

BMI 702: Biomedical Artificial Intelligence

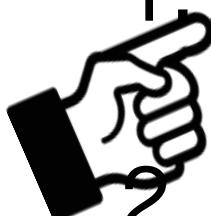
Foundations of Biomedical Informatics II, Spring 2023

Lecture 2: Introduction to AI on clinical datasets

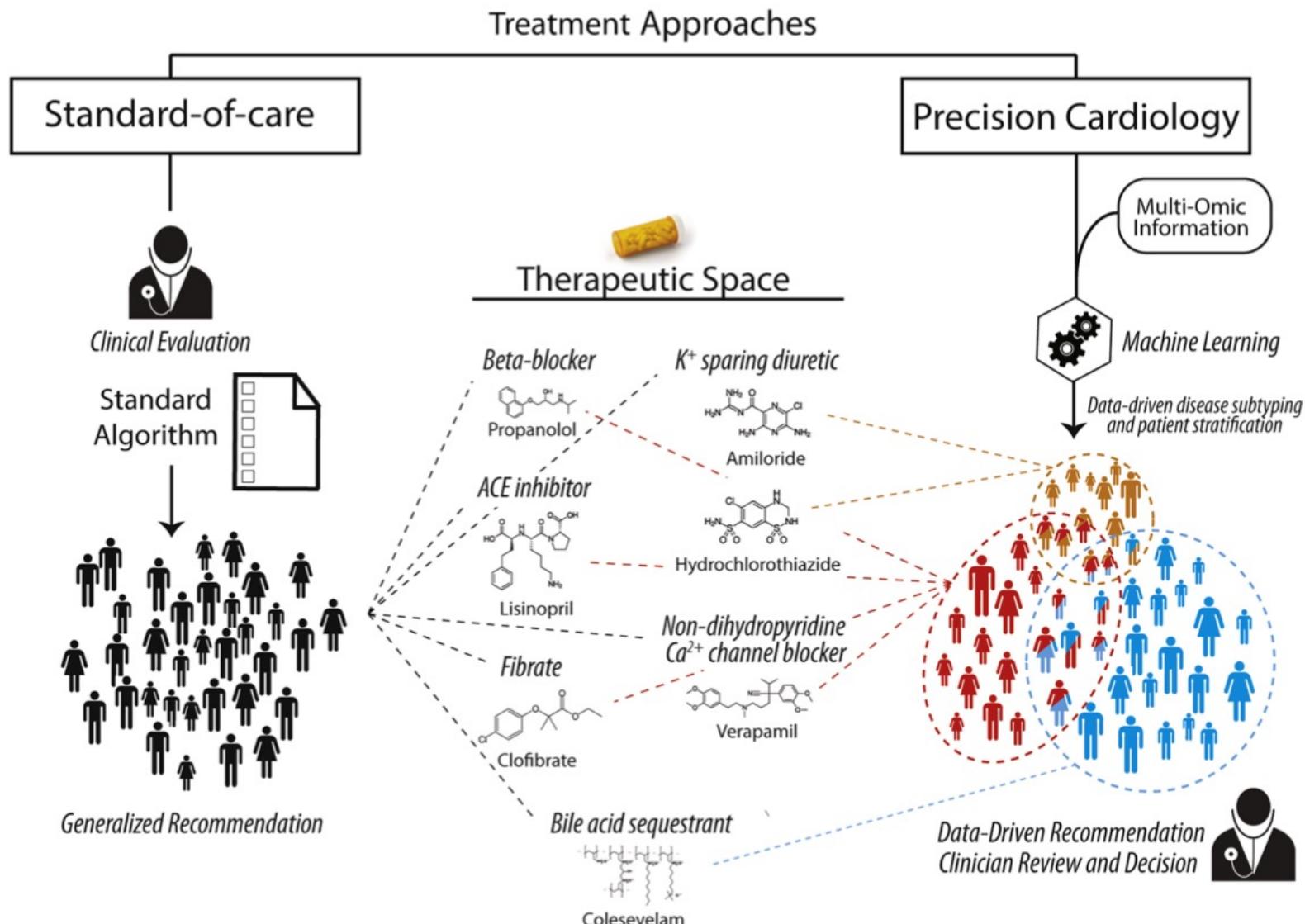


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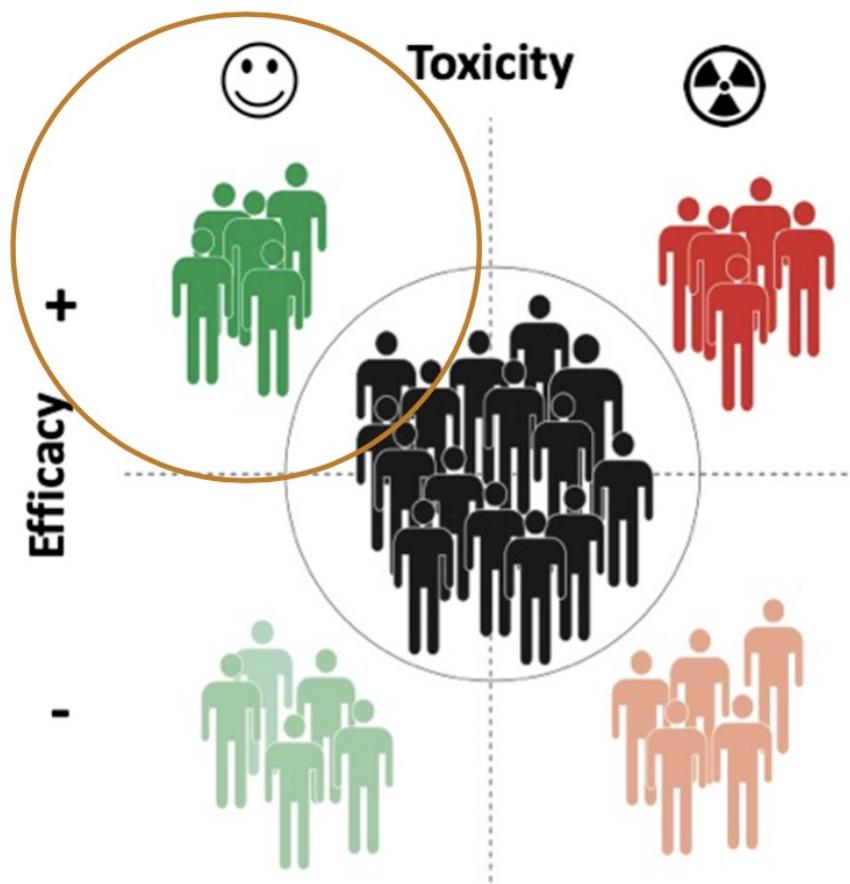
Outline for today's class

- 
1. Why AI for precision medicine?
 2. What are electronic health records (EHR) and why are they useful?
 3. What are limitations & biases of EHR data?
 4. Highlights of ML on EHR data:
 - Polypharmacy and adverse drug events
 - Modeling disease progression

The road from general to personal



Precision medicine goals in theory

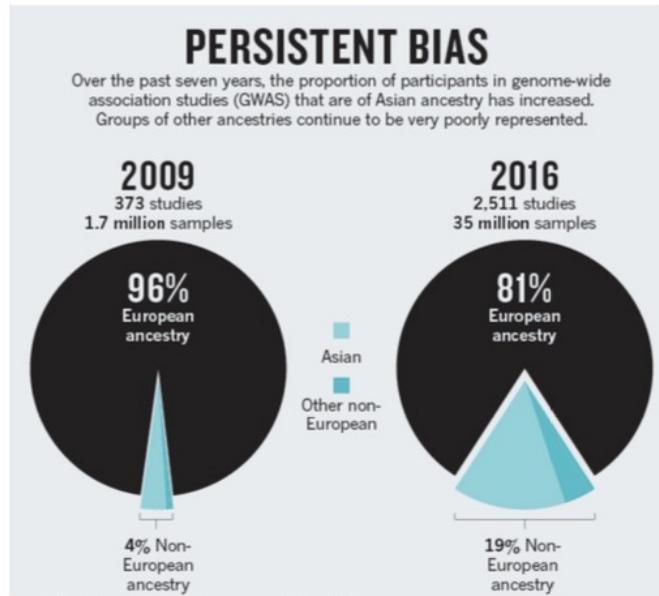


<http://hitconsultant.net/2014/04/03/infographic-the-rise-of-personalized-medicine/>

Why are these goals relevant?

Problem: Underrepresentation in clinical research

Genomics



Clinical Trials

Participation in Cancer Clinical Trials

Race-, Sex-, and Age-Based Disparities

Table 1. Participants in National Cancer Institute Cooperative Group Breast, Colorectal, Lung, or Prostate Cancer Therapeutic Trials, 1996-2002 (N = 75 215)*

Characteristic	Trial Participants, No. (%)	Proportion of Incident Cancer Patients, %†	Proportion of US Population, %†
Race/ethnicity			
White non-Hispanic	64 355 (85.6)	83.1	75.7
Hispanic	2292 (3.1)	3.8	9.1
Black	6882 (9.2)	10.9	10.8
Asian/Pacific Islander	1446 (1.9)	2.0	3.8
American Indian/Alaskan Native	240 (0.3)	0.2	0.7

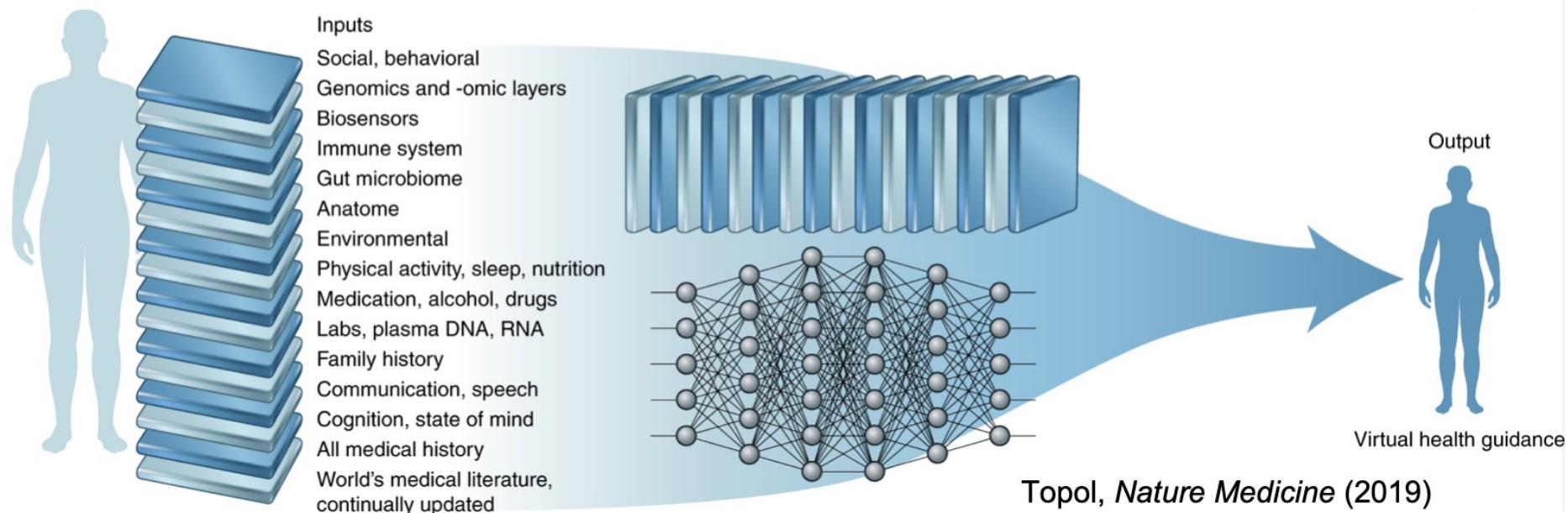
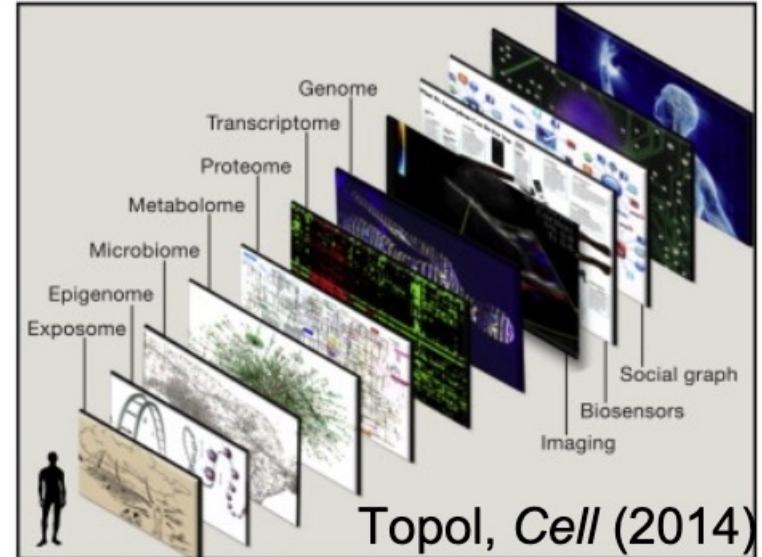
Murthy et al., *JAMA*, 2004.



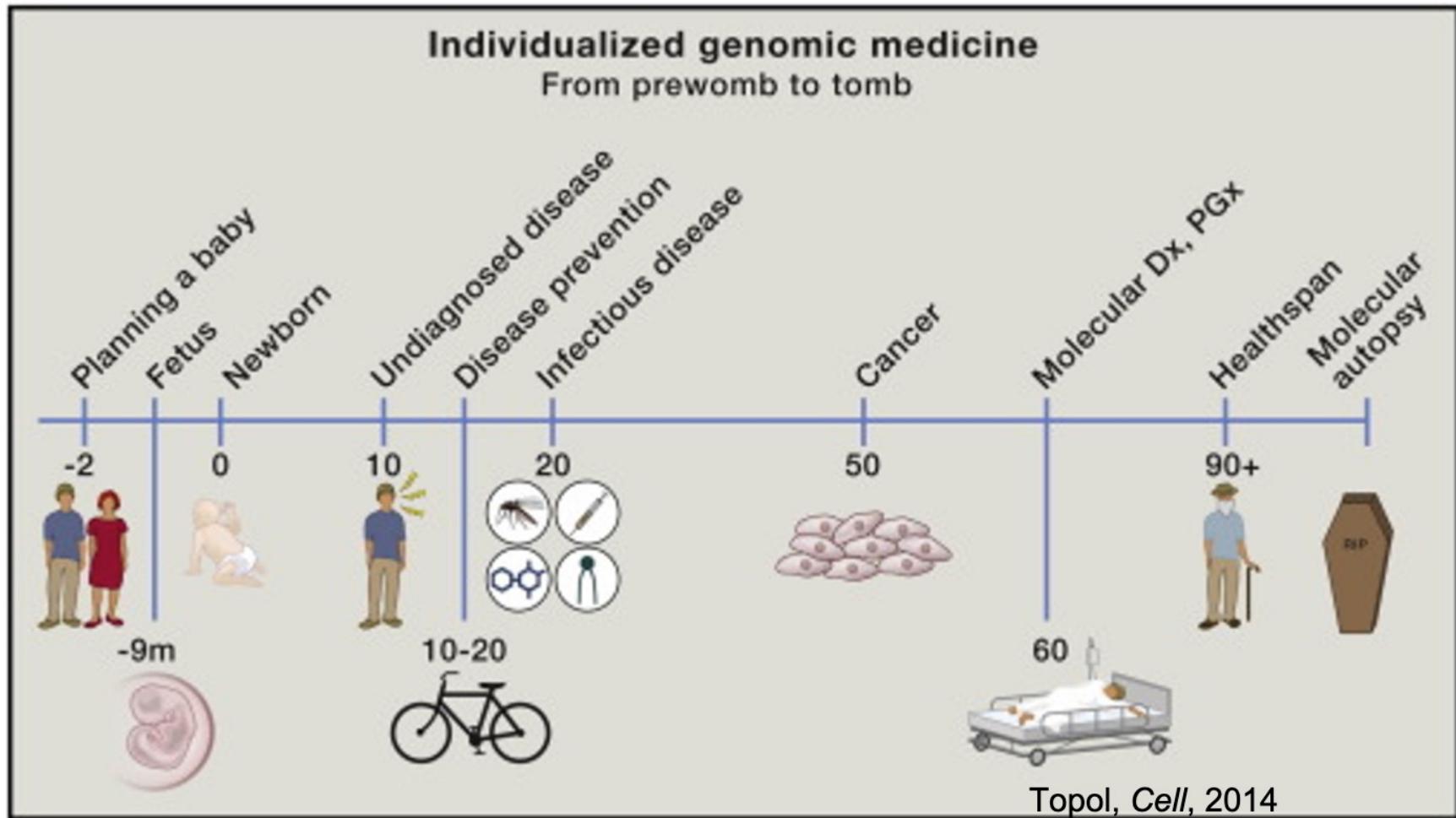
Most clinical decisions involve bridging the **inferential gap**: Clinicians are required to “fill in” where they lack knowledge or where no knowledge yet exists:

- Misdiagnoses, medical errors, prescription errors, surgical errors, under-treatments, over-treatments, unnecessary lab tests are caused by inferential gaps
- Late diagnosis of cancer can be due to the inferential gaps at the primary care
- Crisis caused by misuse, underuse, or overuse of antibiotics is in part due to serious inferential gaps

Achieving precision medicine requires multi-omic understanding of health state



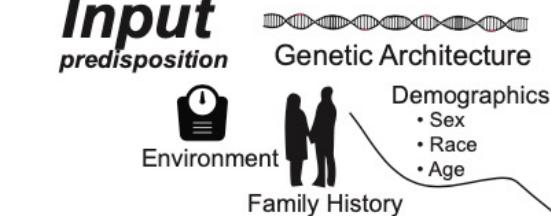
...and understanding how health state evolves



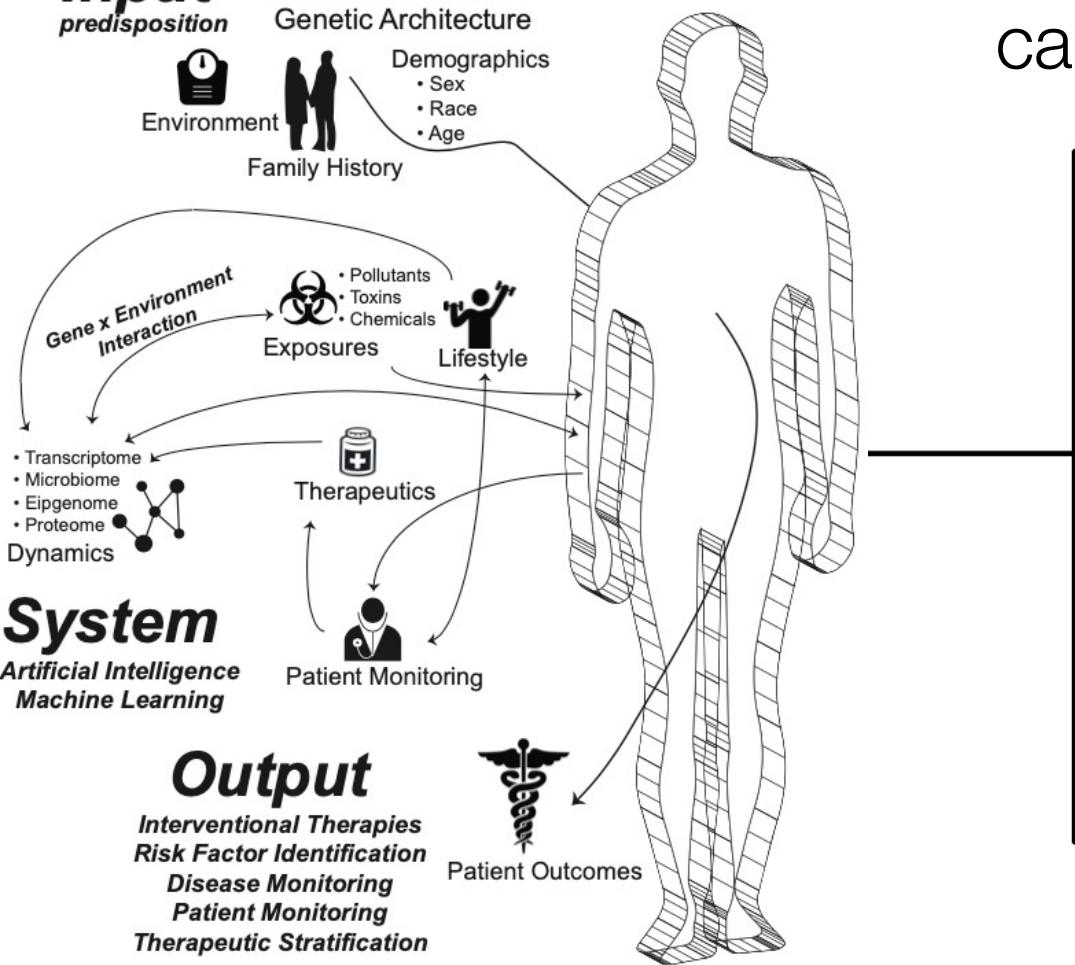
This all-encompassing dataset does not exist...

“The Quantified Self”

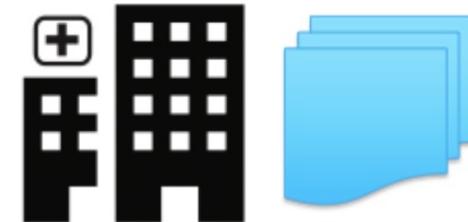
Input



... but real-world data can serve as proxy

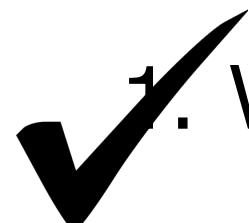


Electronic Health Records



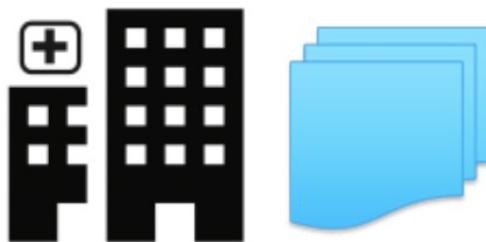
Next: How are electronic health records used for research?

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The Electronic Health Record

- The digitized paper charts
- The underlying goal/purpose of EHRs is **billing/infrastructure**
- Contains any data collected during an individual's interaction with a medical system
- Different software vendors (e.g., EPIC, Cerner)



Data type examples:

Clinical

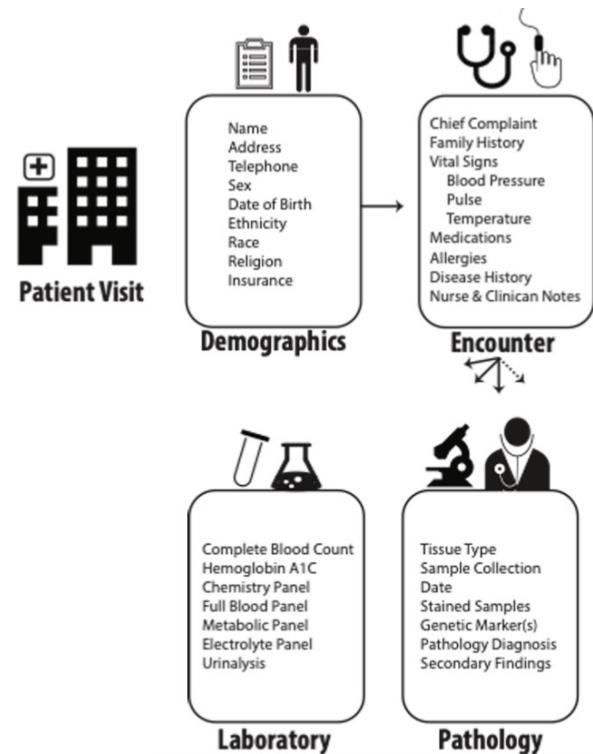
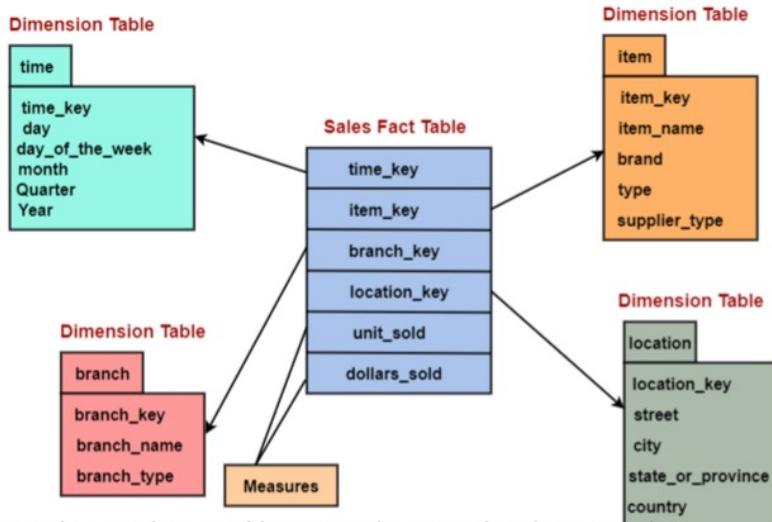
- Diagnoses
- Procedures
- Lab test results
- Imaging
- Medications
- Notes

Non-clinical

- Demographics
- Insurance
- Location
- Lifestyle

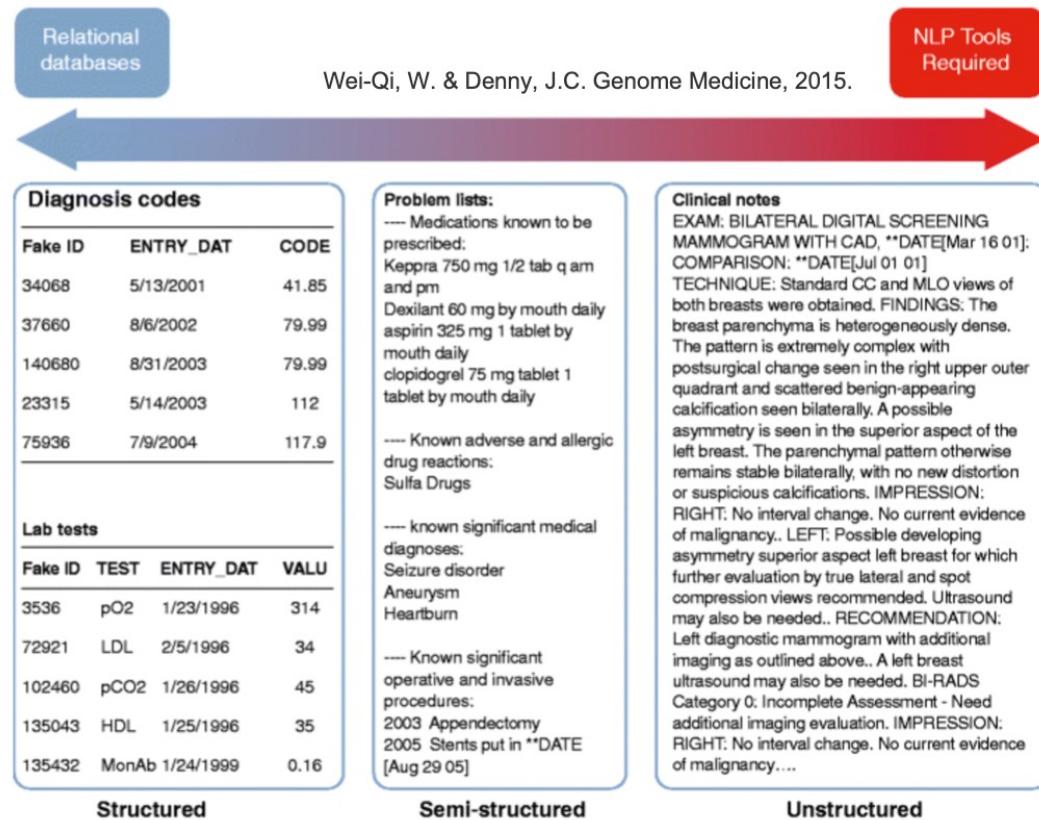
The EHR data types and formats

- Made available by data warehouses
- Are often *encounter-based*
- Typically separated by modality (e.g., demographics table, lab table)
- Often in star-schema format



The EHR data structure

- Structured: labs, medications, etc.
- Semi-structured: smartforms, radiology impressions, echo reports
- Unstructured: clinical notes
- Note: It does not have all data!



Types of research using EHRs?

- Characterize co-morbidities & epidemiological trends
 - Identify disease sub-phenotypes
 - Identify unknown drug adverse events
 - Find symptom clusters
 - Predict medication response
 - Anticipate disease flare-ups
 - Guide triage decisions
 - Track treatment progression and sequelae
 - Couple with other patient data modalities: genetics, images, notes, biosignals, etc.
- + countless more...

Example: Identifying temporal disease trajectories (1/4)

Data: The entire spectrum of diseases covering 14.9 years of EHR data on 6.2 million patients

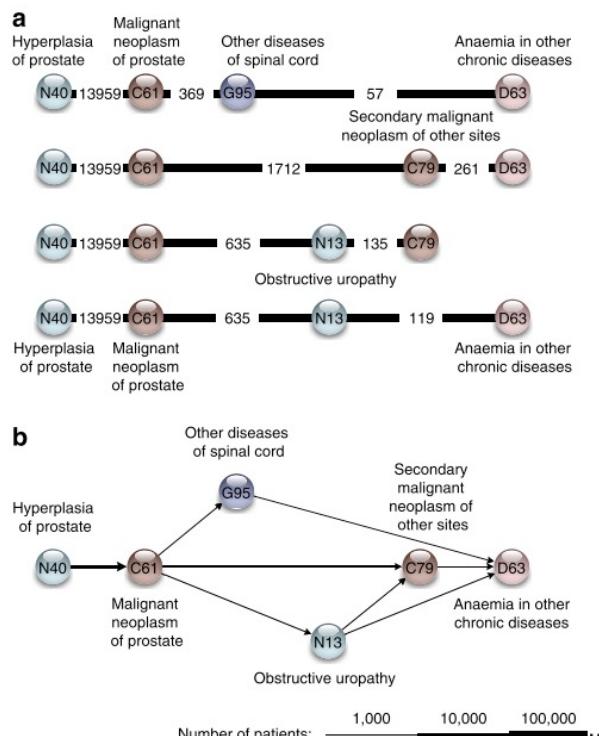


Figure 2 | Disease trajectories and trajectory-cluster for prostate cancer.

The figure illustrates the transition from trajectories to a trajectory cluster. Each circle represents a diagnosis and is labelled with the corresponding ICD-10 code. The colours represent different ICD-10 chapters. The temporal diagnosis progression goes from left to right. (a) All trajectories that contribute to the prostate-cancer cluster. The number of patients, who follow the trajectory until a given diagnosis, is given in the edges. (b) The prostate cancer trajectory cluster that represents all the trajectories. The width of the edges corresponds to the number of patients with the directed diagnosis pair from the full population. The cluster describes a normal progression from having hyperplasia of prostate diagnosed to having prostate cancer, cancer metastasis and anaemia.

