Electronic Phenotyping for Genomic Research

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On behalf of Phenotyping WG

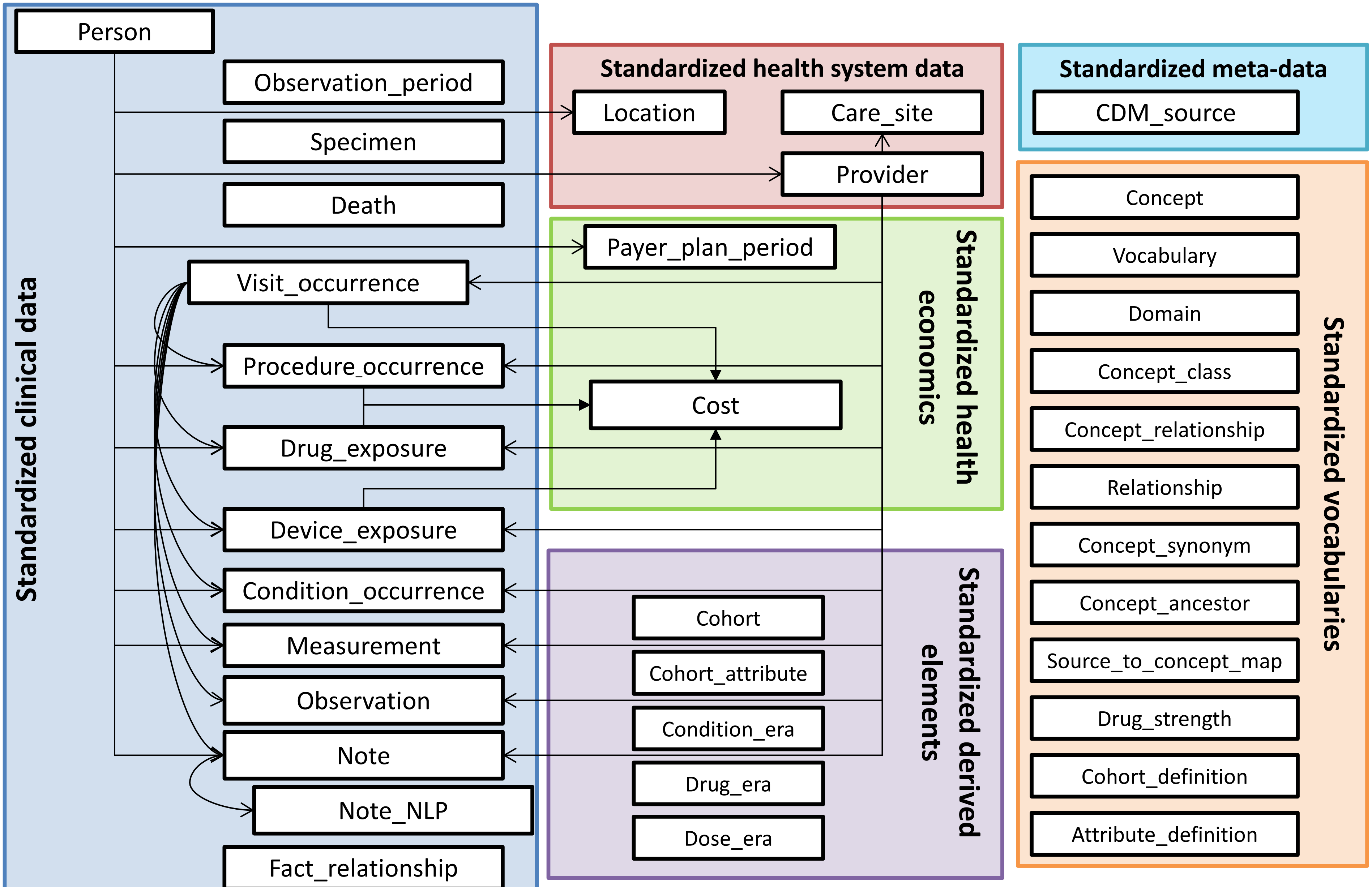
October 30, 2017

1. How can eMERGE improve upon the current labor-intensive phenotyping toward fully-automated phenotyping methods to increase phenotyping efficiency and validity using EMRs?

