Ontologizing Health Systems at Scale: Making Translational Discovery a Reality

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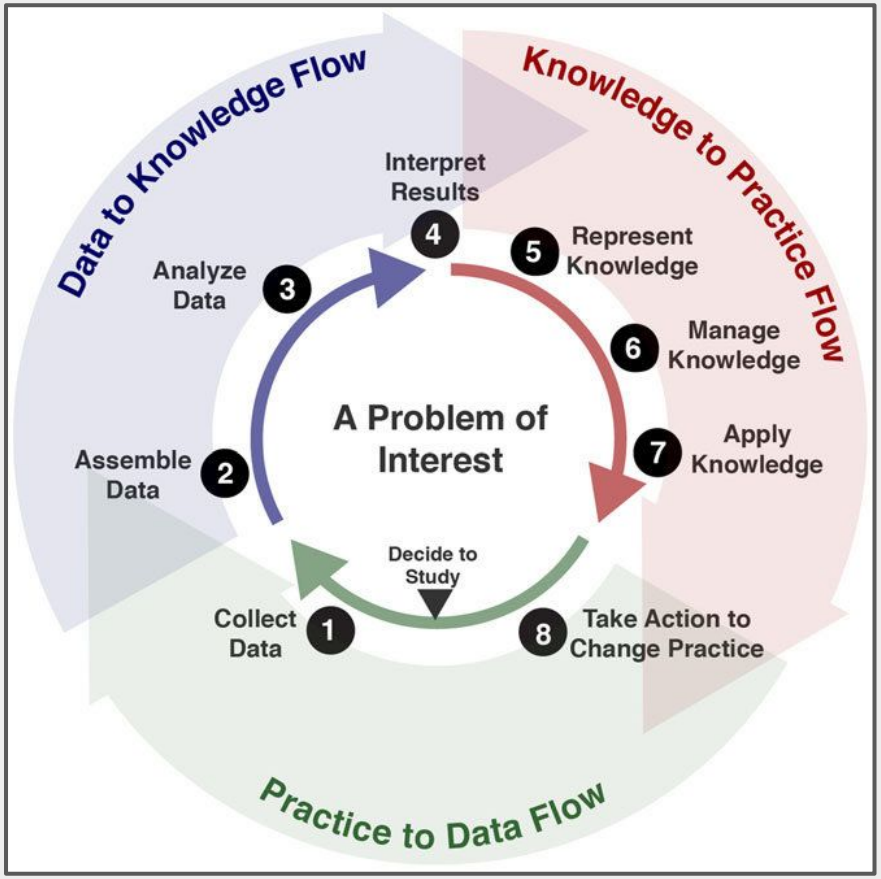
OHDSI Community Call - September 2020

University of Colorado
Anschutz Medical Campus

98% of Hospitals Use Electronic Health Records

"...now is the time to create smarter healthcare systems in which the best treatment decisions are computationally learned from electronic health record data by deep-learning methodologies"[1]



[1]Norgeot et al. *Nat Med*. 2019; Flynn et al. *Knowledge Grid*. 2018

Creating Smarter Healthcare Systems

Current research use of medical record data enables

- Automatic triage of medical conditions
- Prediction of pertinent patient risk factors
- Identification of emerging or important pathogens

Rajkomar, Dean, Kohane *N Engl J Med* 2019

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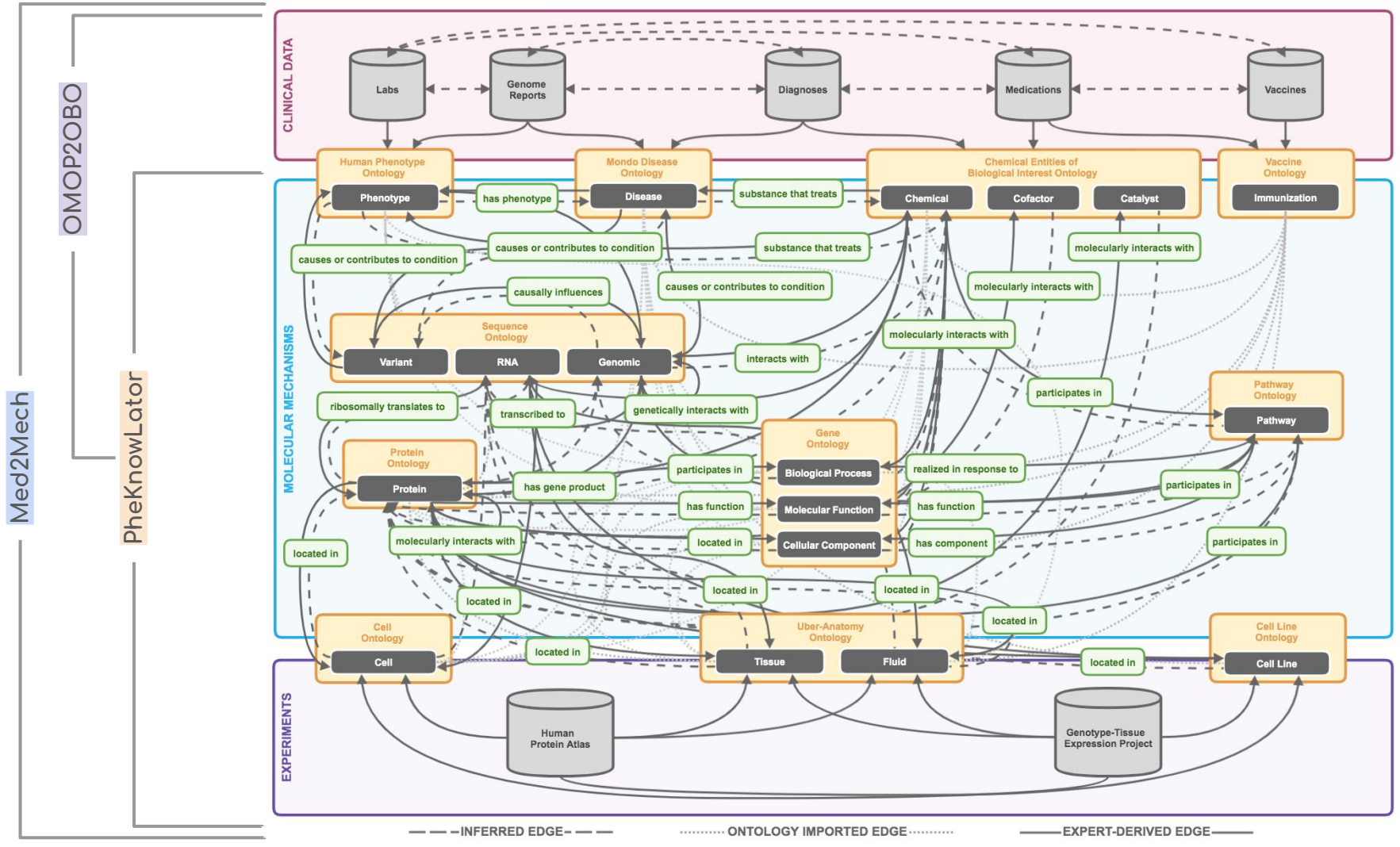
- Prediction of pertinent patient risk factors
- Identification of emerging or important pathogens

