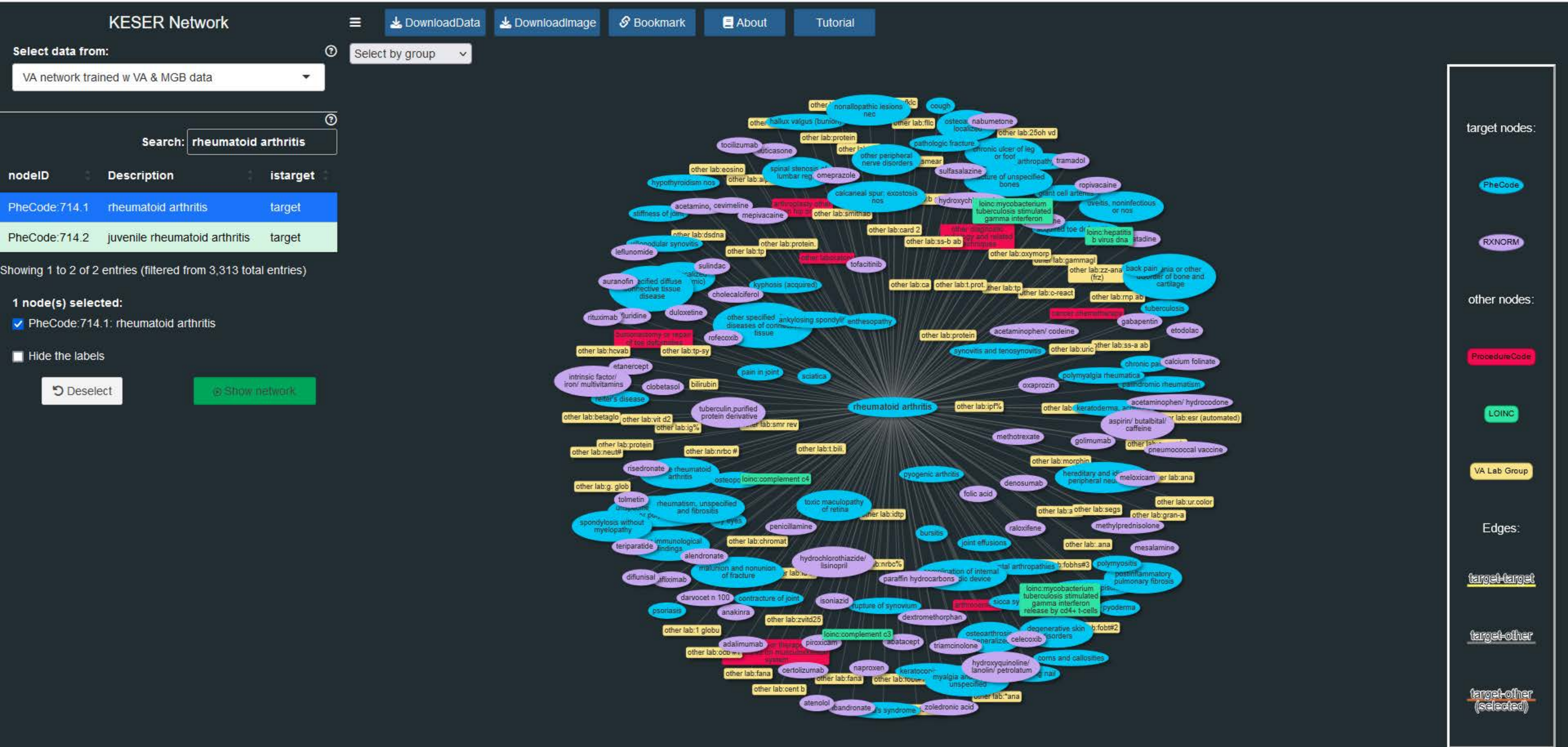
Potential solution: LLM driven knowledge networks/graphs