Phenotype sharing

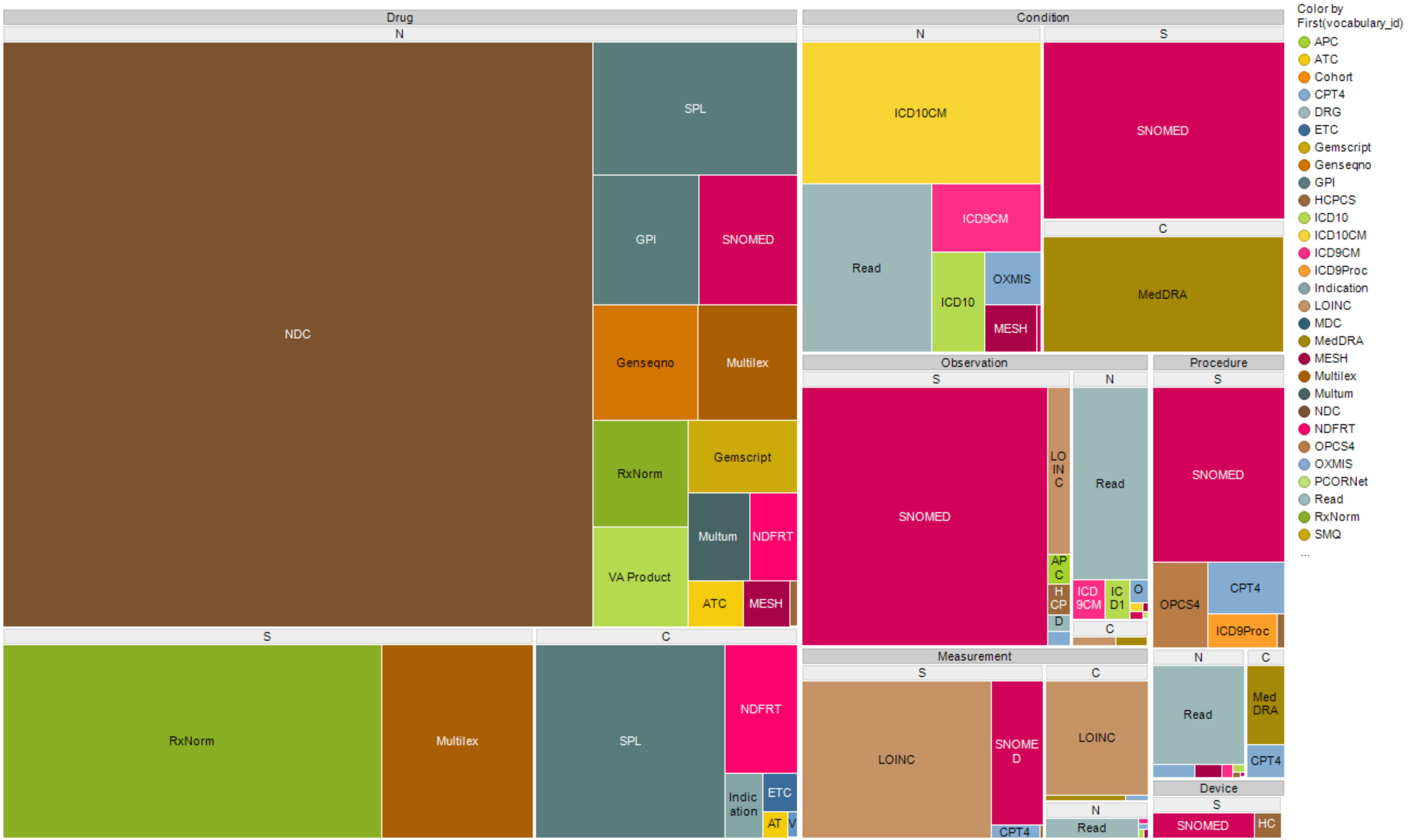
- One part of the labor is sharing
  - eMERGE adopting OHDSI OMOP Common Data Model
  - Convert current eMERGE data warehouses to same schema and vocabulary
  - But preserve source information

Deep Information Model: OMOP v5.2



Extensive vocabularies

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



eMERGE phenotype generation

- eMERGE phenotyping lessons
  - [Kho AN, Sci Trans Med 2011]
- Complexity of eMERGE phenotypes
  - [Conway M, AMIA 2011]
- Multi-modal approaches
  - [Peissig PL, JAMIA 2012]
- Use of NQF Quality Data Model
  - [Thompson WK, AMIA 2012]
- Improving validation
  - [Newton KM, JAMIA 2013]
- Design patterns
  - [Rasmussen LV, JBI 2014]
- PhEMA: Phenotype Execution and Modeling Architecture
  - [Pathak et al.]