Connecting medical record data with biomedical knowledge could enable

- Integration of patient -omics data
- Identification of causal biomarkers
- Mechanistic explanations for specific patient characteristics

Rajkomar, Dean, Kohane *N Engl J Med* 2019


Med2Mech
OMOP2OBO
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Protein Ontology
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has gene product
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Biological Process
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Molecular Function
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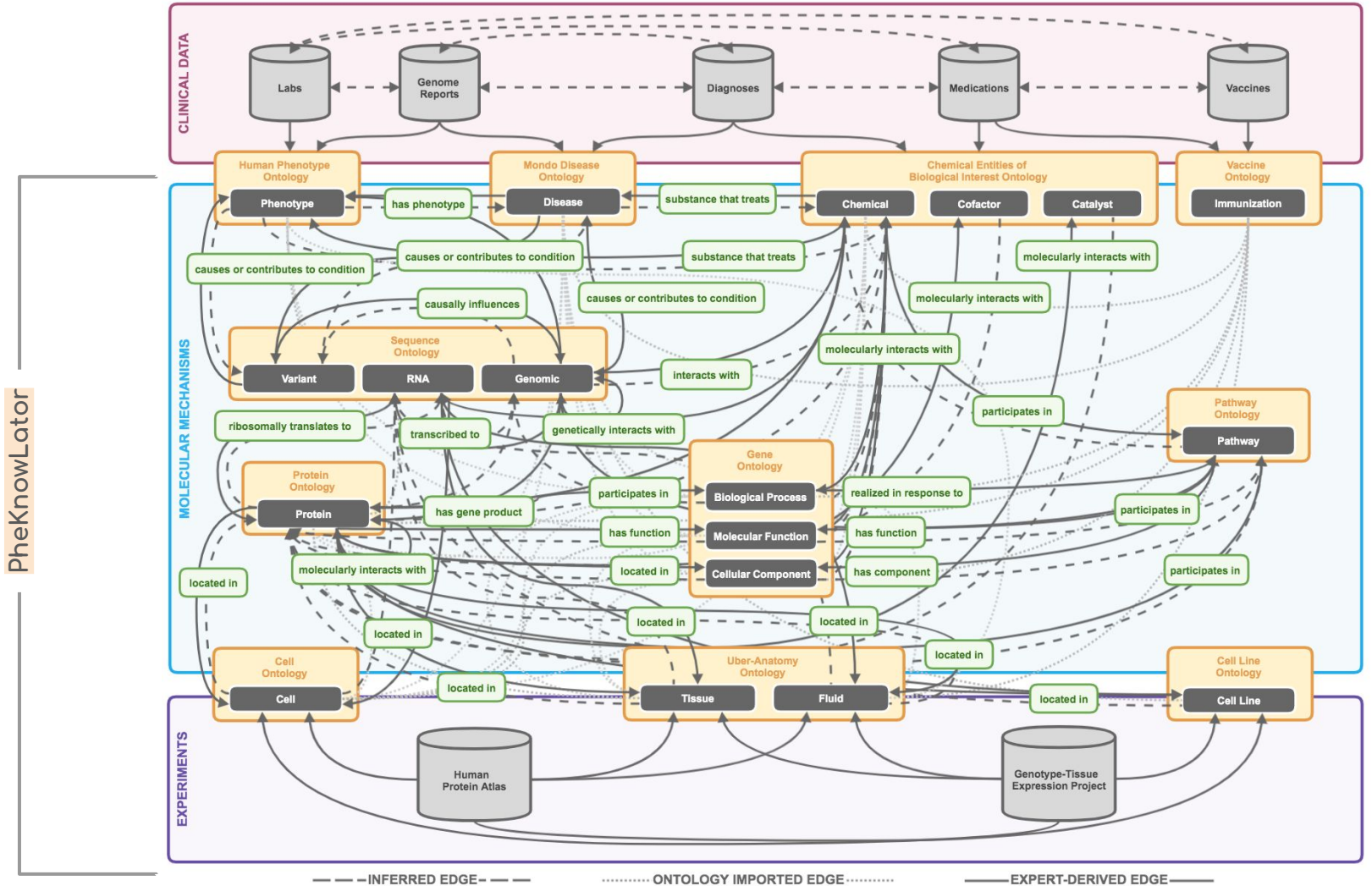
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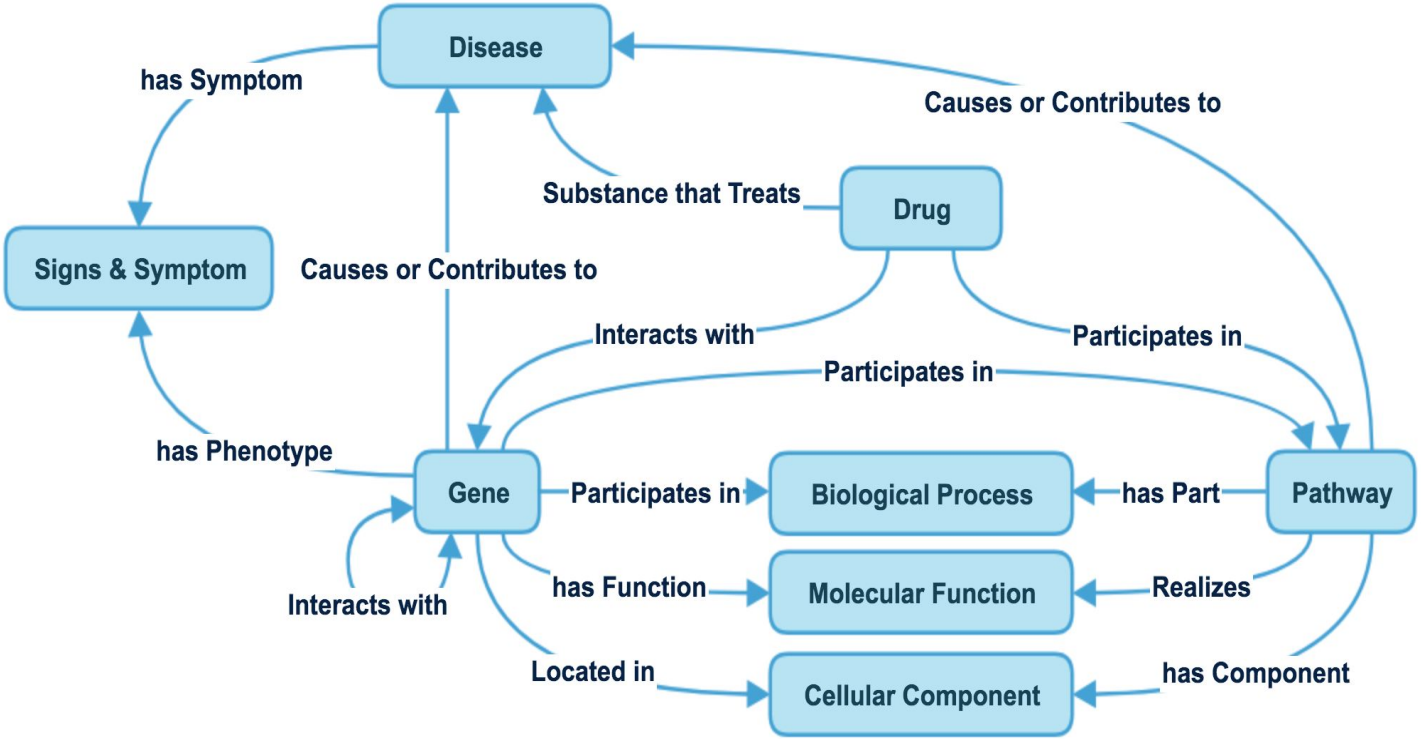
BARRIER 1