Potential solution: LLM driven knowledge networks/graphs

KESER Network

DownloadData | DownloadImage | Bookmark | About | Tutorial

Select data from:

VA network trained w VA & MGB data

Select by group

Search: rheumatoid arthritis

nodeID	Description	istarget
PheCode:714.1	rheumatoid arthritis	target
PheCode:714.2	juvenile rheumatoid arthritis	target

Showing 1 to 2 of 2 entries (filtered from 3,313 total entries)

1 node(s) selected:

PheCode:714.1: rheumatoid arthritis

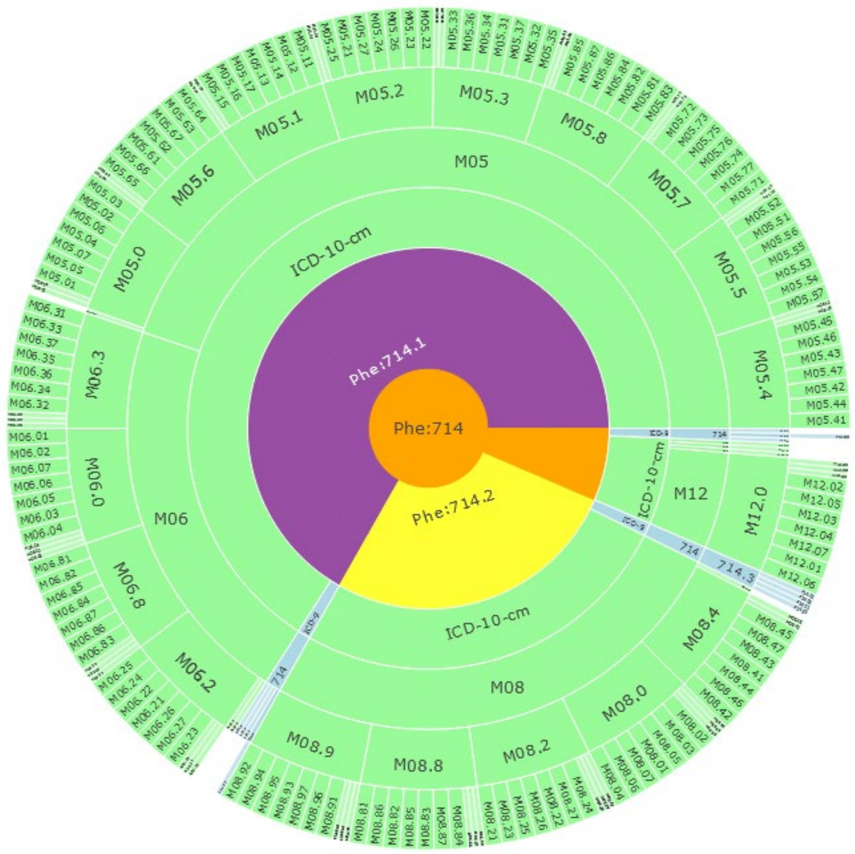
Hide the labels

Deselect

Show network

Application: **universe of codified features, “computed CDEs” for disease activity algorithm**

VA Centralized Interactive Phenomics Resource (CIPHER)



CIPHER
CENTRALIZED INTERACTIVE PHENOMICS RESOURCE

- Standardize meta-data
- Visualization of data
- Real-time comparison of “computable” phenotype definitions by components
- Tools to facilitate use of computable phenotypes
  - ICD hierarchy tool