Phenotype generation lessons

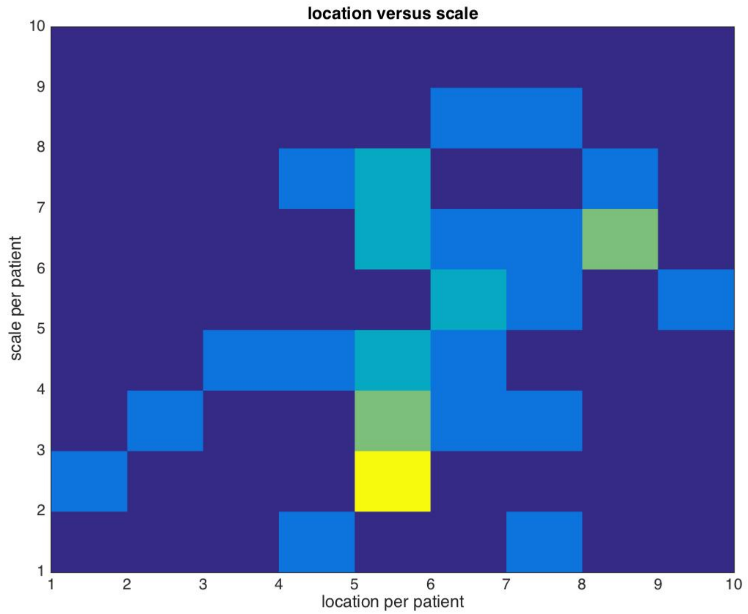
- Challenge of billing codes
- Importance of NLP
  - And multimodal in general
- Complexity of effective phenotype definitions
- Possible improvement from tools and reuse, but mostly just slogging it out
- Differing goals:
  - Knowledge discovery via GWAS needs high PPV
  - Knowledge deployment for decision support also needs sensitivity

Phenotyping for the future

- High-fidelity phenotypes [Hripcsak G, JAMIA 2017]
  - Encode degree, severity of condition
    - Redo for past phenotypes?
  - Exploit time to create more accurate phenotypes
  - Encode time of condition
    - Disease course, response to treatment
  - Continuous states (topology, where not dichotomous)
  - Hidden physiologic phenotypes (data assimilation)
  - Latent abstract states (deep learning)
  - Accommodate health care process bias

High-fidelity phenotypes

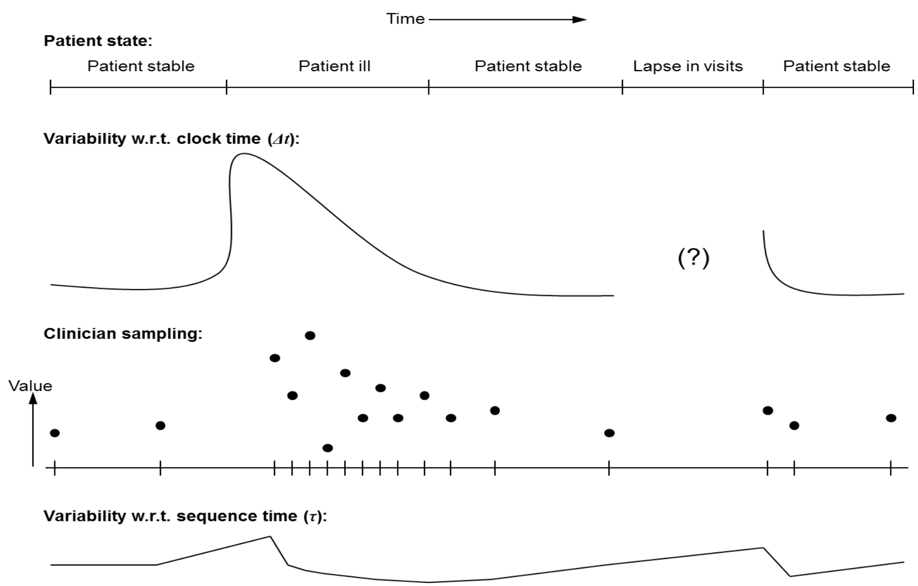
- Encode degree, severity of condition



Albers, AMIA 2015

High-fidelity phenotypes

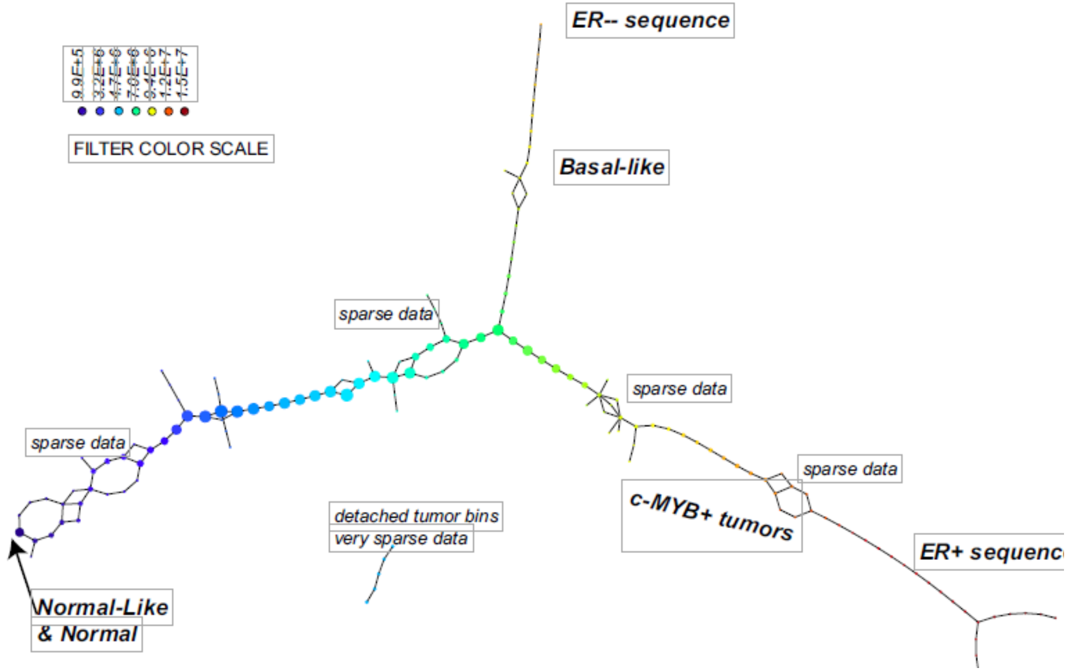
- Exploit time to create more accurate phenotypes
- Encode time of condition