Medical Records are not Connected to Biomedical Knowledge

Knowledge Graphs



Knowledge Graphs Challenges

Design Challenges

- Multiple approaches to modeling biomedical knowledge[1-3]
- Decisions impact downstream learning

Implementation Challenges

- Methods have varying functional, logical, and semantic consequences[1]
- Semantic Web standard is expressive, but unwieldy and of uncertain benefit[2]

PheKnowLator: A Python framework to build large-scale heterogeneous biomedical knowledge graphs

https://github.com/callahantiff/PheKnowLator

[1]Hunter *EPJ Data Science* 2017; [2]Callahan et al *Ann Rev Biomed Data Sci* 2020; [3]Ji et al *arXiv* 2020

Human Disease Mechanisms

Ontologies

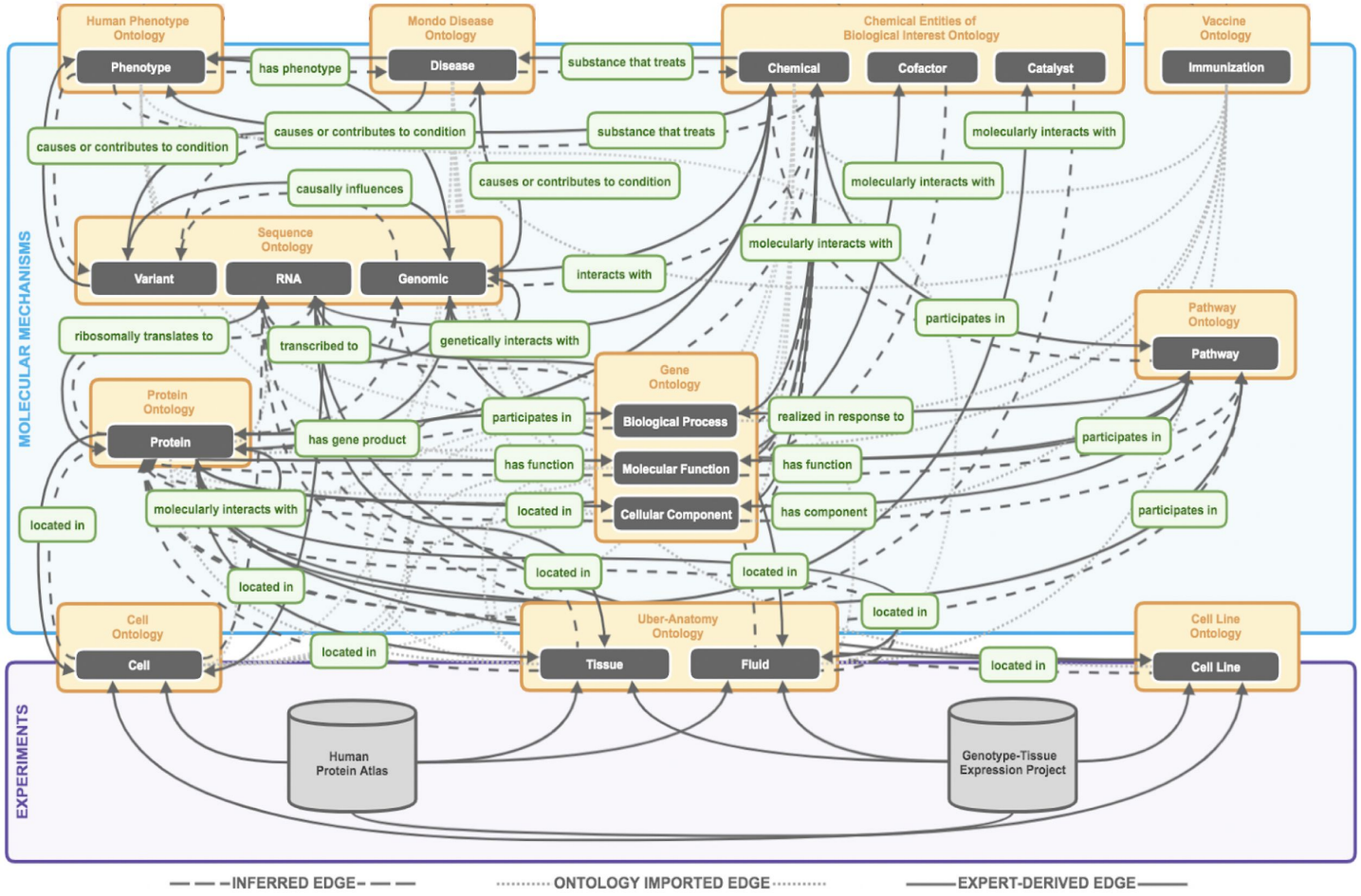
12 OBO ontologies
366,846 classes
3,923,625 axioms

Edge Data

22 Linked Open Data
2 Experimental
34 edge-types

Validation

PhD Molecular Biologist



OBO = Open Biomedical Ontologies

Summary

- First fully custom biomedical knowledge graph construction framework
- Evaluation in progress