Example: Identifying temporal disease trajectories (2/4)

Approach

1. Analyze temporal co-morbidity:

- From the full data set, identify pairs ($D1 \rightarrow D2$) of diagnoses where $D2$ occurs within a 5-year time frame of $D1$
- Test pairs for significant directionality: Identify those where a significantly higher number of patients had $D1$ occurring before $D2$ compared with the opposite direction or in the same admission
- This analysis yielded 1,171 four-long diagnosis trajectories

2. Cluster trajectories:

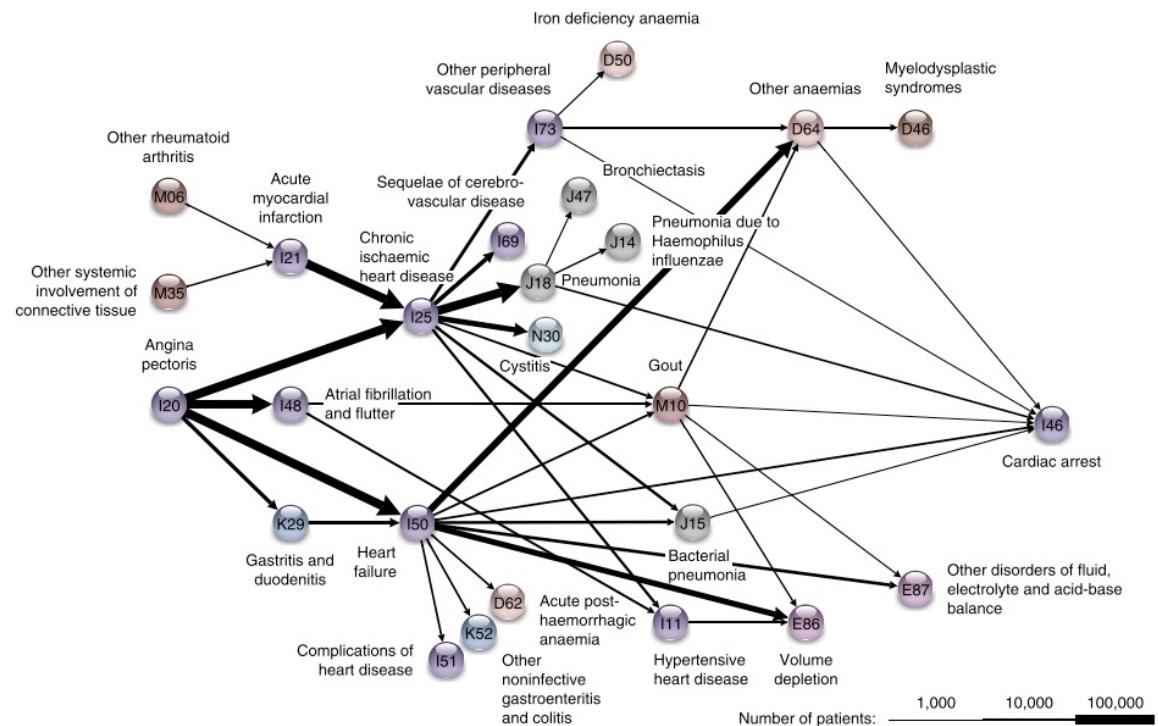
- Objective: Cluster trajectories that have large diagnosis overlap and represent variants of general patterns of disease progression.
- Cluster trajectories based on which diagnoses they share
 - Use the **Markov Cluster Algorithm** that assigns each code that appears in 1,171 trajectories to a cluster
 - Use the **Jaccard index** as a similarity measure: count how many trajectories both diagnoses are part of and normalize by the total number of trajectories either is part of
 - Combine trajectories with all diagnoses within the same cluster into **directed trajectory clusters** in which the patterns can be examined

Example: Identifying temporal disease trajectories (3/4)

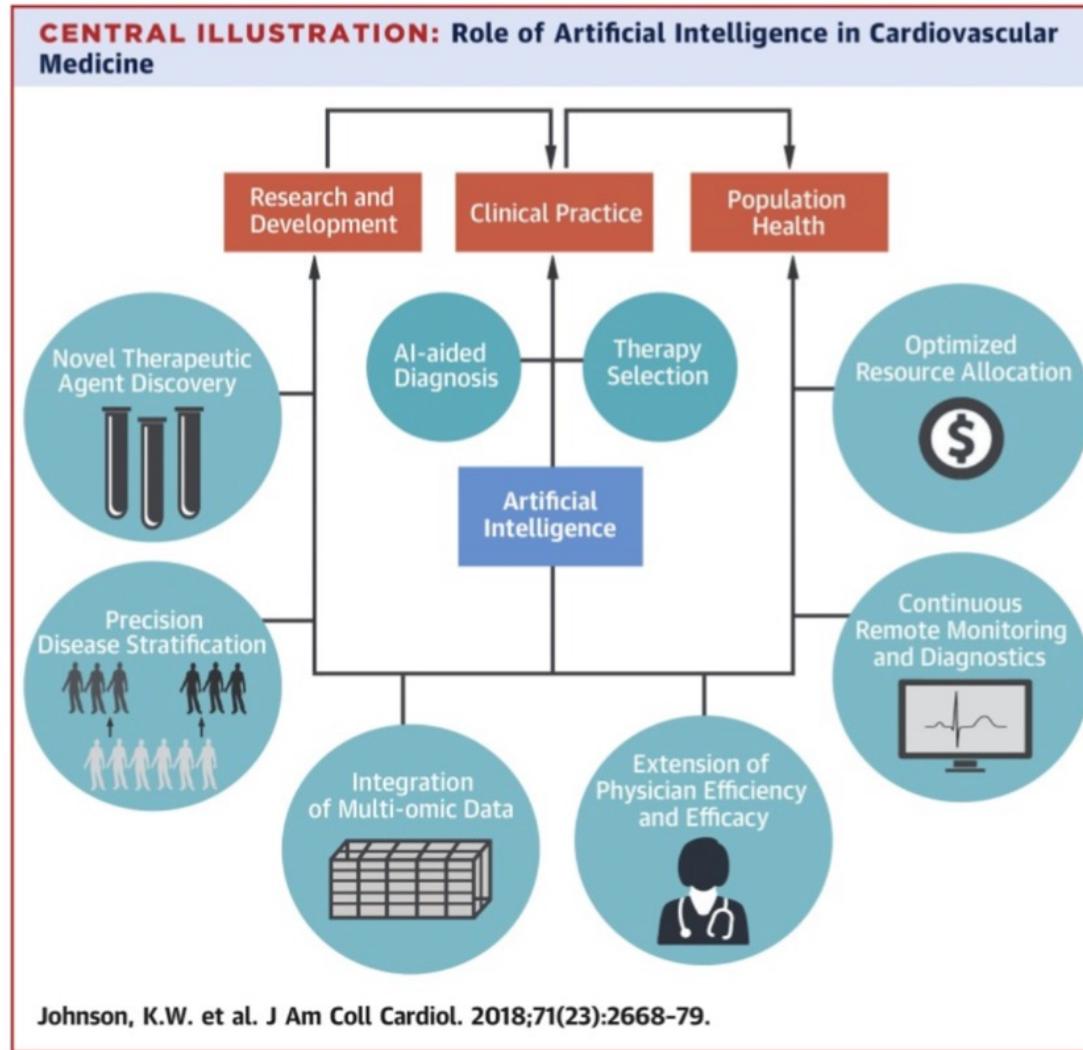
- Clustering identified 15 clusters:
 - The five largest clusters covered 46, 25, 12, 9, and 8 diagnoses each
 - Each is a group of patterns centered on a small number of key diagnoses, which are central to disease progression and important to diagnose early to mitigate the risk of adverse outcomes
 - The five largest clusters were enriched for:
 - Diseases of the prostate
 - Chronic obstructive pulmonary disease
 - Cerebrovascular disease
 - Cardiovascular disease
 - Diabetes mellitus

Example: Identifying temporal disease trajectories (4/4)

Cardiovascular cluster. A key finding is that gout is a central diagnosis in the cardiovascular cluster, supporting evidence that gout is important to progression of cardiovascular diseases in a keystone manner



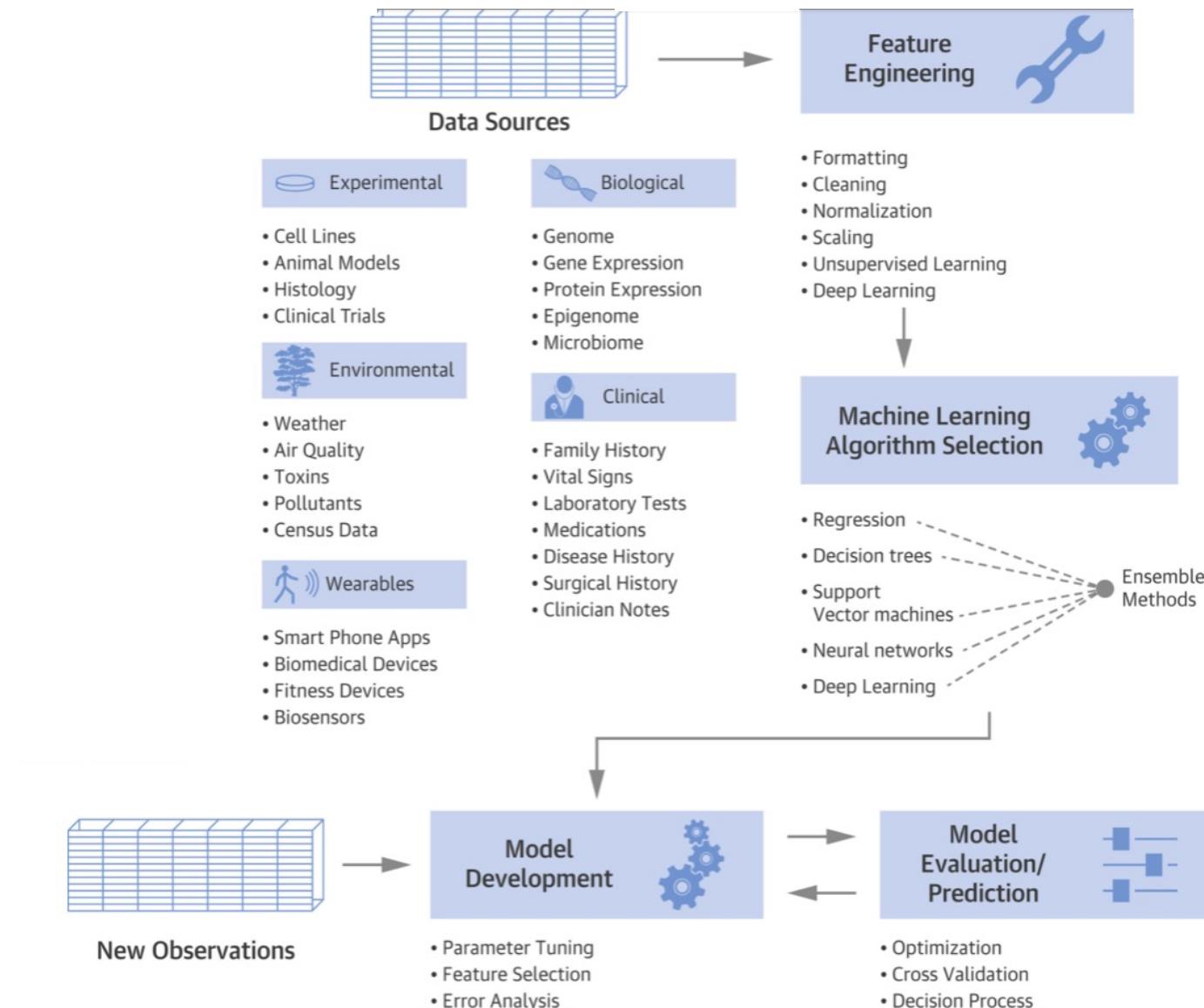
Goals of ML for healthcare using EHR



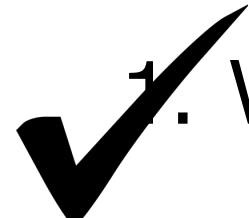
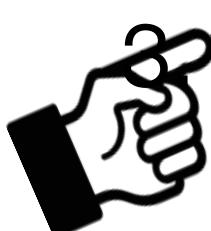
Typical ML workflow for EHR data

- Gather (identify relevant feature)
- QC values (wrong unit?)
- Check for/address missingness
- Phenotype and design cohort
- Define outcome (label) and study period
- Use relevant ML techniques
- Pre-process data to fit the ML technique
- Refine and repeat

Typical ML workflow for EHR data



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What is a disease?

- A disease is not easily defined in EHRs!
- Many ways in which a disease can be represented (and often wrong)
- Phenotyping algorithms and standardized concepts to the rescue: accurately identify patients with a specific observable trait from imperfect EHR data



How well do various data types define a disease? (1/3)

- **Goal:** To evaluate the phenotyping performance of three major EHR data types:
 - International Classification of Disease (ICD) diagnosis codes
 - Primary notes
 - Specific medications
- **Approach:**
 - Preselect ten diseases: atrial fibrillation, Alzheimer's disease, breast cancer, gout, human immunodeficiency virus infection, multiple sclerosis, Parkinson's disease, rheumatoid arthritis, and types 1 and 2 diabetes mellitus
 - For each disease, classify patients into seven categories based on the presence of evidence for disease in a) diagnosis codes, b) primary notes, and c) specific medications
 - For each disease, select 175 random patients for **manual chart review**
 - Use review results to estimate **positive predictive value (PPV)** for each EHR data type alone and in combination

How well do various data types define a disease? (2/3)

- PPV is the ratio of patients that truly have the disease according to manual chart review to all patients who had been identified as having the disease in a data type
- The PPVs of single data types were inadequate for accurate phenotyping (0.06–0.71)
- Using two or more ICD codes improved the average PPV to 0.84

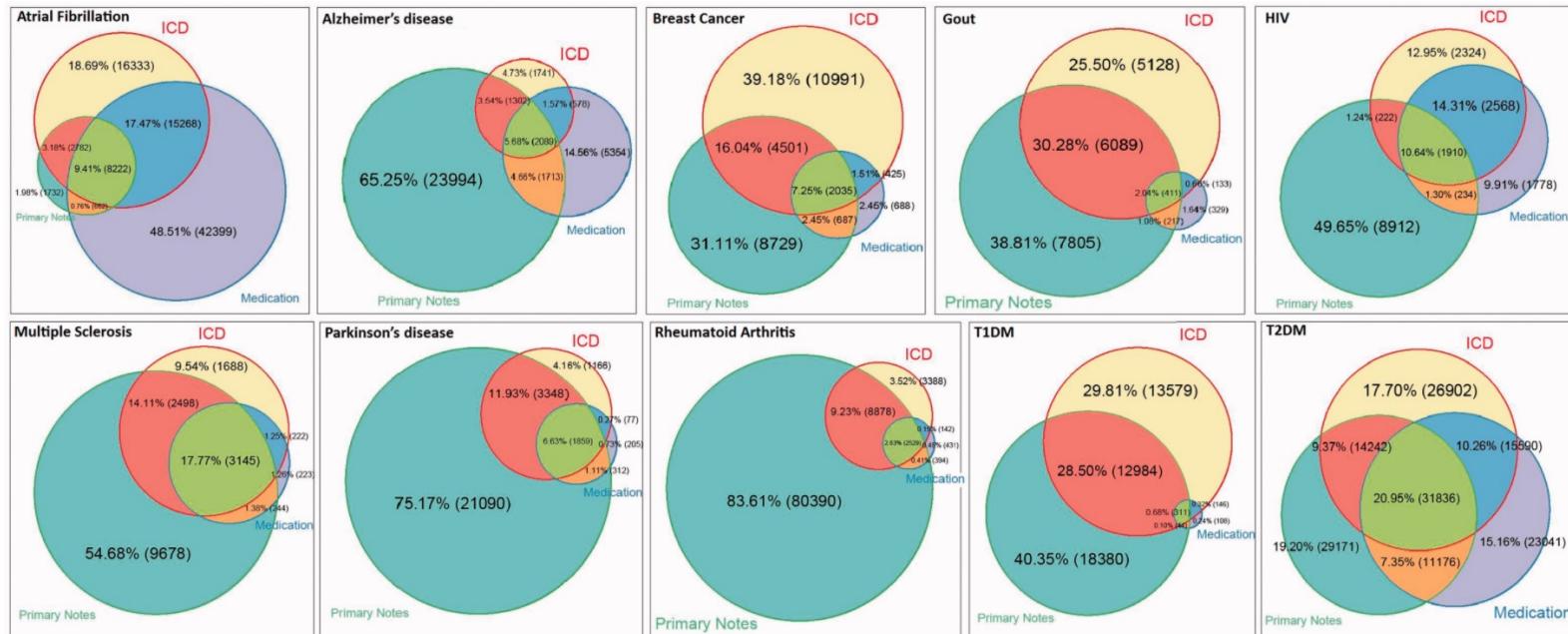
Table 1:

Positive prediction values of various categories based on chart review results

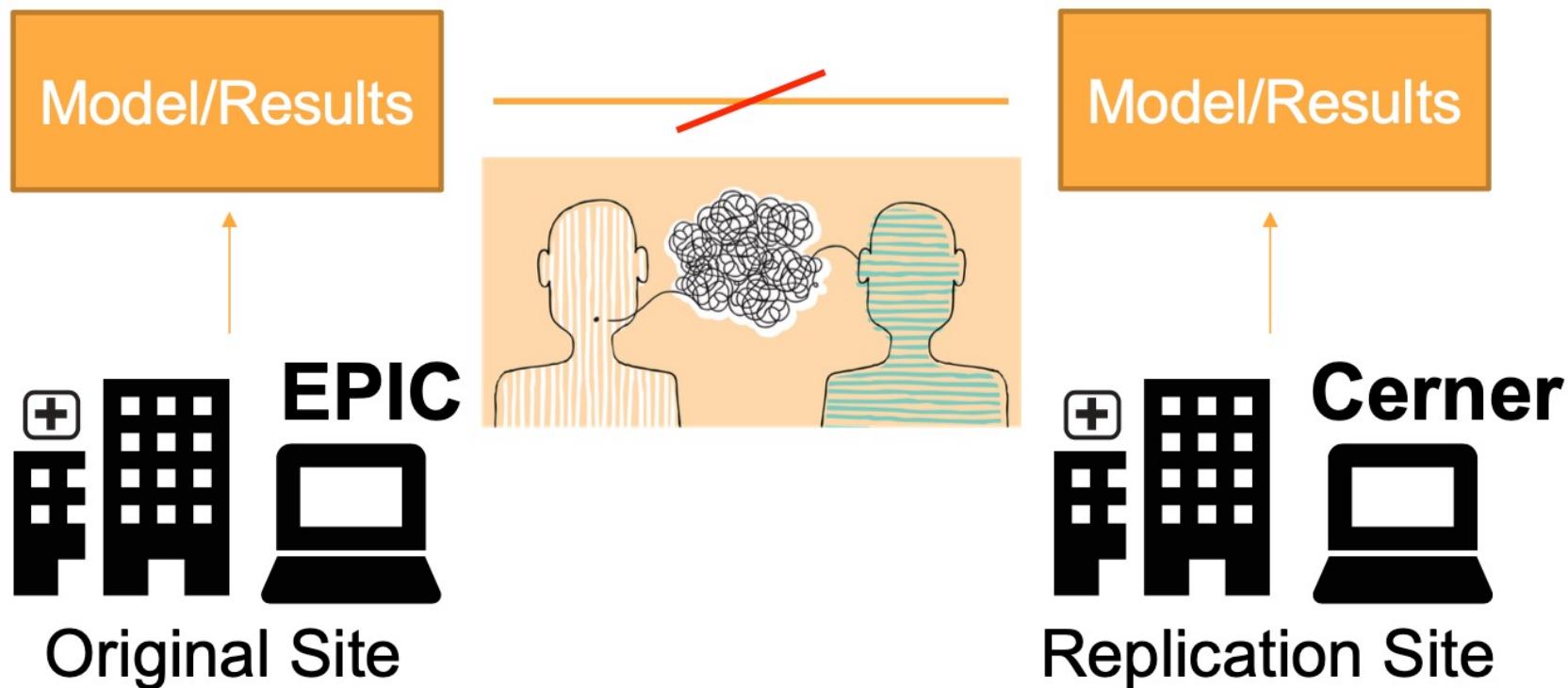
Disease	ICD-9 Only	PN Only	Meds Only	ICD-9+Meds	ICD-9+PN	Meds+PN	ICD-9+both	ICD-9	Meds	PN	≥2 ICD-9's	≥2 Components
AFIB	0.52	0.72	0.08	0.72	1.00	1.00	1.00	0.72	0.35	0.96	0.88	0.84
Alzheimer's	0.28	0.20	0.00	0.80	0.88	0.92	0.88	0.69	0.40	0.32	0.74	0.88
Breast CA	0.12	0.72	0.04	0.88	0.96	1.00	1.00	0.45	0.81	0.84	1.00	0.97
Gout	0.56	0.84	0.00	0.92	1.00	1.00	1.00	0.81	0.69	0.91	0.93	1.00
HIV	0.52	0.00	0.00	0.92	0.84	0.88	1.00	0.81	0.69	0.20	0.89	0.95
MS	0.20	0.08	0.12	0.88	0.88	0.88	1.00	0.78	0.93	0.41	0.86	0.94
Parkinson	0.48	0.16	0.04	0.84	1.00	0.88	0.96	0.89	0.87	0.33	0.94	0.98
RA	0.36	0.20	0.00	0.64	0.76	0.88	0.84	0.68	0.73	0.27	0.77	0.78
T1DM	0.28	0.12	0.04	0.16	0.92	0.84	0.76	0.59	0.49	0.45	0.62	0.91
T2DM	0.36	0.68	0.24	0.60	0.80	1.00	0.84	0.65	0.65	0.80	0.73	0.81
Average	0.37	0.37	0.06	0.74	0.90	0.93	0.93	0.71	0.66	0.55	0.84	0.91
Standard Deviation	0.15	0.32	0.08	0.23	0.09	0.06	0.09	0.13	0.20	0.29	0.12	0.08

How well do various data types define a disease? (3/3)

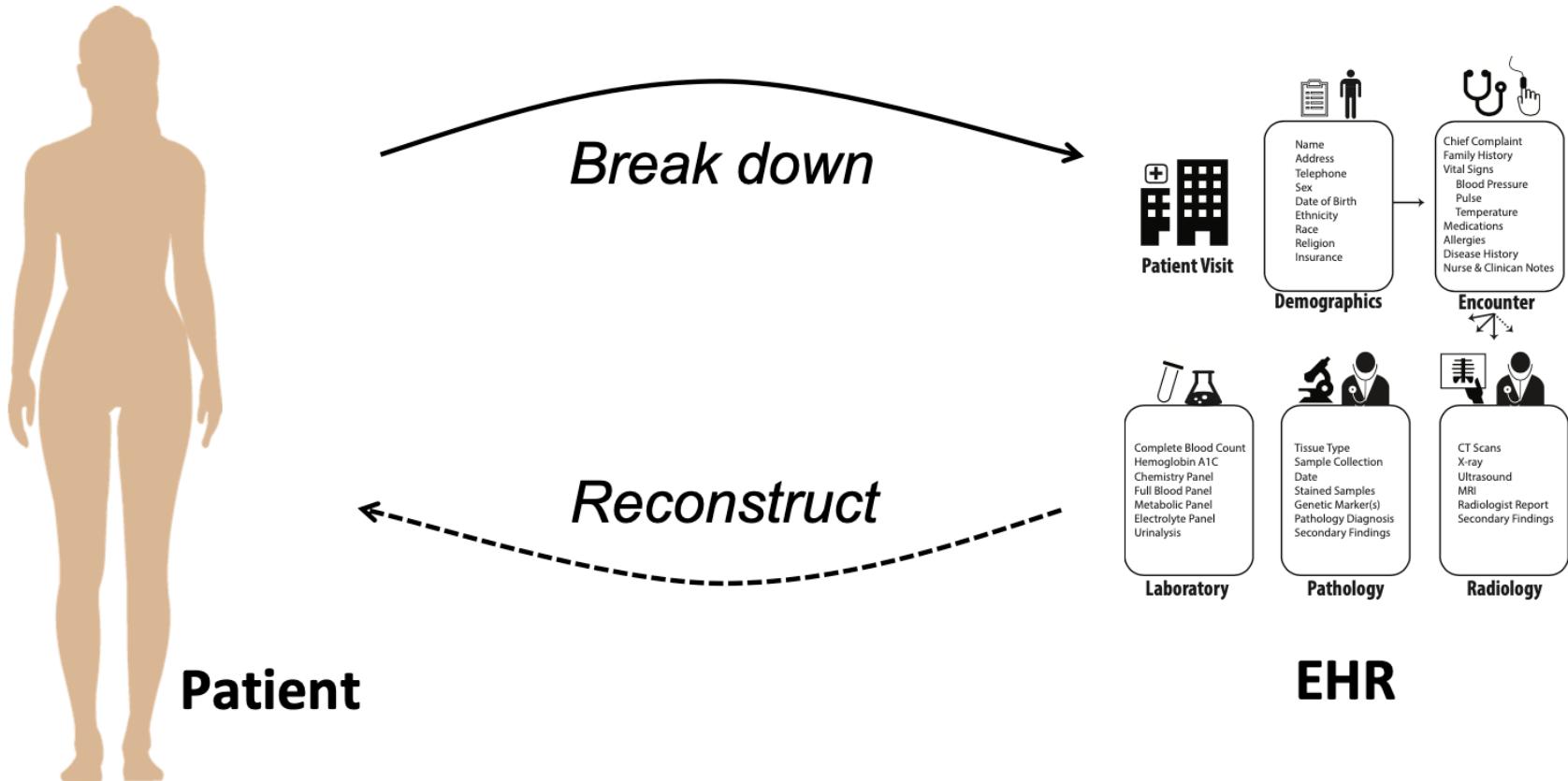
- Multiple data types provide a more consistent and higher performance than a single one
- Use multiple EHR data types for disease phenotyping



External replication is necessary but not easy to facilitate



It is challenging to capture health state from EHR



ML can learn the wrong information

RESEARCH

OPEN ACCESS

Biases in electronic health record data due to processes within the healthcare system: retrospective observational study

Denis Agniel,¹ Isaac S Kohane,^{1,2} Griffin M Weber^{1,3}

RESULTS

The presence of a laboratory test order, regardless of any other information about the test result, has a significant association ($P<0.001$) with the odds of survival in 233 of 272 (86%) tests. Data about the timing of when laboratory tests were ordered were more accurate than the test results in predicting survival in 118 of 174 tests (68%).

CONCLUSIONS

Healthcare processes must be addressed and accounted for in analysis of observational health data. Without careful consideration to context, EHR data are unsuitable for many research questions. However, if explicitly modeled, the same processes that make EHR data complex can be leveraged to gain insight into patients' state of health.

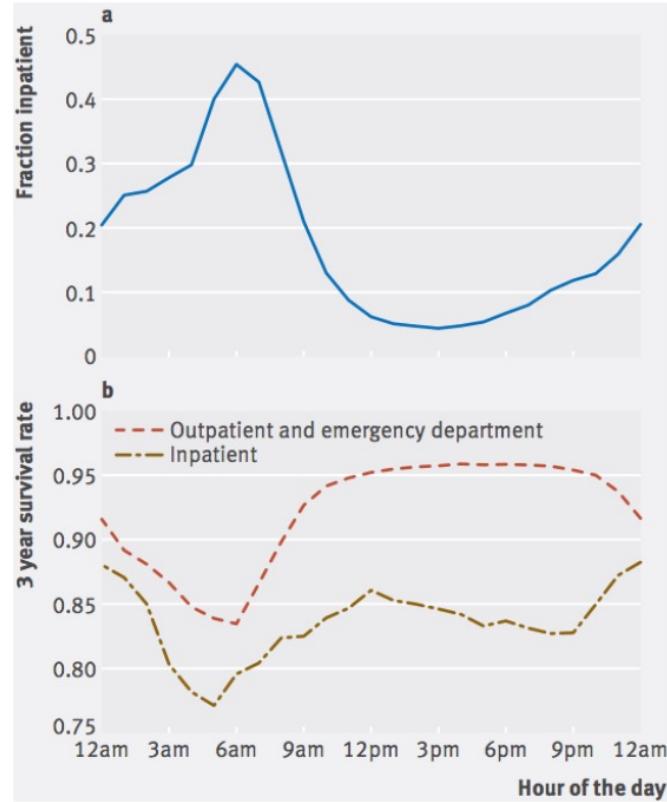


Fig 4 | White blood cell count by hour of the day. Note that (b) was smoothed using a three point running average

ML algorithms can “cheat” (1/3)

- **Objective:** Hip fractures are a leading cause of death and disability among older adults
 - Most commonly missed diagnosis on pelvic radiographs
 - Delayed diagnosis leads to higher cost & worse outcomes

Deep learning predicts hip fracture using confounding patient and healthcare variables

[Marcus A. Badgeley](#), [John R. Zech](#), [Luke Oakden-Rayner](#), [Benjamin S. Glicksberg](#), [Manway Liu](#), [William Gale](#), [Michael V. McConnell](#), [Bethany Percha](#), [Thomas M. Snyder](#) & [Joel T. Dudley](#) 

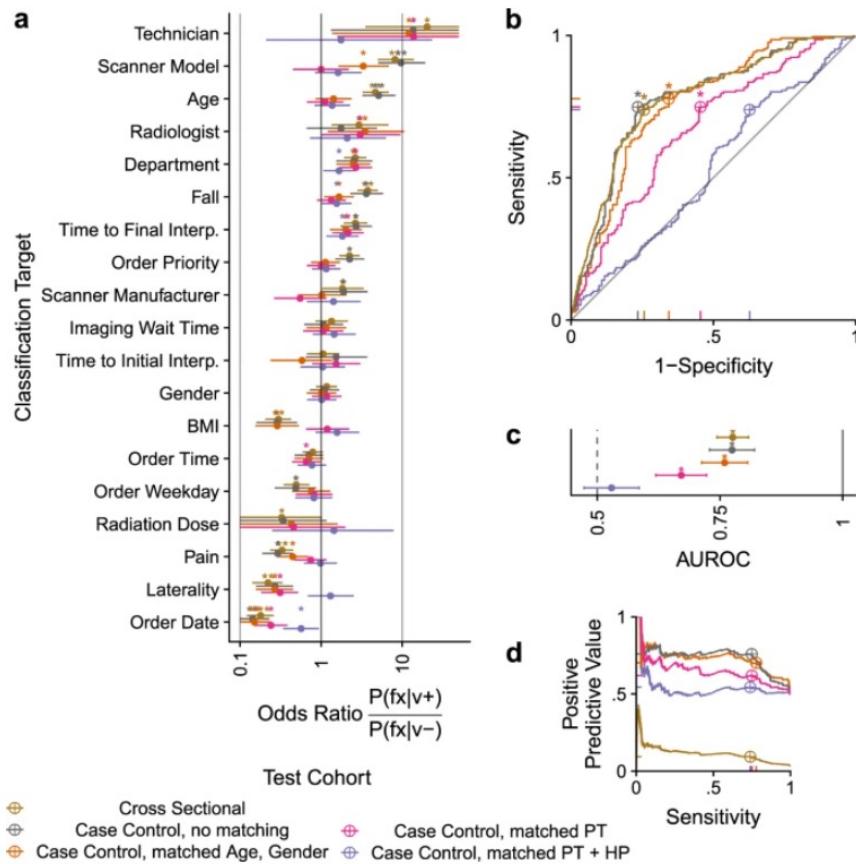
- **Data:** Collect 23,602 hip radiographs from 9,024 patients, patient and hospital process EHR data:
 - Prevalence of fracture is 3% (779/23,602), and patients with fractures were more likely to report a recent fall and less likely to report pain
 - Extracted information: image (**IMG**), disease (i.e., fracture) class, 5 patient (**PT**), 14 hospital process (**HP**) features