Hripcsak, JAMIA 2015

High-fidelity phenotypes

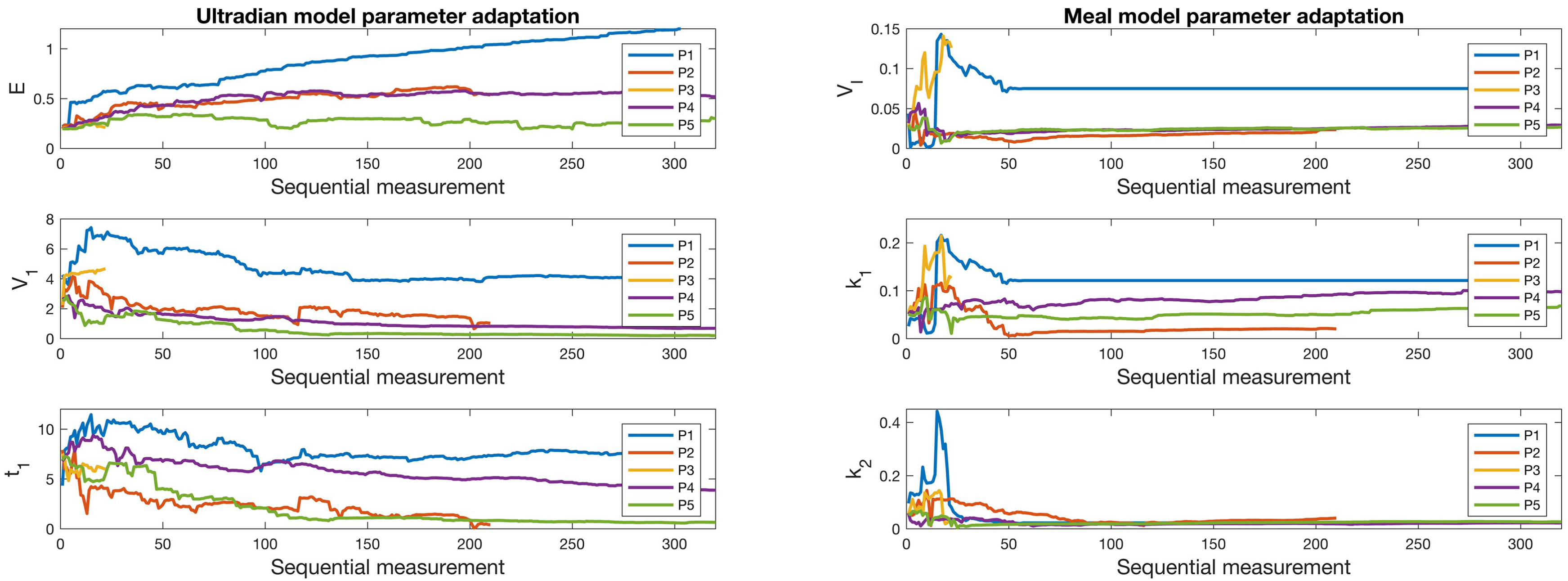
- Continuous states (topology, where not dichotomous)