- Promising applications
  - Biomedical hypergraphs → *Joslyn, Aksoy, Callahan et al., arXiv. 2020*
  - Toxicogenomic mechanistic inference → *Tripodi, Callahan et al. Tox InVitro. 2020*
- Full testing and continuous integration; Dockerized

https://github.com/callahantiff/PheKnowLator

BARRIER 2

Medical Records were not Built to Facilitate Translational Research

Clinical Research Challenges

Problem

- Hospital databases/EHRs incomplete and not standardized[1-3]
- Diagnosis codes used for billing, not research[2,4]

Solution

- CDMs help different data sources speak the same language
- Ontologies contain meaningful representations of molecular knowledge

EHRs = Electronic Health Records; **CDMs** = Common Data Models

[1]Sinnott et al. *J Amer Med Inform Assoc.* 2018; [2]Haendel et al. *N Engl J Med.* 2018; [3]Kahn, **Callahan** et al. *eGems. 2016*; [4]Zhang, Yates, Vasilevsky, Gourdine, **Callahan et al.** *Nat Digit Med. 2019*

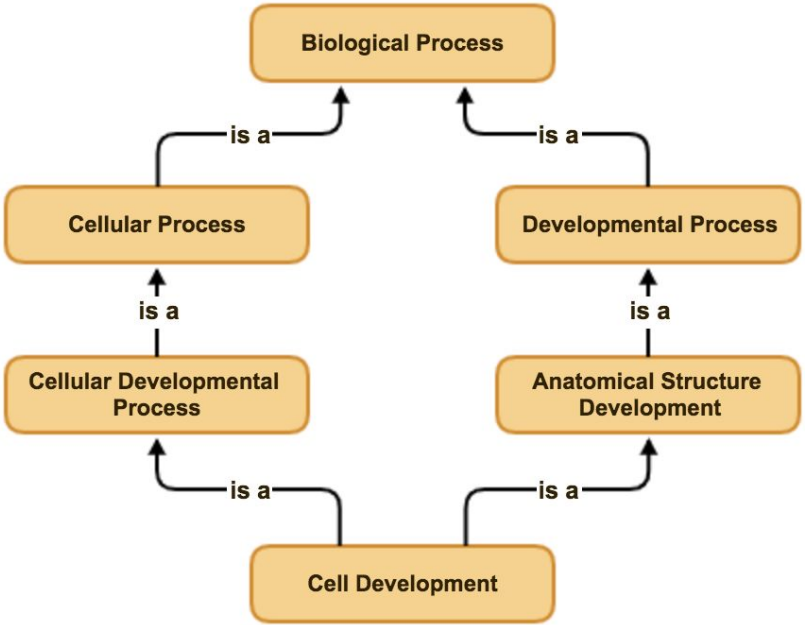
Ontologies

Ontology → Graph of entities and relationships[1,2]