Kirby et al., JAMIA 2016;
Honerlaw et al., JAMIA 2024 accepted

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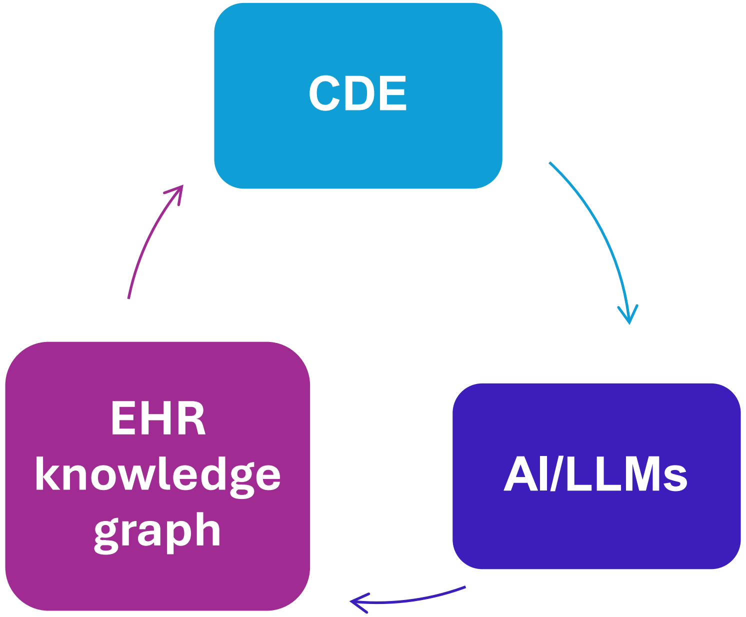
A clinical investigator's CDE wish list

- Resource for knowledge sources standardizing health care data
  - NIH, ONC, FDA & gov't agencies
- Consensus for core set(s) of CDEs for clinical research, "code book"
  - ICD→Phecodes
  - Groupings for LOINC, RxNorm + NDC
- Interactive, moderated platform for sharing CDEs
  - CDE easily findable, comparable to another study
  - Provenance, initial use case(s)

Future directions & thoughts

- Diversity of CDEs for clinical research
  - Meta-data for CDEs
  - Clinical trial vs large-scale EHR study
    - Flexibility on mandating CDE
    - Applicability varies



- CDE evolve w/ technologies
  - Input to ML algorithms manual ICD lists → ICD list from knowledge network ("computed CDEs")

- CDE foundation to develop and benchmark new AI methods

Thank you

TRANSLATIONAL DATA SCIENCE
CELEHS
CENTER FOR A LEARNING HEALTH SYSTEM

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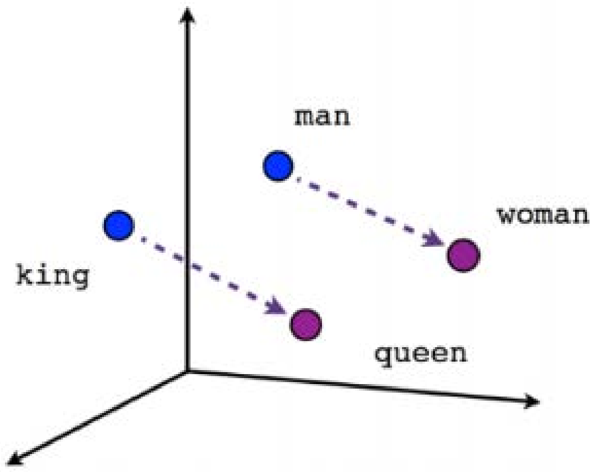
NIAMS
P30 AR072577
R21 AR078339
R01 AR080193

FDA
U01 FD007929
mPI: Bourgeois, Cai

Creating an EHR clinical knowledge graph

using methods from language models



- Create a co-occurrence matrix
  - Relationship of all structured data to each other
    - ICD, electronic prescriptions, lab codes
  - 17 million Veterans
    - Collaboration with Dept of Energy and use of supercomputers
- Transform concept relationships to numbers
  - Create embedding vectors based on information from relationships
  - Vectors encode the "meaning" of the codes
- Quantify relationship of concepts to each with embedding vectors

Hong et al., NPG Digit Med 2021;
Mikolov, et al. arxiv 2013,
https://arxiv.org/pdf/1310.4546

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