Nicolau, PNAS 2011

High-fidelity phenotypes

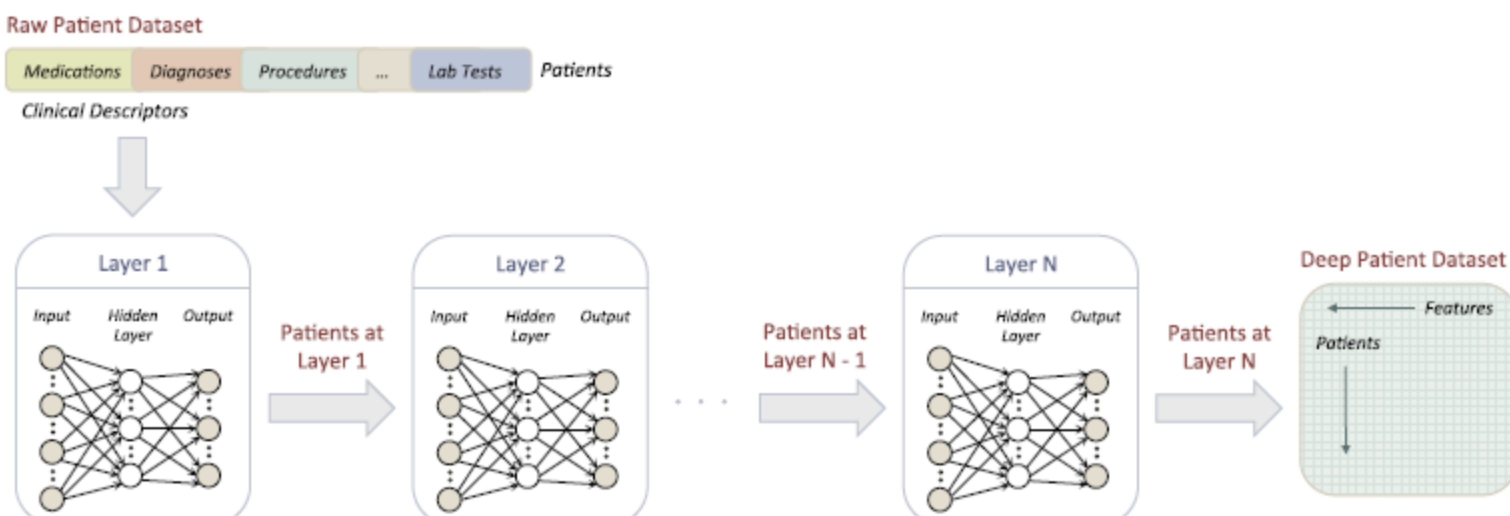
- Hidden physiologic phenotypes (data assimilation)



Albers, PLOS Comp Bio 2017

High-fidelity phenotypes

- Latent abstract states (deep learning)

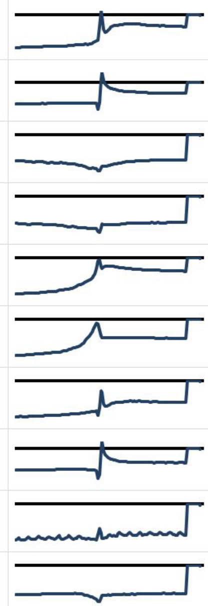


Miotto, Scientific Reports 2016

High-fidelity phenotypes

- Accommodate health care process bias

concept	hc	sparkline
inr	admit	
ptt	admit	
inr	ambsurg	
ptt	ambsurg	
inr	discharge	
ptt	discharge	
inr	ed	
ptt	ed	
inr	outpatient	
ptt	outpatient	



Hripcsak, JAMIA 2013

2. How might machine-learning and other advanced computational tools be used to improve electronic phenotyping in the eMERGE network?

Advanced computational tools

- Natural language processing
  - Large proportion of phenotypes employ it
  - Disparate systems across the network
  - Most get by with relatively simple processing
  - Working on sharing NLP!

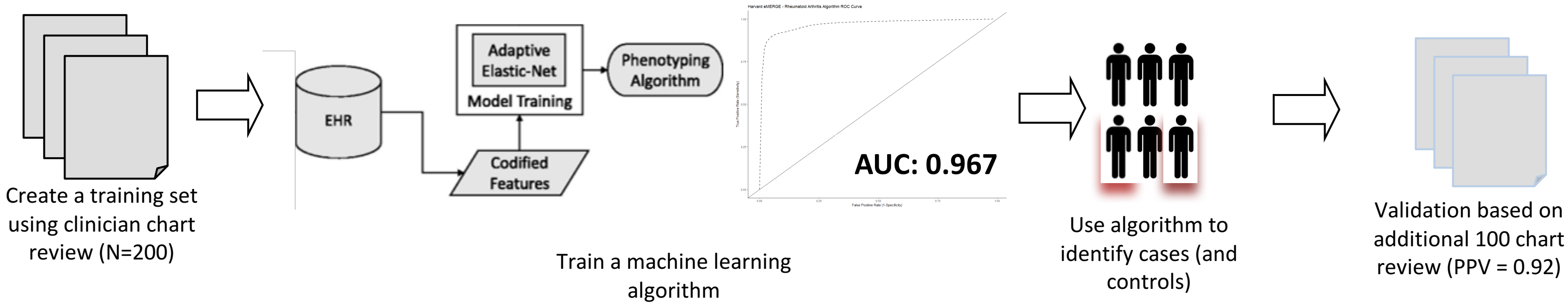
Advanced computational tools

- Machine learning research
  - eMERGE research: see following slides
  - Anchors, noisy sets to learn from imperfect training data (MIT, Stanford, Columbia)
  - Active learning to reduce training set labor (Marshfield, …)
  - Deep learning to characterize patients (Mt. Sinai, …)
  - Physiologic phenotypes via data assimilation (Columbia)
    - E.g., kidney & liver function, body space, insulin excretion
  - Topology for continuous phenotypes (Stanford, Columbia)