- Domain-specific
- Community consensus
- Hierarchical

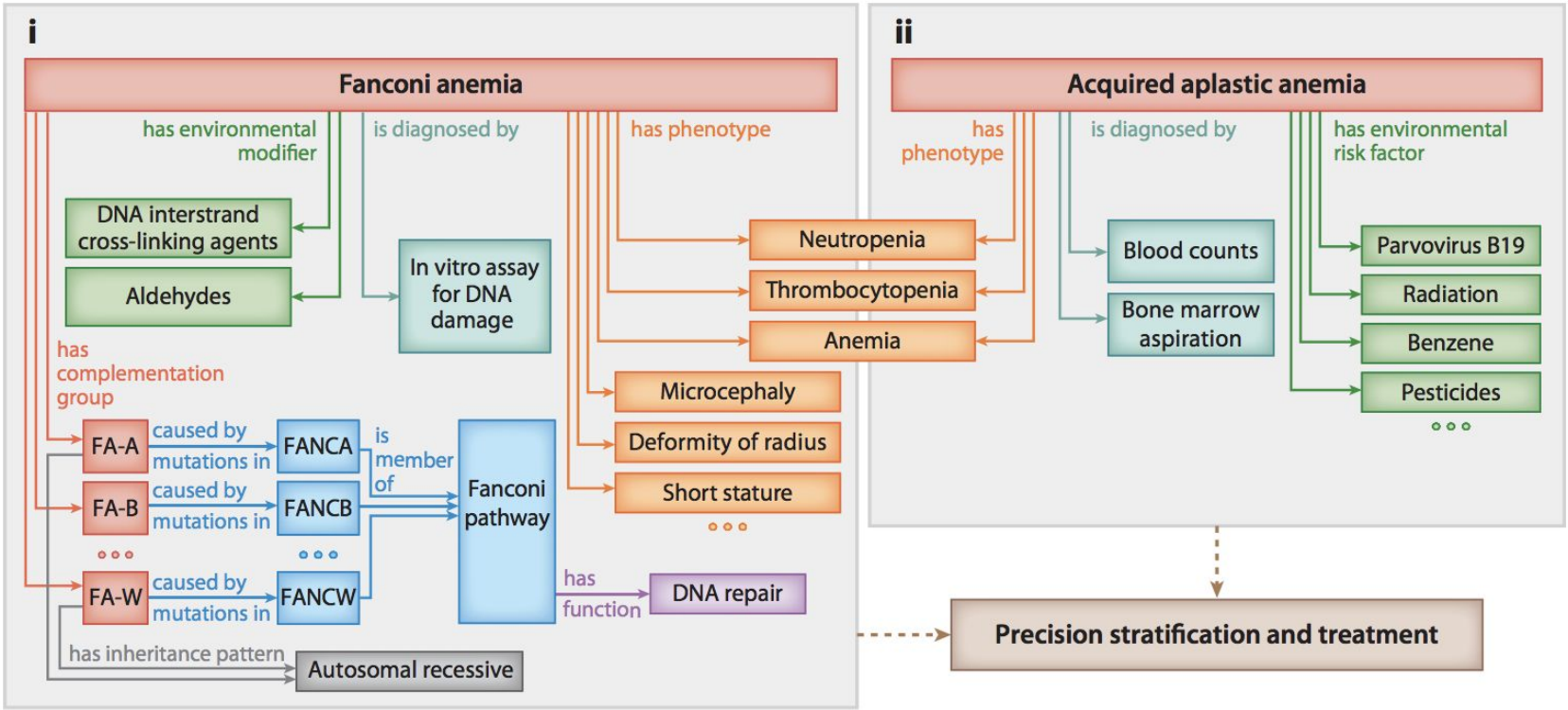
Open Biomedical Ontologies

- Phenotypes (`Human Phenotype Ontology`)
- Diseases (`Disease Ontology`)
- Chemicals/Metabolites/Hormones (`ChEBI`)
- Anatomical Entities (`UBERON`)
- Cell Types (`Cell Line Ontology`)



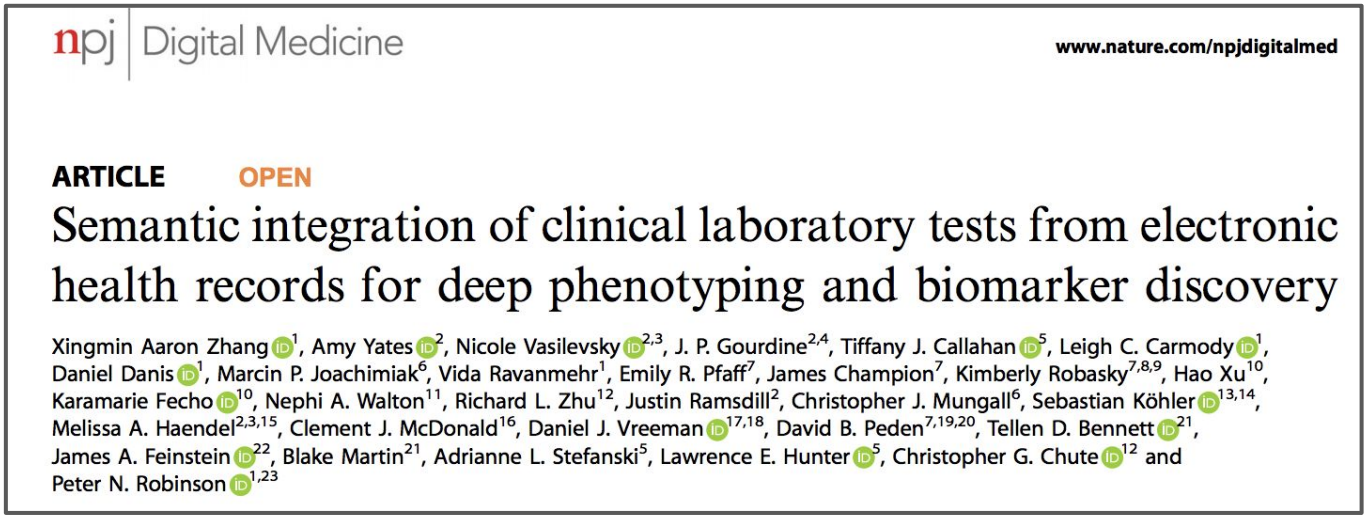
[1]Hunter. *Data Science*. 2017; [2]**Callahan** et al. *Annu. Rev. Biomed. Data Sci.* 2020