ML algorithms can “cheat” (2/3)

- **ML model:** Train a neural network on radiographs to classify fracture
- **Results:** Fracture is predicted:
 - Moderately well from the **IMG** data alone ($AUC=0.78$)
 - Better when combining **IMG + PT** ($AUC=0.86$)
 - Better when combining **IMG + PT + HP** ($AUC=0.91$)
- **Follow-up analysis:**
 - Seek to test ML model whether it can **directly detect fracture** versus **indirectly predict fracture by detecting confounding variables associated with fracture**
 - On a test set with fracture risk balanced across PT and HP variables, the fracture detector is no better than random ($AUC=0.52$)

ML algorithms can “cheat” (3/3)

- On a test set with fracture risk balanced across PT and HP features, **the fracture detector is no better than random (AUC=0.52)**
- PT + HP features are the main source of fracture predictions
- It is unclear how radiologists should interpret radiographs relative to other patient data

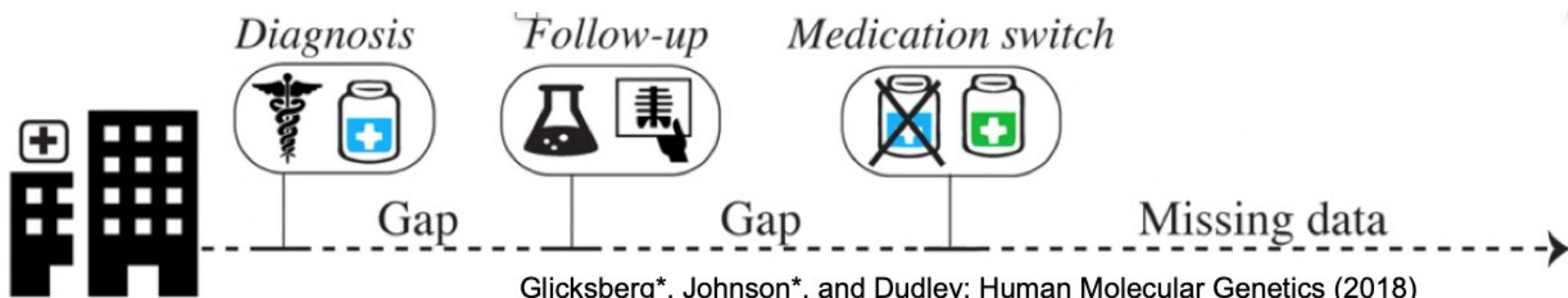


Recap: Limitations & biases of EHR

- Diseases are not easily defined in EHRs!
- External replication is not easy to facilitate
- It is challenging to capture health state from EHR
- ML algorithms can learn the wrong information
- ML algorithms can “cheat”
- ML algorithms can fail on other patient populations
- Biased real-world data can lead to real-world consequences

Fine print of using EHR for research

- In USA (and elsewhere), the healthcare is fragmented and EHRs do not extend beyond specific health system
- EHRs capture only data that is entered and how it is entered: “Garbage in, garbage out”
- EHR systems are messy, redundant, incomplete, heterogenous, erroneous, etc.
- Interfacing with EHR data is challenging and requires domain expertise
- Biases are propagated through!
- Poorly encoded key information: i.e., social determinants of health
- The “missing phenotype”



Quick Check

<https://forms.gle/N85jAoUVPuBFyG3U8>

BMI 702: Biomedical Artificial Intelligence

Foundations of Biomedical Informatics II, Spring 2023

Quick check quiz for lecture 2: Introduction to AI on clinical datasets

Course website: <https://zitniklab.hms.harvard.edu/BMI702>

*Required

First and last name *

Your answer

Harvard email address *

Your answer

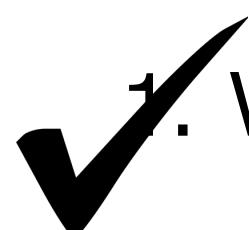
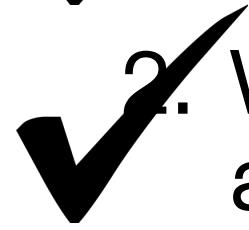
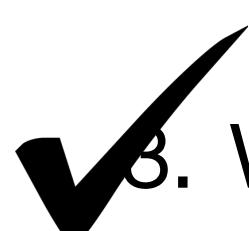
Give an example of inferential gap in clinical decision making *

Your answer

Select one EHR-based research project from slide 13 and briefly describe how a * typical ML workflow (slide 19) for the project would look like

Your answer

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Polypharmacy

Patients take multiple drugs to treat complex or co-existing diseases

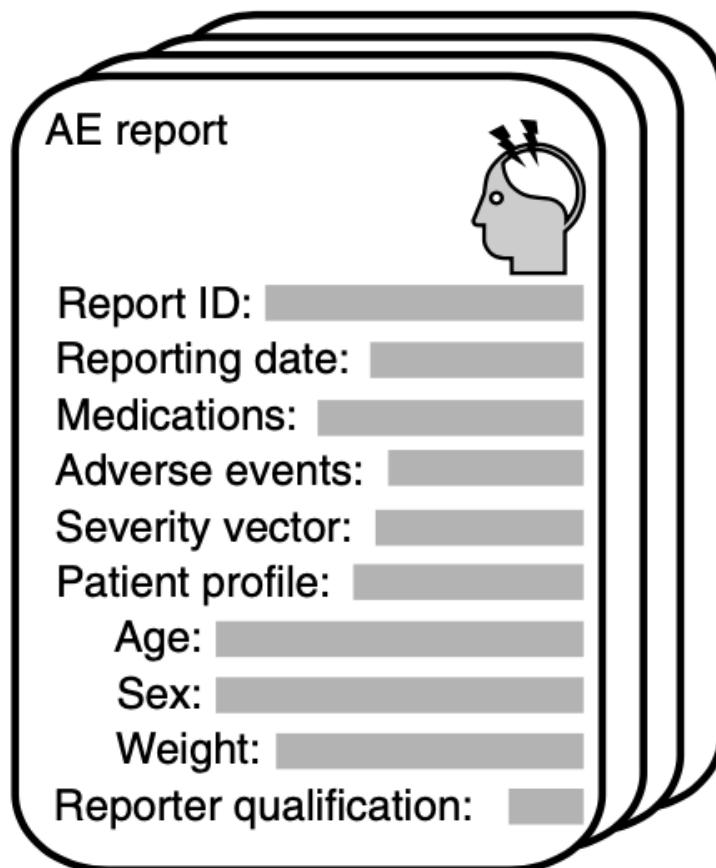
46% of people over 65 years take more than 5 drugs

Many take more than 20 drugs to treat heart diseases, depression or cancer

15% of the U.S. population affected by unwanted side effects

Annual costs in treating side effects exceed \$177 billion in the U.S. alone

FDA Adverse Event Reporting System (FAERS)



Unwanted side effects

The FDA Adverse Event Reporting System (FAERS)

Drugs taken	Unwanted side effects
	Peliosis hepatitis (0.2%), Heart rate increased (0.5%), Aortic aneurysm (0.1%)
	Joint stiffness (3%), Joint swelling (1%), Bone marrow fibrosis (0.01%)
	Anaemia (1%), Bone marrow fibrosis (0.5%), Intestinal ulcer (0.001%)
	Anaemia (1%), Bone marrow fibrosis (0.1%), Intestinal ulcer (0.01%), Joint stiffness (3%), Joint swelling (1%)
	Peliosis hepatitis (0.2%), Heart rate increased (0.5%), Aortic aneurysm (0.1%), Joint stiffness (3%), Joint swelling (1%), Bone marrow fibrosis (0.01%)
...	...

Unwanted side effects

The FDA Adverse Event Reporting System (FAERS)

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...	...

Unwanted side effects

The FDA Adverse Event Reporting System (FAERS)

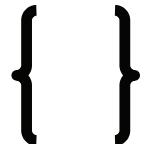
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	Joint stiffness (3%), Joint swelling (1%), Bone marrow fibrosis (0.01%)
	Anaemia (1%), Bone marrow fibrosis (0.5%), Intestinal (0.001%)
	Anaemia (1%), Bone marrow fibrosis (0.1%), Intestinal ulcer (0.01%), Joint stiffness (3%), Joint swelling (1%), Colon cancer (0.1%) , Fatigue (2%)
	Peliosis hepatitis (0.2%), Heart rate increased (0.5%), Aortic aneurysm (0.1%), Joint stiffness (3%), Joint swelling (1%), Bone marrow fibrosis (0.01%)
...	...

Unexpected Drug Interactions

Co-prescribed drugs



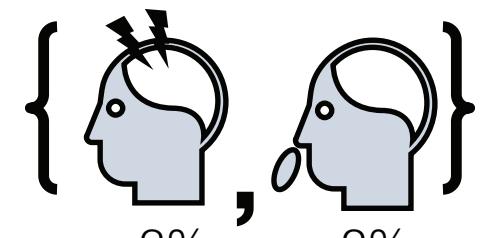
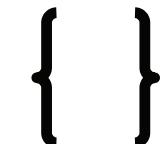
Side Effects



Task: How likely will a particular combination of drugs lead to a particular side effect?



?



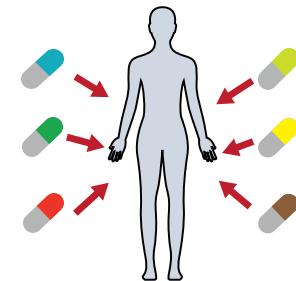
3%
prob.

2%
prob.

Why is modeling polypharmacy a hard problem?

Combinatorial explosion

- >13 million possible combinations of 2 drugs
- >20 billion possible combinations of 3 drugs



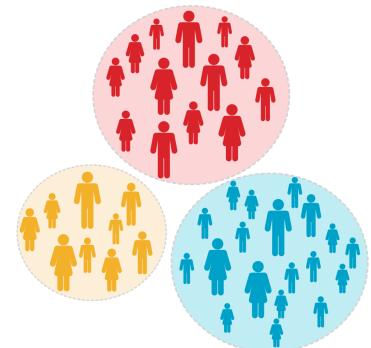
Non-linear & non-additive interactions



- Different effect than the additive effect of individual drugs

Small subsets of patients

- Side effects are interdependent
- No info on drug combinations not yet used in patients

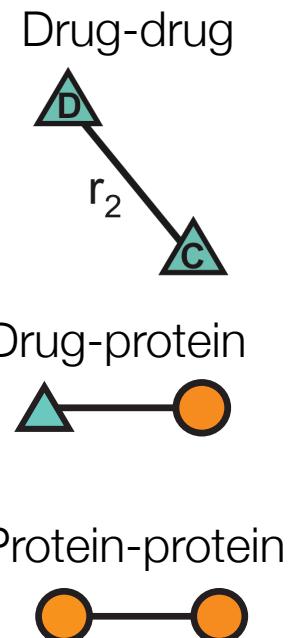


Polypharmacy dataset

Objective: Capture molecular, drug, and patient data for all drugs prescribed in the U.S.

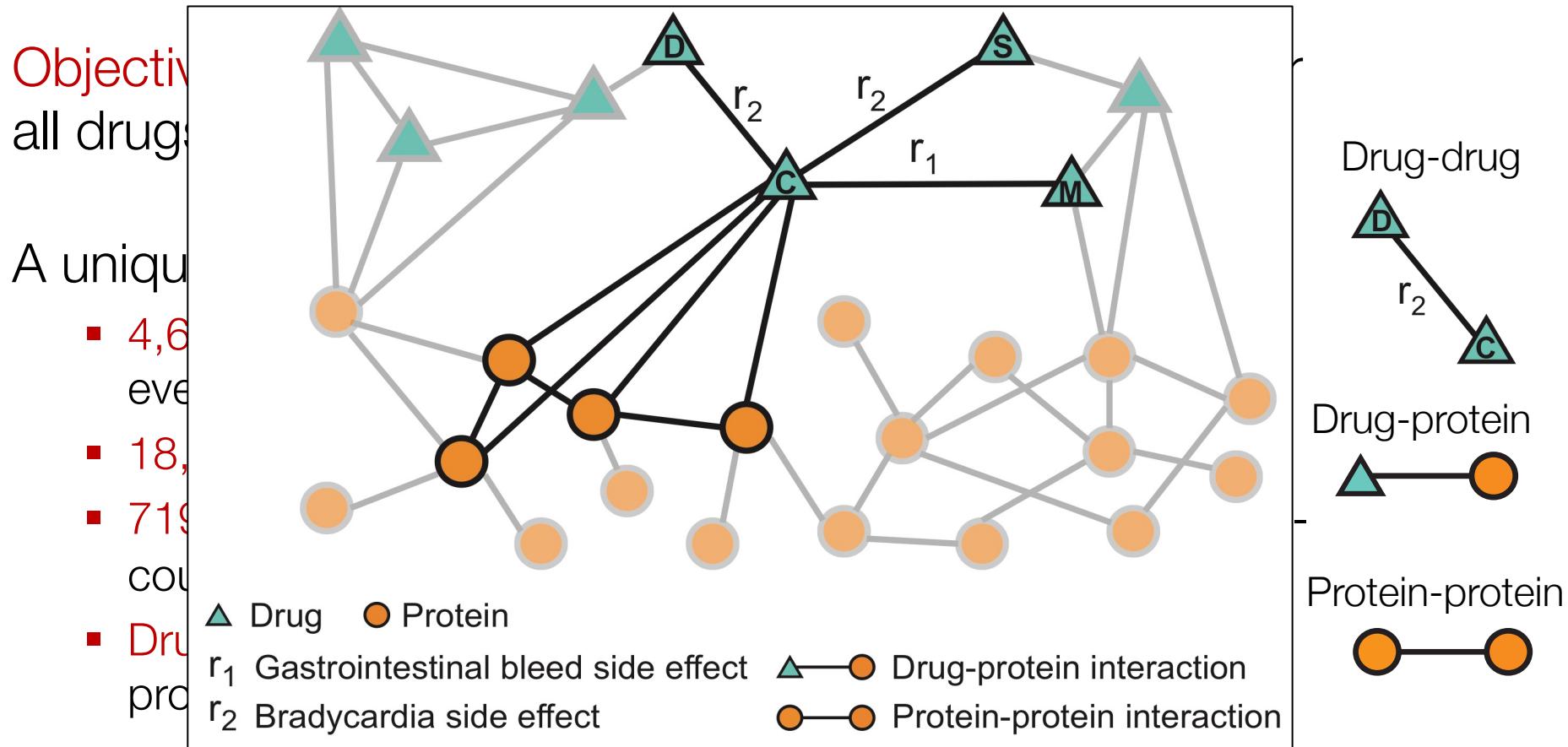
Dataset:

- 4,651,131 drug-drug edges: Patient data from adverse event system, tested for confounders [FDA]
- 18,596 drug-protein edges
- 719,402 protein-protein edges: Physical, metabolic enzyme-coupled, and signaling interactions
- **Drug and protein features:** drugs' chemical structure, proteins' membership in pathways