Harvard eMERGE – Rheumatoid Arthritis Machine Learning Phenotype Algorithm

- Machine learning algorithms can be effectively and efficiently applied to a large population to accurately phenotype patients
- Algorithms provide flexibility to adjust sensitivity and specificity to varied use cases compared to pre-defined rules-based algorithms

Rheumatoid Arthritis Algorithm Development Workflow



Rheumatoid Arthritis Algorithm Final Feature Betas

Feature_ID	Beta (weight)	Feature Description
(Intercept)	-1.017	Model Intercept (beta 0)
patient_dxenct	-0.954	Number of encounters with an ICD-9 code
RA_COD_DX_RheumatoidArthritis_v2	1.937	Number of coded Rheumatoid arthritis diagnoses
RA_COD_DX_Psoriaticarthritis_v2	-0.122	Number of coded Psoriatic arthritis diagnoses
RA_COD_DX_Lupus	-0.529	Number of coded Lupus diagnoses
RA_COD_LAB_RFpos1	1.639	Binary indicator where 1=any positive Rheumatoid Factor (RF) lab, else = 0

On Mapping Textual Queries to a Common Data Model

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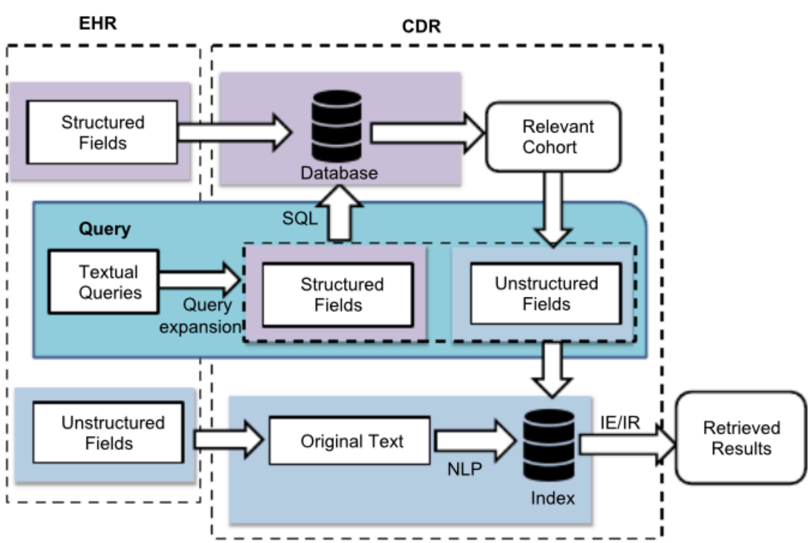
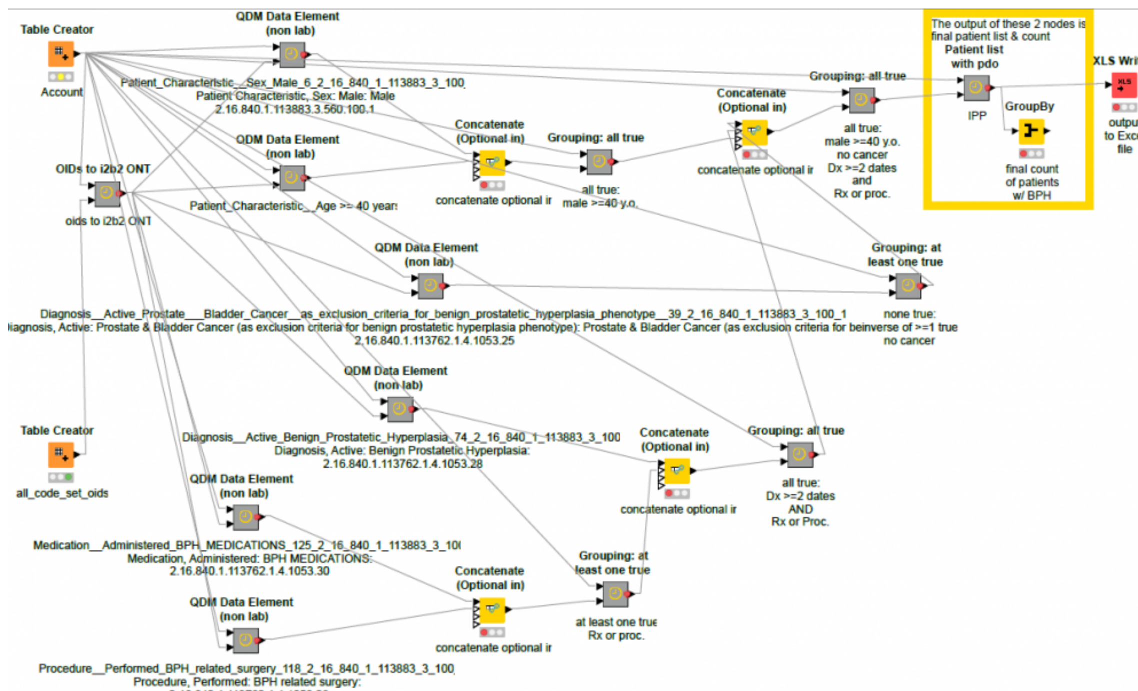
- Challenges faced in using NLP for computational phenotyping
  - Poor portability caused by syntactic, semantic, and process variations
  - Semantic gaps among users, experts, and data
  - It is not "one size fits all" solutions for computational phenotyping
- Solutions proposed
  - Improve **syntactic interoperability** by adopting common data models
  - Mitigate the semantic gaps through a combination of deep learning representation, information retrieval, informatics extraction, and late binding NLP and data normalization
  - Develop a platform for sharing NLP knowledge artifacts and mapping between data semantics and expert semantics