Ontologies Translate Clinical Concepts



Haendel et al., *Annu. Rev. Biomed. Data Sci.* 2018

Existing Mapping Work



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ARTICLE OPEN

Semantic integration of clinical laboratory tests from electronic health records for deep phenotyping and biomarker discovery

Xingmin Aaron Zhang[1], Amy Yates[2], Nicole Vasilevsky[2,3], J. P. Gourdine[2,4], Tiffany J. Callahan[5], Leigh C. Carmody[1], Daniel Danis[1], Marcin P. Joachimiak[6], Vida Ravanmehr[1], Emily R. Pfaff[7], James Champion[7], Kimberly Robasky[7,8,9], Hao Xu[10], Karamarie Fecho[10], Nephi A. Walton[11], Richard L. Zhu[12], Justin Ramsdill[2], Christopher J. Mungall[6], Sebastian Köhler[13,14], Melissa A. Haendel[2,3,15], Clement J. McDonald[16], Daniel J. Vreeman[17,18], David B. Peden[7,19,20], Tellen D. Bennett[21], James A. Feinstein[22], Blake Martin[21], Adrianne L. Stefanski[5], Lawrence E. Hunter[5], Christopher G. Chute[12] and Peter N. Robinson[1,23]

- Manually curated 2,923 LOINC lab tests to HPO
- Validated with 15,681 patients with respiratory complaints → known asthma biomarkers
  - Abnormal metabolism/vitamin metabolism
  - ↑ Red blood cell count and VLDL cholesterol concentration

Mapping Strategies

"Chronic deep venous thrombosis of right calf"

1:1 Mapping Approach:

"Chronic deep venous thrombosis of right calf" → "Abnormality of the calf"

1:Many Mapping Approach:

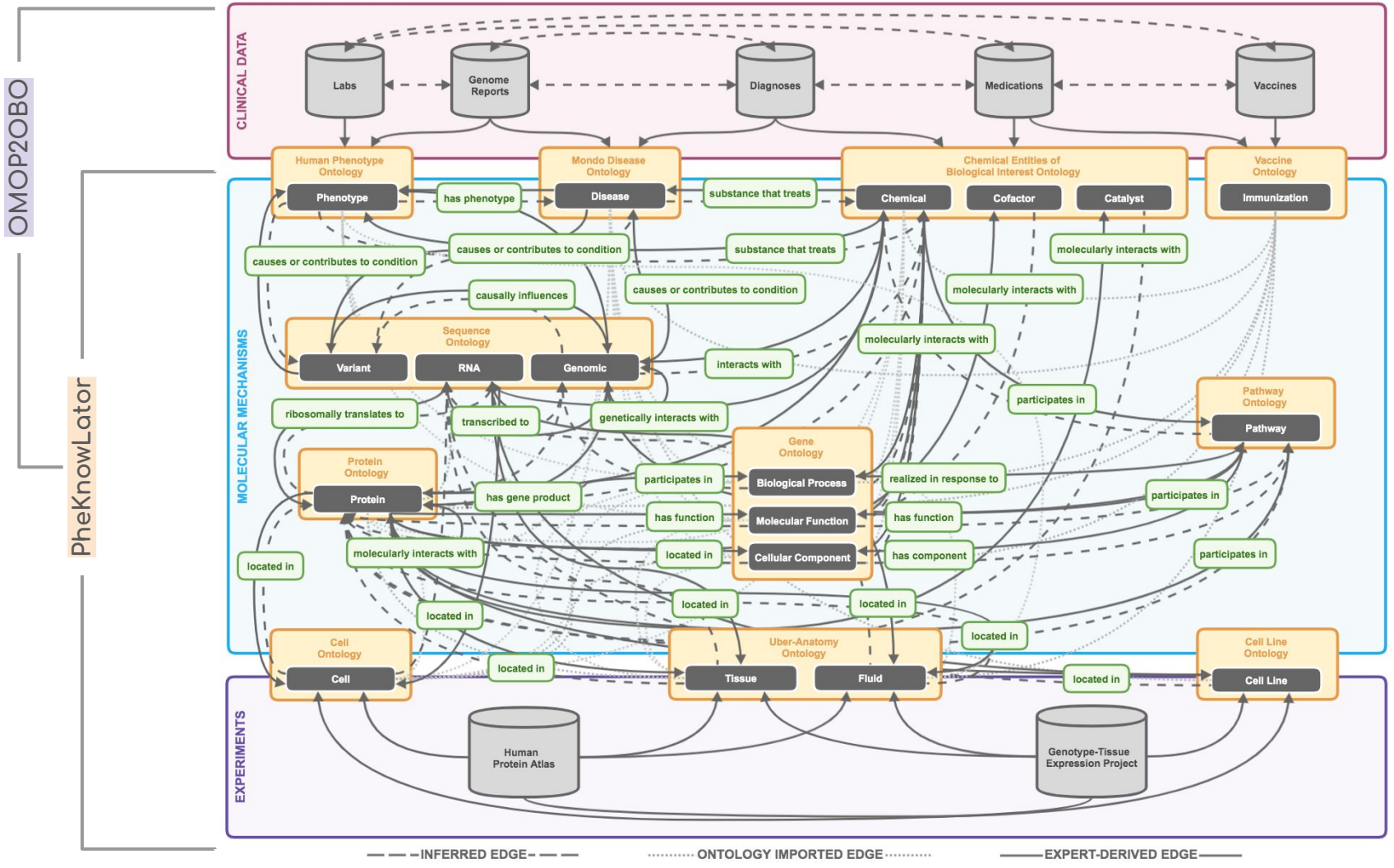
"Chronic deep venous thrombosis of right calf" → "Chronic"
"Deep venous thrombosis"
"Abnormality of the calf"
"Right"