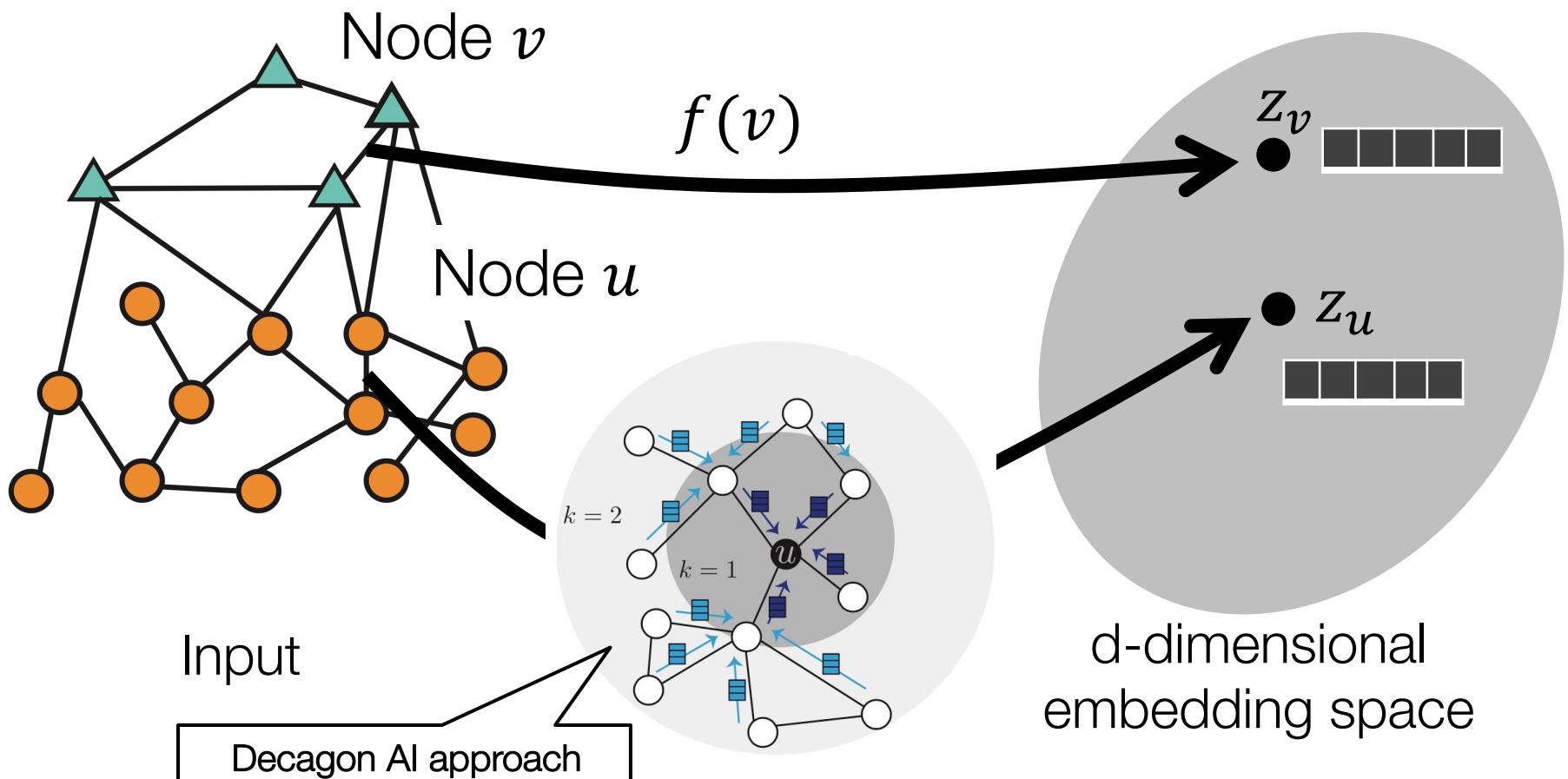
Gives polypharmacy network with over 5 million edges separated into 1,000 different edge types

Polypharmacy dataset



Gives polypharmacy network with over 5 million edges separated into 1,000 different edge types

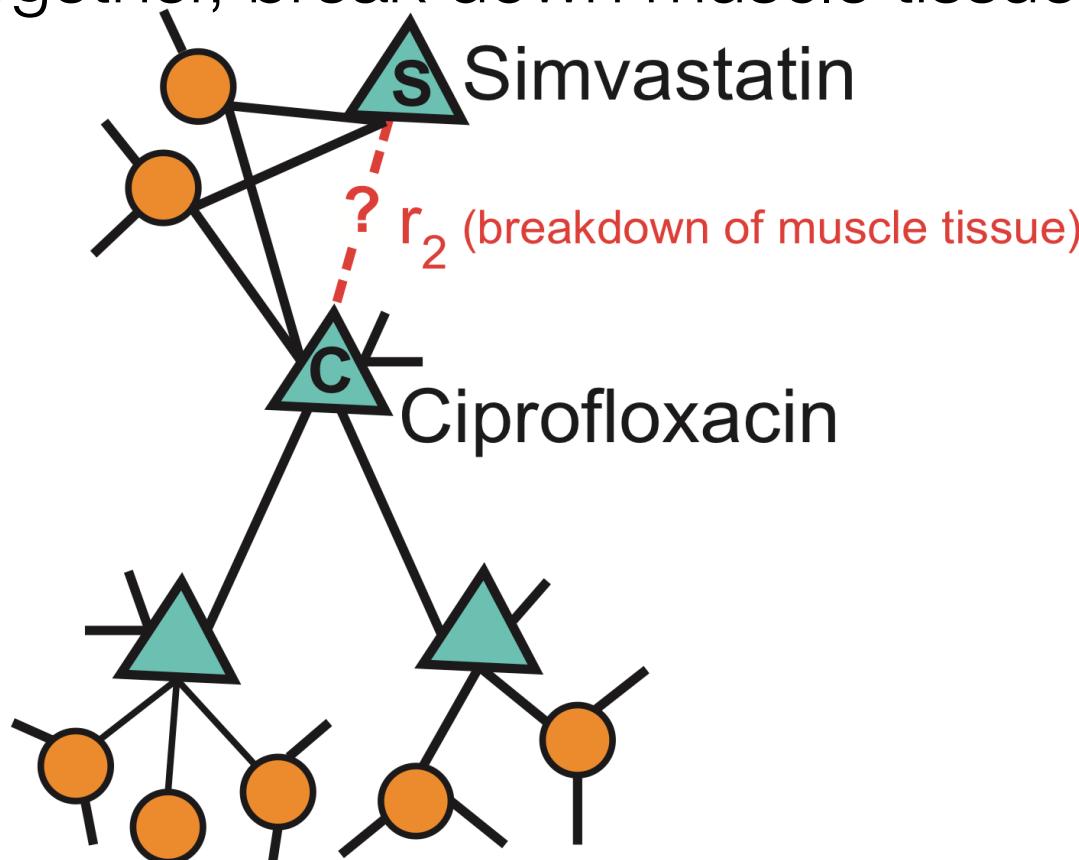
Approach: Graph Neural Network



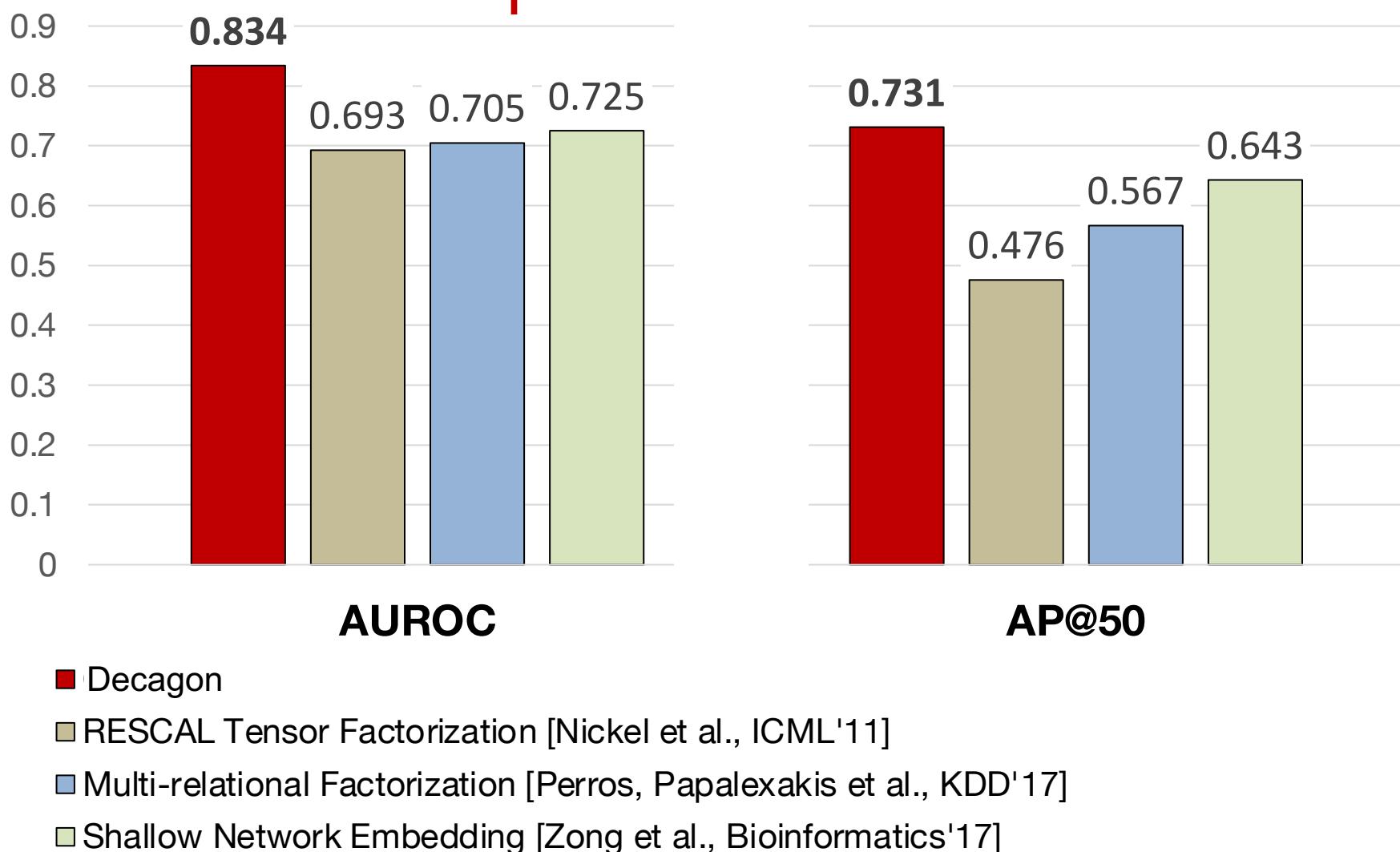
Map nodes to d -dimensional embeddings such that **nodes with similar network neighborhoods** are **embedded close together**

Apply Decagon AI algorithm to the polypharmacy network

E.g.: How likely will Simvastatin and Ciprofloxacin, when taken together, break down muscle tissue?



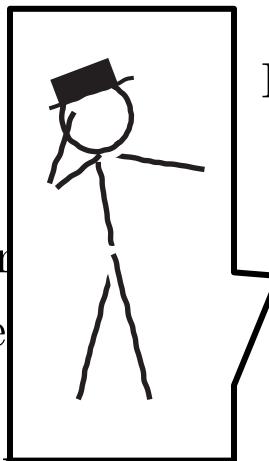
Results: Polypharmacy side effect prediction



Results: Polypharmacy side effects

Approach:

- 1) Train deep model on data generated prior to 2012
- 2) How many predictions have been confirmed after 2012?

Rank	Drug	Drug	Side effect	Evidence found
1	Pyrimethamine	Aliskiren	Sarcoma	
2	Tigecycline	Bimatoprost	Autonomic n.	
3	Telangiectases	Omeprazole	Dacarbazine	
4	Tolcapone	Pyrimethamine	Blood brain	

Case Report

Severe Rhabdomyolysis due to Presumed Drug Interactions between Atorvastatin with Amlodipine and Ticagrelor

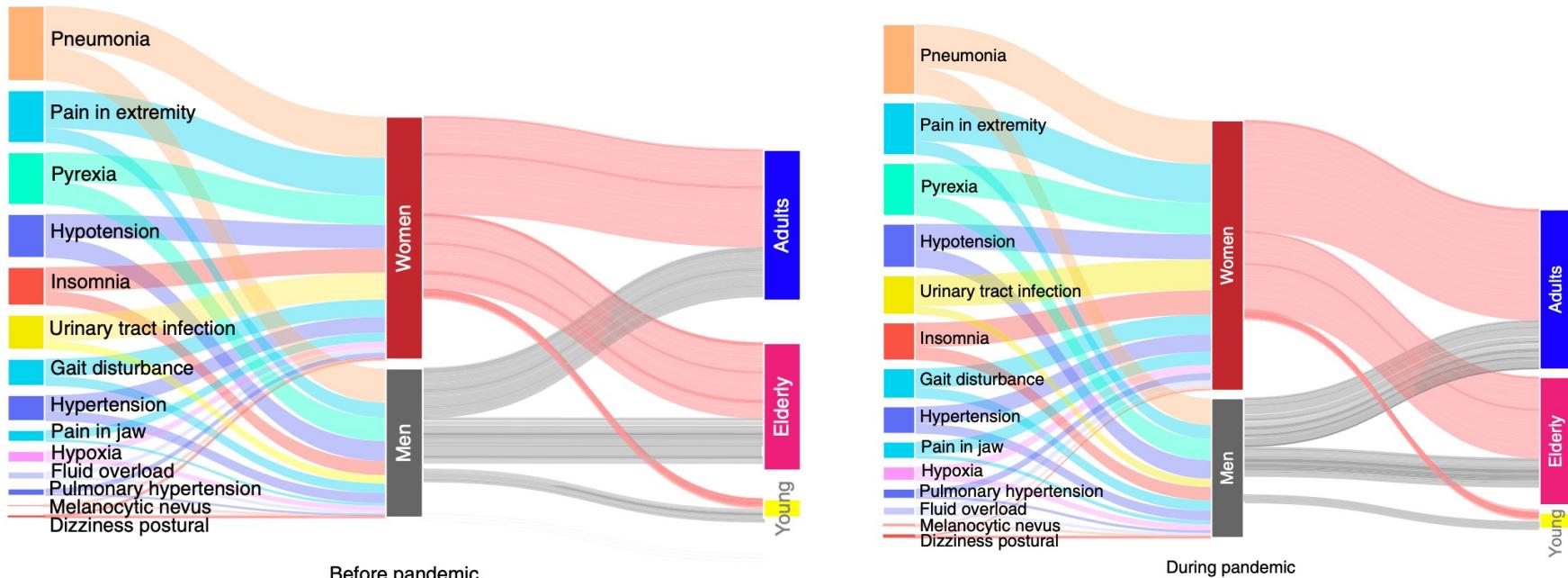
7	Anagrelide	Azelaic acid	Cerebral thrombosis
8	Atorvastatin	Amlodipine	Muscle inflammation
9	Aliskiren	Tioconazole	Breast inflammation
10	Estradiol	Nadolol	Endometriosis

Where do we go from here?