Mayo

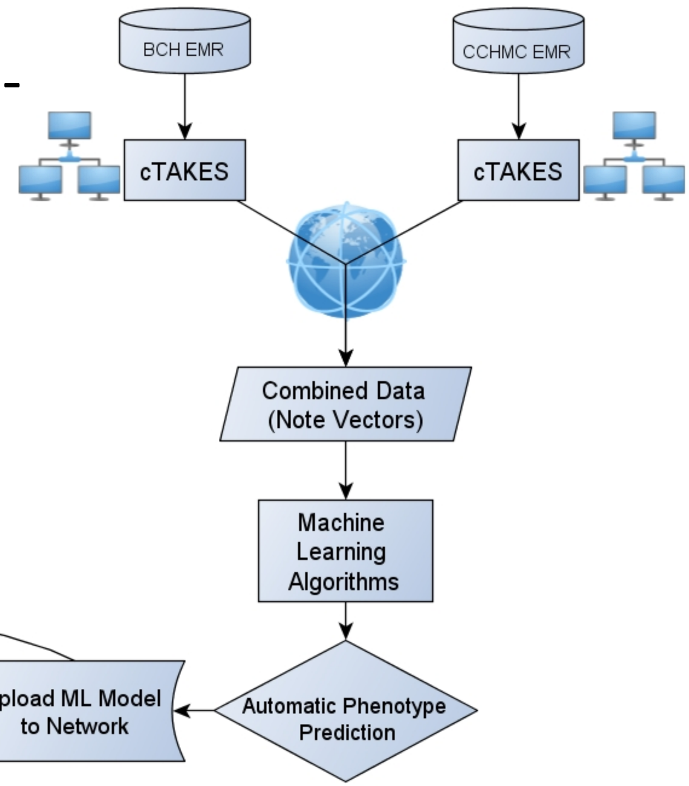
PhEMA

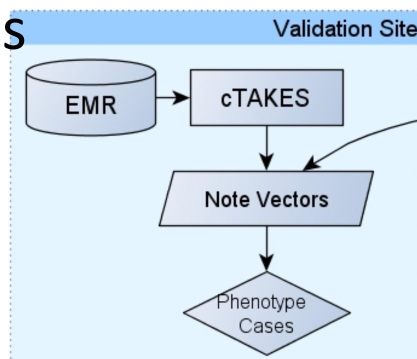
- PhEMA: Phenotype Execution and Modeling Architecture [Pathak et al.]
  - Standards-based representation of phenotypes
  - Visual tool for authoring phenotypes (PhAT)
  - Execution against OMOP or i2b2 (PheX)
  - Developing NLP & ML extensions
  - Integrates with PheKB



NLP – ML Approach

- Apply exclusion and inclusion criteria based on ICD9 code filtering
- Acquire EMR data for the filtered patients
- Process clinical notes to discover SNOMED-CT and RxNORM concepts with their attributes (Apache cTAKES) and generate feature vectors
- Apply machine learning prediction on feature vectors based on training from expert-provided labels
- Communicate ML model to other sites to run on their data





Phenotyping using Relational Machine Learning

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Relational machine learning for electronic health record-driven phenotyping