Objective

- Extend and expand existing mapping work → more than 1:1 mappings
- Map ontologies to OMOP
- Hospital scale, disease-agnostic

OMOP2OBO: the first health system-wide integration and alignment between OMOP standardized clinical terminologies and eight OBO biomedical ontologies

https://github.com/callahantiff/OMOP2OBO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Available Data

Clinical Domain	OMOP Table	Concept Class	Concept Vocabularies	Ontologies
Conditions	Condition Occurrence	Conditions	SNOMED CT Source Codes: *“Mapped to”, “Mapped From”,* *"Concept poss_eq from"* *"Concept same_as from"*	Human Phenotype Ontology Mondo Disease Ontology
Medications	Drug Exposure Immunizations	Drugs Ingredients	RxNorm Standard Non-Standard	ChEBI Protein Ontology NCBITaxon Vaccine Ontology
Measurements	Measurements	Measurements	LOINC Standard Non-Standard	Human Phenotype Ontology ChEBI Uber Anatomy Ontology Protein Ontology NCBITaxon Cell Ontology

Available Data

Clinical Data - OMOP CDM	
Concept ID*	138994
Source Code	snomed:109995007 icd10cm:D46.9 mesh:D009190 icd9cm:238.75
Concept Name	Myelodysplastic syndrome
Concept Synonym	Myelodysplastic syndrome (disorder) | Myelodysplastic syndrome (clinical)

*OMOP Data also includes all ancestors

Ontology Data - Open Biomedical Ontologies	
Class ID	HP_0002863
Class Label	Myelodysplasia
Class Synonym - Broad - Exact - Narrow - Related	Hypoplastic myelodysplasia
Class Definition	Clonal hematopoietic stem cell disorders characterized by dysplasia (ineffective production) in one or more hematopoietic cell lineages, leading to anemia and cytopenia
Class DbXRef	UMLS:C1851971 MSH:D009190 SNOMEDCT_US:109995007

Mapping Approach

Mapping Strategies

- Database Cross-References
- Exact String Match
  - Labels
  - Synonyms
- Bag-of-Words + TF-IDF Weighting
  - Labels
  - Synonyms
  - Definitions (ontologies only)

Mapping Categories

Category	Definition
Automatic Exact - Concept	Exact label or synonym, dbXRef, or expert validated mapping @ concept-level; 1:1
Automatic Exact - Ancestor	Exact label or synonym, dbXRef, or expert validated mapping @ concept ancestor-level; 1:1
Manual Exact - Concept Similarity	Concept similarity score suggested mapping -- manually verified; 1:1
Automatic Constructor - Concept	Exact label or synonym, dbXRef, cosine similarity, or expert validated mapping @ concept-level; 1:Many
Automatic Constructor - Ancestor	Exact label or synonym, dbXRef, cosine similarity, or expert validated mapping @ concept-level; 1:Many
Manual Constructor	Hand mapping created using expert suggested resources; 1:Many
Manual	Hand mapping created using expert suggested resources; 1:1
UnMapped	No suitable mapping or not mapped type

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Manual	Hand mapping created using expert suggested resources; 1:1
UnMapped	No suitable mapping or not mapped type

Example: Apraxia (`OMOP_132342`)

Mapping Type: Automatic Exact - Concept

Ontology Concept: Apraxia (`HP_0002186`)

Mapping Evidence:

CONCEPT_DBXREF:snomed_68345001
OBO_LABEL-OMOP_CONCEPT_LABEL:apraxia
OBO_LABEL-OMOP_CONCEPT_SYNONYM:apraxia
CONCEPT_SIMILARITY:HP_0002186_1.0
ANCESTOR_DBXREF:snomed_68345001
OBO_LABEL-OMOP_ANCESTOR_LABEL:apraxia

Conditions Occurrence Mappings

Mapping Type		Condition Concept ID	Phenotype (Human Phenotype Ontology)	Disease (Mondo Disease Ontology)
Automatic Mapping	Concept	Macular Hole (OMOP_4338894)	Macular Hole (HP_0011508)	Macular Hole (DOID_7633)
	Ancestor	Major histocompatibility complex class I deficiency (OMOP_4100979)	Severe Combined Immunodeficiency (HP_0004430)	Severe Combined Immunodeficiency (DOID_627)
Manual Mapping	Similarity	Malakoplakia of colon (OMOP_4024250)	Abnormality of the large intestine morphology (HP_0005210)	Colonic Disease (DOID_5353)
	Constructor	Macular edema and retinopathy due to type 2 diabetes mellitus (OMOP_45770830)	AND | Type II Diabetes Mellitus (HP_0005978) | Macular Edema (HP_0040049) | Retinopathy (HP_0000488)	AND | Type 2 Diabetes (DOID_9352) | Macular Retinal Edema (DOID_4449)