- Adverse events from medications accounted for over 110,000 deaths in the US alone in 2019
- It remains largely unknown:
 - How a nationwide pandemic (such as COVID-19) can influence patient safety
 - What inequalities in patients are exacerbated more than expected had the pandemic not occurred
- Dependencies between aspects of the pandemic, **drug effects**, and **patient characteristics** create additional challenges for understanding patient safety during a public health emergency

Results: Variation of adverse events across patient groups

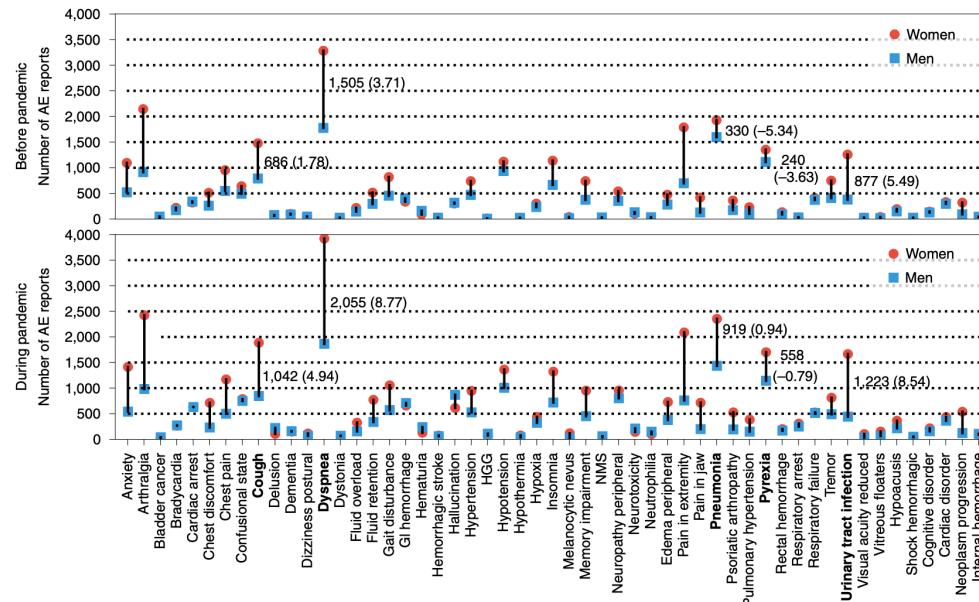
- Substantial variation in adverse events before and during the pandemic:
 - Among 64 adverse events identified by our analyses, 54 have increased incidence rates during the pandemic, even though adverse event reporting decreased by 4.4% overall relative to 2019



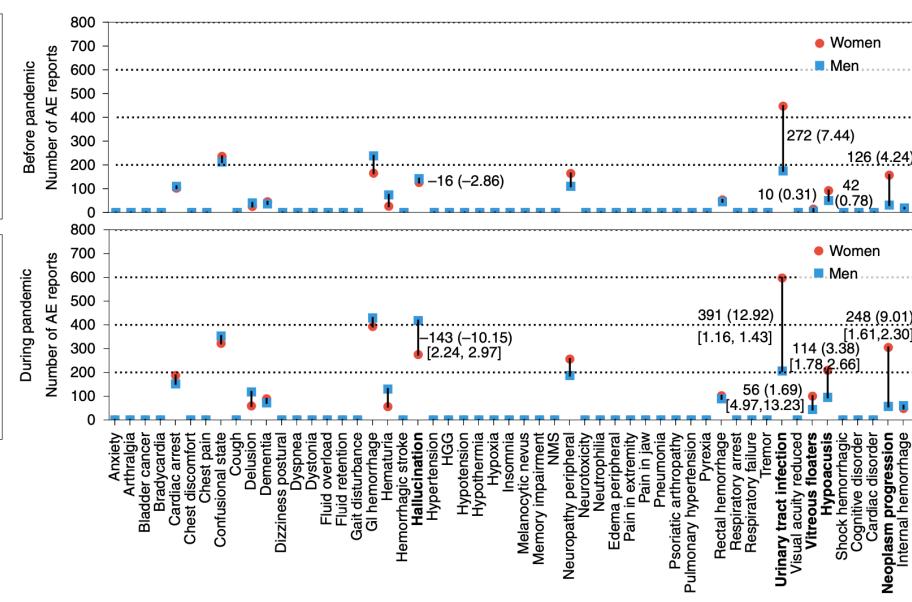
Results: Variation of adverse events across patient groups

- Adverse events whose reporting frequency has changed relative to pre-pandemic levels tend to be reported considerably more often than expected:
 - Pre-pandemic gender differences are exaggerated during the pandemic
 - Women suffer from more adverse events than men relative to pre-pandemic, across all ages
 - Anxiety and insomnia were disproportionately increased in women and elderly

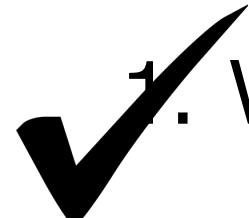
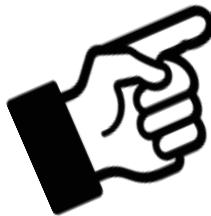
All patients



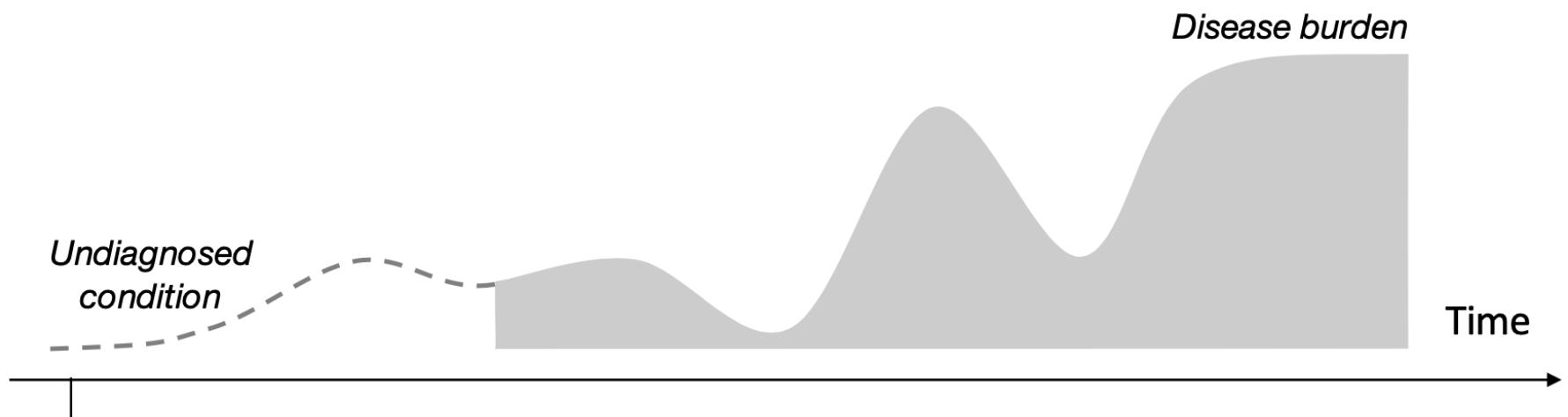
Elderly



Outline for today's class

- 
1. Why AI for precision medicine?
 2. What are electronic health records (EHR) and why are they useful?
 3. What are limitations & biases of EHR data?
 4. Highlights of ML on EHR data:
 - Polypharmacy and adverse drug events
 - Modeling disease progression

Prognosis: Where is a patient in their disease trajectory? When will the disease progress? How will treatment affect disease progression?



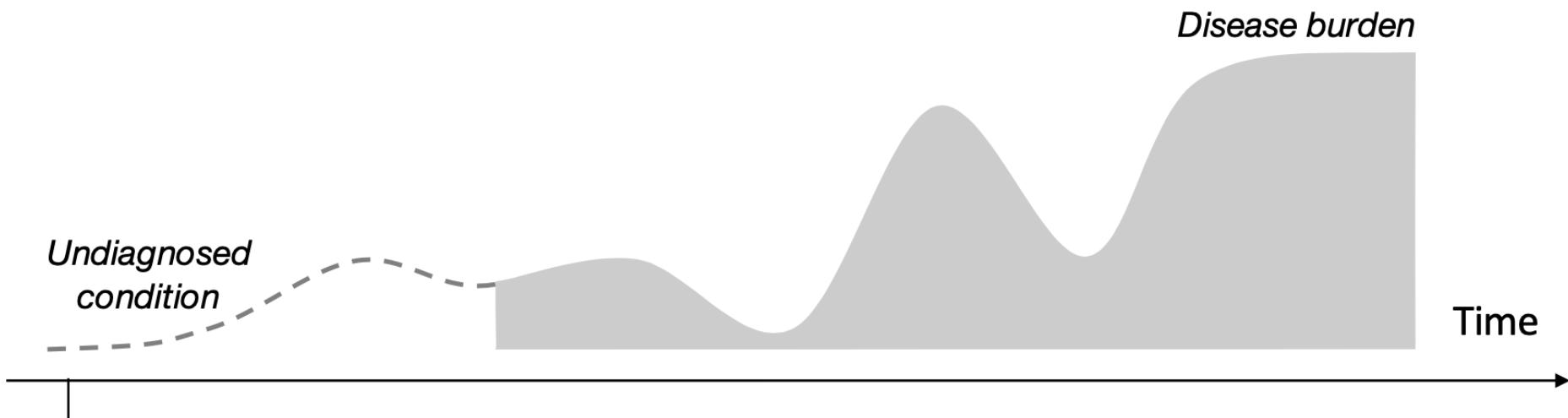
Predicted risk of developing disease or predicting outcome



Example: Multiple myeloma

- Rare blood cancer
- MMRF CoMMpass Study has ~1000 patients

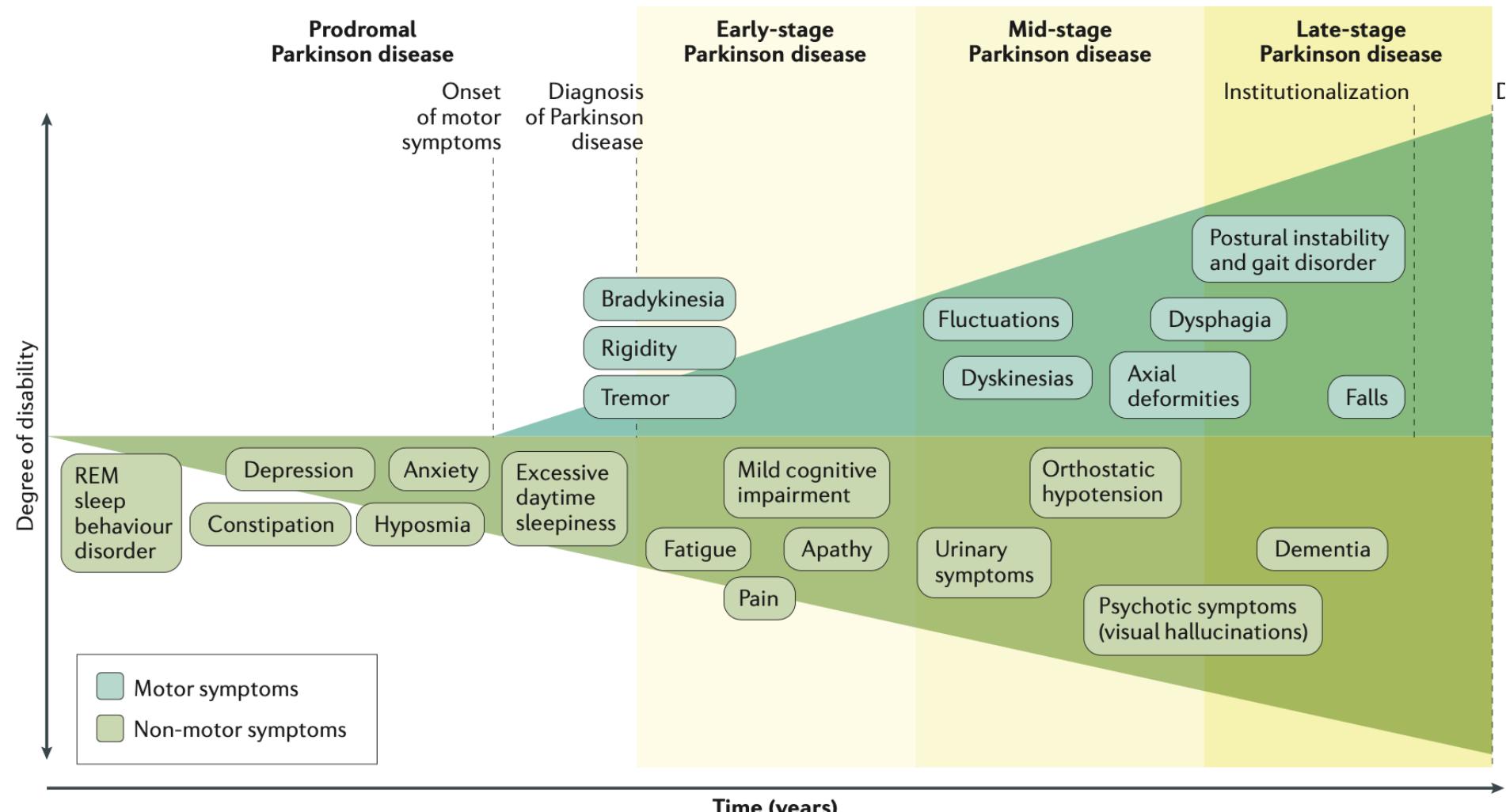
Descriptive: What does a typical trajectory look like?