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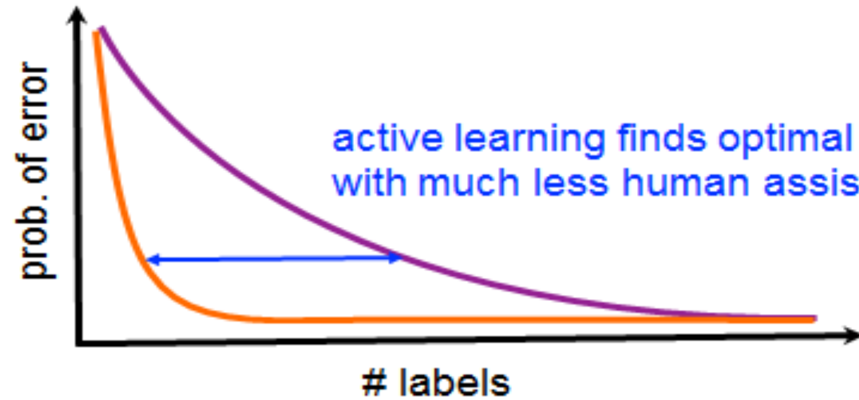
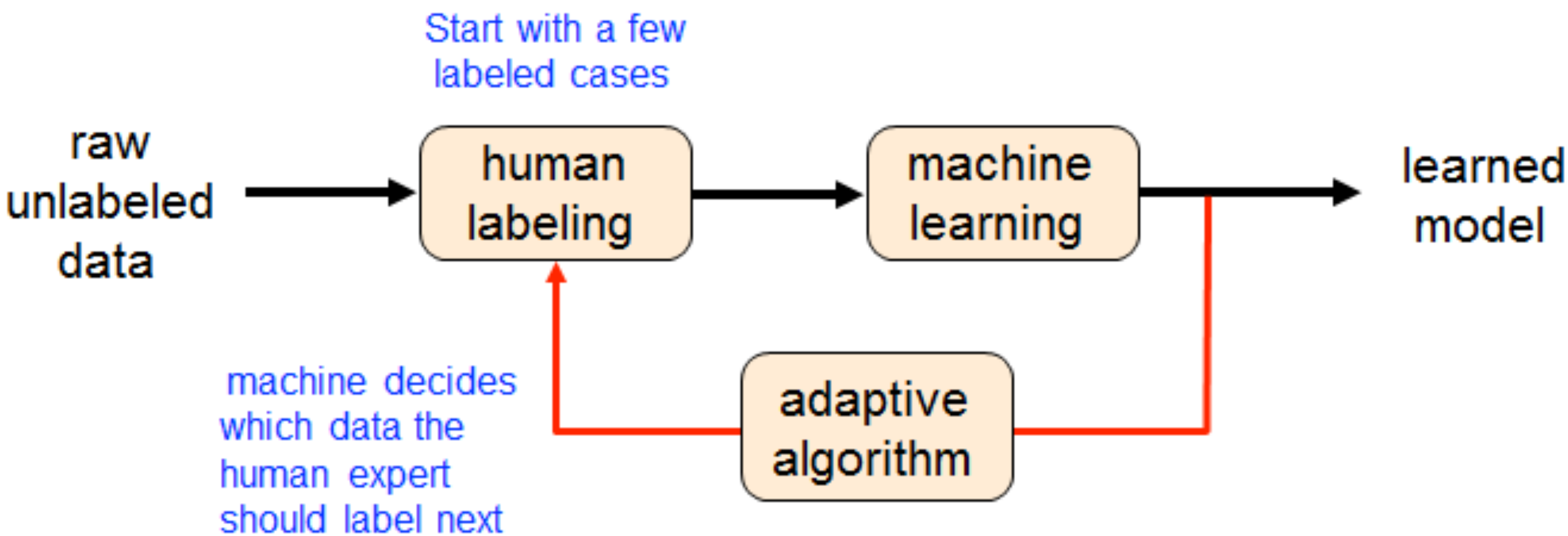
Table 5. Comparison of eMERGE phenotyping model precision to *ILP+BP*

	eMERGE[1]	*eMERGE at Marshfield*	*ILP+BP*[4]
Cataract	0.960 - 0.977	0.956[2]	0.877
Dementia	0.730 – 0.897	0.897[3]	0.936
Type 2 Diabetes	0.982 – 1.000	0.990[3]	0.926
Diabetic Retinopathy	0.676 – 0.800	0.800[3]	0.976

[1] eMERGE precision range taken from Table 3 in Newton et al [6]. The range represents multiple eMERGE institution precision estimates.
[2] Precision for Marshfield eMERGE cohort indicating the combined cohort precision definition in Peissig et al [28].
[3] eMERGE precision for Marshfield taken from Table 3 in Newton et al [6].
[4] *LP+BP*: Inductive Logic Programming + Borderline Positives taken from Table 3.

Active Machine Learning





Marshfield, Castro 2008

3. How can eMERGE assess phenotype comparability across diverse patient populations and diverse healthcare settings (e.g. academic and county hospitals, community clinics and other national healthcare systems)?

Diverse populations and settings

- Design specific eMERGE experiments
  - Busy now with exisiting phenotypes
- Collaborate with All of Us Research Program
  - Getting up to speed; uses same data model
- Collaborate with OHDSI
  - Large, international set for phenotype part