Conditions Occurrence Mappings

- UMLS CUIs (*MRCONSO 2020AB*) and Semantic Types (*MRSTY 2020AB*)
- 28,129 unique condition occurrence codes

Evaluation: 20% of manually mapped concepts verified by clinicians; several iterations

- 24,285 OMOP concepts → 4,661 Phenotypes
- 19,664 OMOP concepts → 3,614 Diseases

Ontology	Automatic Exact - Concept	Automatic Exact - Ancestor	Manual Exact - Concept Similarity	Automatic Constructor - Concept	Automatic Constructor - Ancestor	Manual Constructor	Manual
HPO	3465	2851	1055	174	1825	9477	5438
MONDO	4965	6103	484	723	2301	3109	1979

Drug Exposure Mappings

Mapping: Ingredients and mechanism of action (DrugBank and CHEMBL)

Example: balsalazide (`OMOP_934262`)

Ingredient mapping:

- Automatic Exact - Concept
- balsalazide (`CHEBI_267413`)

Mechanism of Action:

- Automatic Constructor - Concept
- **agonist:** peroxisome proliferator-activated receptor gamma (`PR_P37231`)
- **Inhibitor:** prostaglandin G/H synthase 2 (`PR_P35354`), prostaglandin G/H synthase 1 (`PR_P23219`), arachidonate 5-lipoxygenase-activating protein (`PR_P20292`)
- **organism:** homo sapien (`NCBITaxon_9606`)

Drug Exposure Mappings

- 11,937 drug-ingredient combinations → 1,697 unique ingredients

Evaluation: 20% of manually mapped concepts verified by clinical pharmacist; 3 iterations

- 1,618 OMOP concepts → 1,422 Chemicals, hormones, or metabolites
- 139 OMOP concepts → 91 Proteins
- 317 OMOP concepts → 39 Organisms
- 127 OMOP concepts → 54 Vaccines/Immunizations

Ontology	Automatic Exact - Concept	Automatic Exact - Ancestor	Manual Exact - Concept Similarity	Automatic Constructor - Concept	Automatic Constructor - Ancestor	Manual Constructor	Manual	Unmapped
CHEBI	1176	3	64	9	1	58	306	80
PRO	2	0	10	0	0	8	119	1558
NCBITaxon	20	0	0	0	0	10	287	1380
VO	92	0	8	1	0	1	25	1570

Measurement Mappings

- Leverage LOINC scale and results type
- Data-drive confirmation

Somatotropin [Mass/volume] in Serum or Plasma (OMOP_3023709)
- OR blood serum(UBERON_0001977) | blood plasma (UBERON_0001969)
- Somatotropin (PR_000007968)
    - Normal: NOT Abnormality of circulating hormone level (HP_0003117)
    - Low: Growth Hormone Deficiency (HP_0000824)
    - High: Growth Hormone Excess (HP_0000845)

Transitional cells [Presence] in Urine sediment by Light microscopy (OMOP_3028475)
- Urine (UBERON_0001088), Transitional epithelial cell (CL_0000244)
    - Negative: NOT Increased urinary transitional epithelial cell count (HP_0032214)
    - Positive: Increased urinary transitional epithelial cell count (HP_0032214)

Measurement Mappings

- 4,382 lab tests, 11,072 lab test results

Evaluation:

- 270 results verified by 3 MDs, 1 epidemiologist
- 15% verified by a biocurator, 3 iterations
  - 10,888 OMOP concepts → 920 Phenotypes | 10,876 OMOP concepts → 25 Anatomical entities
  - 1,075 OMOP concepts → 27 Cell Types | 9,710 OMOP concepts → 338 Chemicals, Hormones
  - 8,269 OMOP concepts → 194 Organisms | 4,842 OMOP concepts → Proteins

Ontology	Automatic Exact - Concept	Automatic Exact - Ancestor	Manual Exact - Concept Similarity	Automatic Constructor - Concept	Automatic Constructor - Ancestor	Manual Constructor	Manual
HPO	6891	22	171	4	0	49	3751
UBERON	0	1612	0	0	0	3307	5957
CL	0	227	207	0	87	30	524
CHEBI	5	3535	1098	151	241	922	3758
NCBITaxon	0	693	0	0	0	459	7117
PRO	0	44	259	0	0	175	4364

OMOP2OBO

- Determine coverage of mappings on two independent samples

Data Source	Domain	Unique Concepts	Coverage
MIMIC-III	Conditions	5608	92.13%
	Medications	4426	96.36%
UCHealth	Conditions	15056	79.78%
	Medications	23972	91.35%

Summary

- First hospital scale mapping between OMOP and the OBOs
- Preliminary coverage examined on adult and ICU populations
- Added over 200 new concepts to HPO
- Adopted by National COVID-19 Cohort (N3C)

National COVID Cohort Collaborative

Next Steps:

- Coverage study in subset of Concept Prevalence data
- Comparing to Juan Banda's Mappings

https://github.com/callahantiff/OMOP2OBO

ACKNOWLEDGEMENTS

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Trivisory

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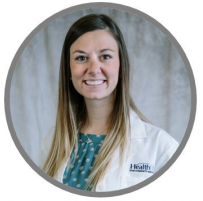

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Organizations

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