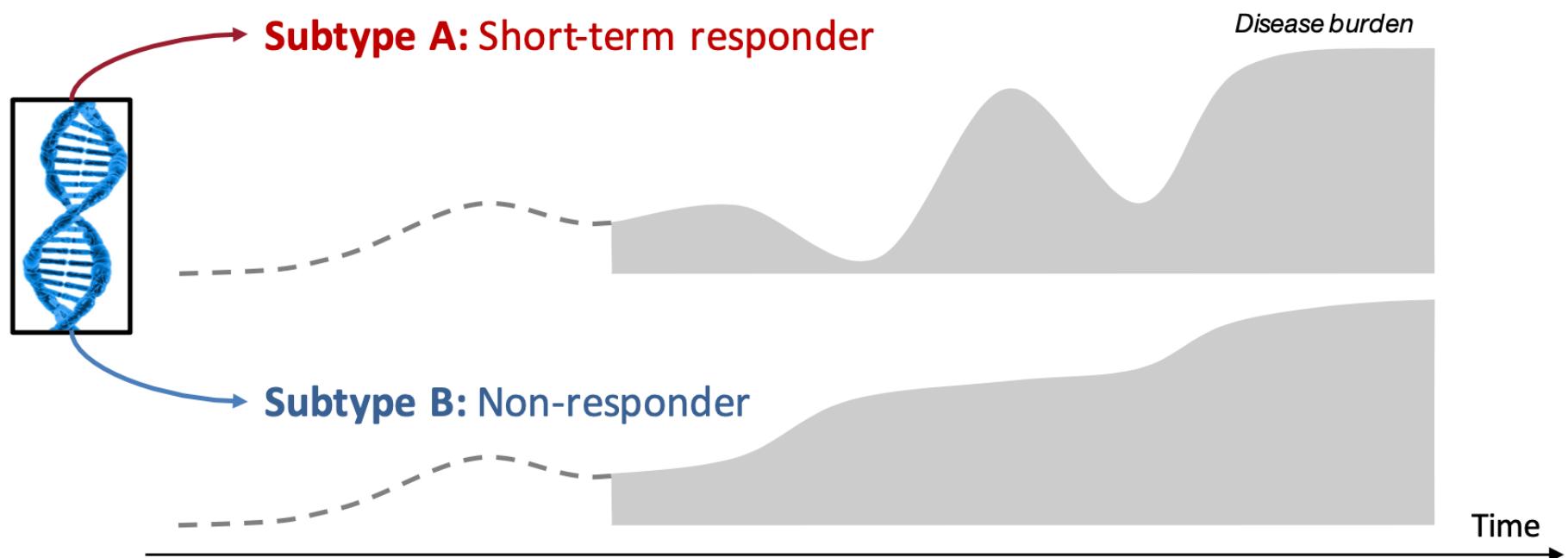
Example: Parkinson's

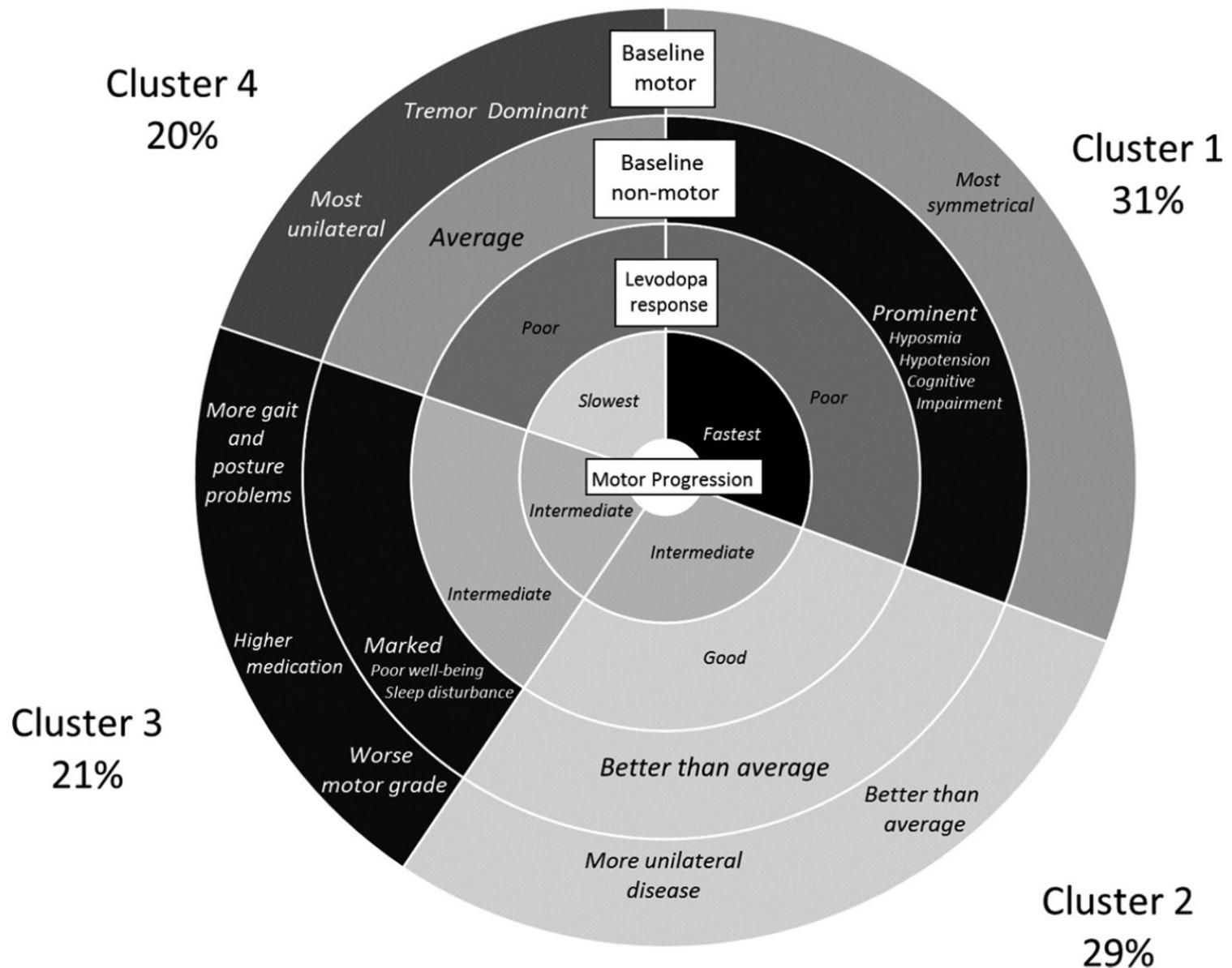
- ▶ Progressive nervous system disorder
- ▶ Affects 1 in 100 people over age 60
- ▶ PPMI dataset follows patients across time

Clinical symptoms associated with Parkinson's disease progression



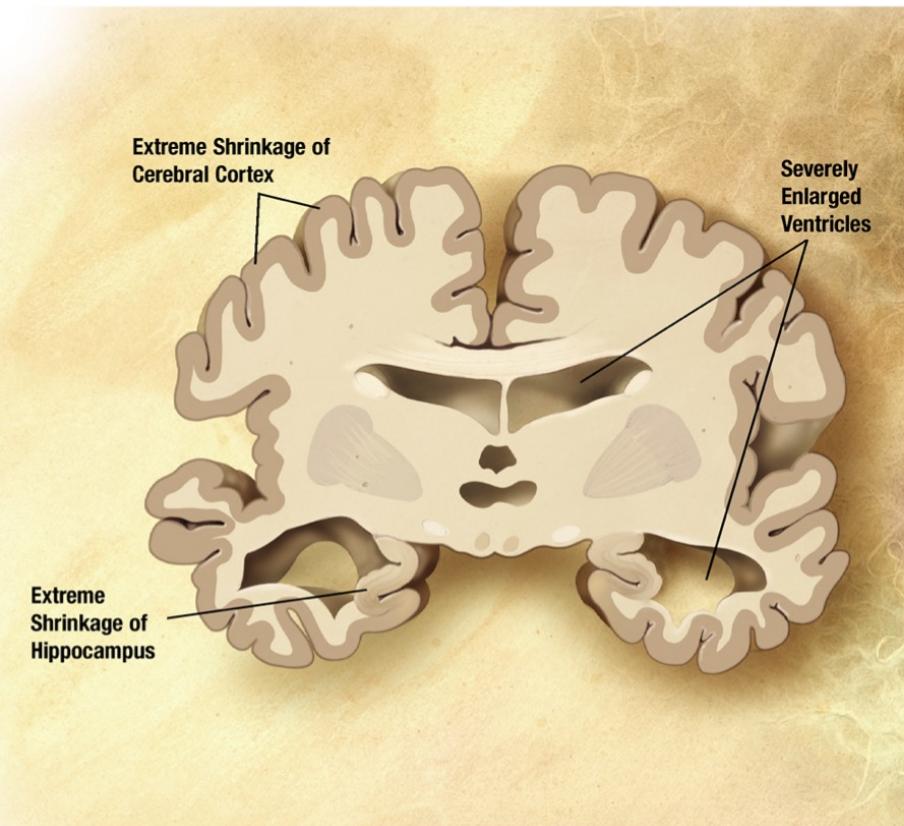
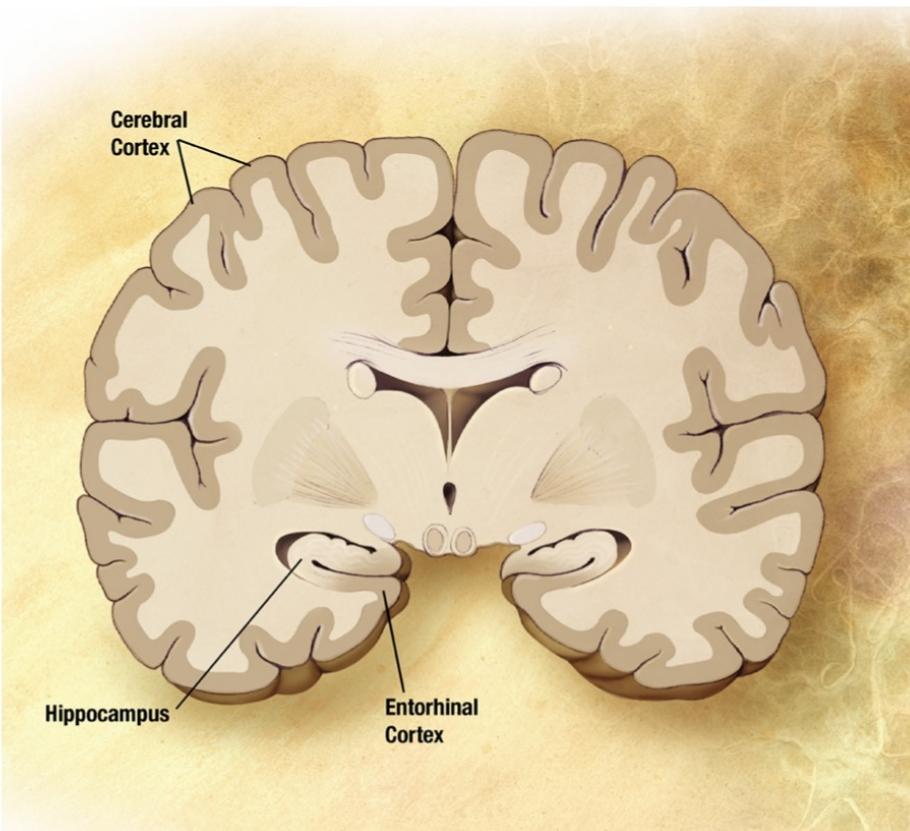
Subtyping: Can we re-define the disease altogether?





[Lawton et al., Developing and validating Parkinson's disease subtypes and their motor and cognitive progression. *J Neurol Neurosurg Psychiatry*, 2018]

Predicting disease progression in Alzheimer's disease



[Image credit: Wikipedia; "Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging."]

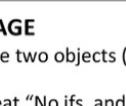
MINI MENTAL STATE EXAMINATION (MMSE)

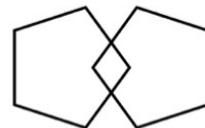
Name _____

DOB

Hospital Number

Disease status
quantified by
cognitive score
(continuous valued)

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time/ 5/ 5/ 5
Country Town District Hospital Ward/Floor/ 5/ 5/ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct)./ 3/ 3/ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW)./ 5/ 5/ 5
RECALL Ask for the names of the three objects learned earlier./ 3/ 3/ 3
LANGUAGE Name two objects (e.g. pen, watch). Repeat "No ifs, ands, or buts". Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear"). Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes". Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb./ 2 / 1 / 3 / 1 / 1/ 2 / 1 / 3 / 1 / 1/ 2 / 1 / 3 / 1 / 1
COPYING: Ask the patient to copy a pair of intersecting pentagons			
/ 1/ 1/ 1
TOTAL:/ 30/ 30/ 30



MMSE scoring

24-30: no cognitive impairment

18-23: mild cognitive impairment

0-17: severe cognitive impairment

Patient dataset

MRI scans (white matter parcellation volume, etc.) +

Demographic	age, years of education, gender
Genetic	ApoE- ε 4 information
Baseline cognitive scores	MMSE, ADAS-Cog, ADAS-MOD, ADAS subscores, CDR, FAQ, GDS, Hachinski, Neuropsychological Battery, WMS-R Logical Memory
Lab tests	RCT1, RCT11, RCT12, RCT13, RCT14, RCT1407, RCT1408, RCT183, RCT19, RCT20, RCT29, RCT3, RCT392, RCT4, RCT5, RCT6, RCT8

371 in total

Predicting disease progression in Alzheimer's disease

- Goal: Predict disease status in 6, 12, 24, 36, and 48 months
- Five different regression tasks?
- Challenge: **data sparsity**
 - Total number of patients is small
 - Labels are noisy
 - Due to censoring, fewer patients at later time points

Predicting disease progression in Alzheimer's disease

- Goal: Predict disease status in 6, 12, 24, 36, and 48 months
- Approach:
 - Five regression tasks: M06, M12, M24, M36, M48?
- Challenge: Small sample size

Number of patients M months after baseline
(Alzheimer's Disease Neuroimaging Initiative)

M06	M12	M24	M36	M48
648	642	569	389	87

M06 = 6 months after baseline

Approach: Multi-task learning

- Goal: Predict disease status in 6, 12, 24, 36, and 48 months
- Rather than learning 5 independent models, we can formulate the problem as **multi-task learning**:
 - Select a common set of biomarkers for all time points
 - Allow for specific set of biomarkers at different time points → candidate disease state biomarkers
 - Encourage temporal smoothness in models when making predictions for neighboring time points

Approach: Fused sparse group lasso

- Simultaneously learn all 5 models by solving the optimization problem:

Feature importance values: Weight matrix that we want to learn

$$\min_W L(W) + \lambda_1 \|W\|_1 + \lambda_2 \|RW^T\|_1 + \lambda_3 \|W\|_{2,1}$$

- Squared loss: $L(W) = \|S \odot (XW - Y)\|_F^2$

(S is a mask to account for labels missing in s)

Matrix of patient features, demographics, genetics, cognitive scores, lab tests

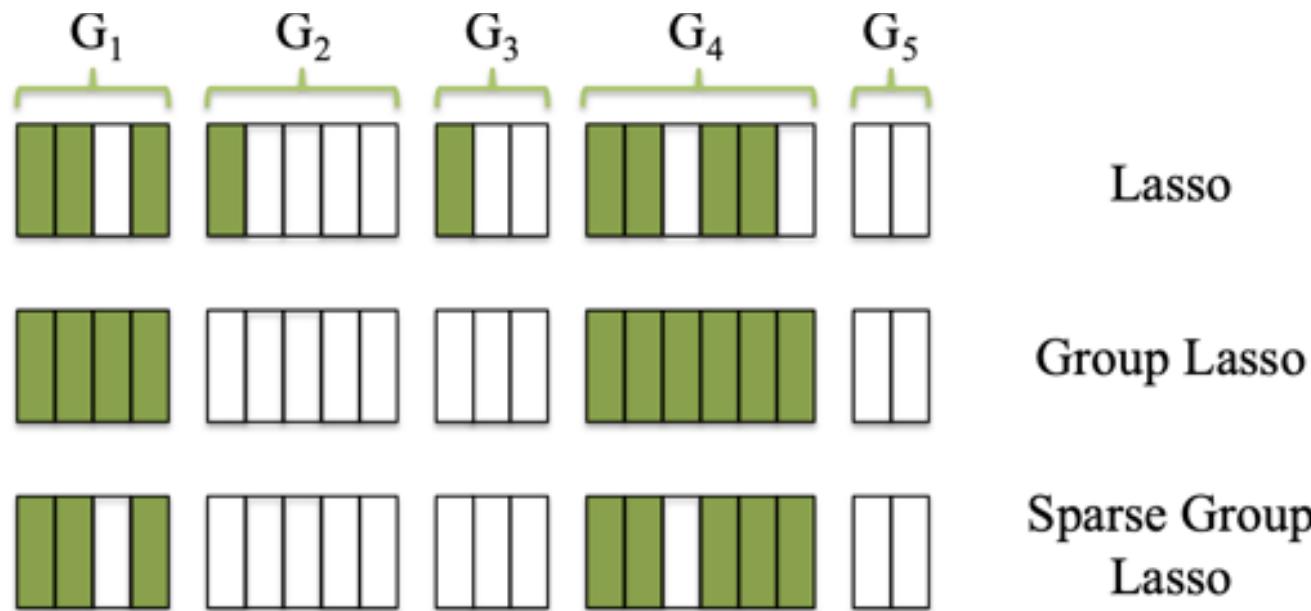
- Group Lasso penalty $\|W\|_{2,1}$ given by $\sum_{i=1}^d \sqrt{\sum_{j=1}^t W_{ij}^2}$

- $R =$

$$R = \begin{matrix} & & 5 \\ & 1 & -1 \\ 4 & & 1 & -1 \\ & & & 1 & -1 \end{matrix}$$

Ground-truth outcomes

Approach: Sparse Group Lasso



- “Fused” version of lasso penalizes the norm of both the coefficients and their successive differences
 - It encourages sparsity of the coefficients and sparsity of their differences—local constancy of the coefficient profile

Results: Averaged across 5 time points

Baseline –
independent
regressors

Temporal smoothing helps!

$$\lambda_2 = 20$$

$$\lambda_2 = 50$$

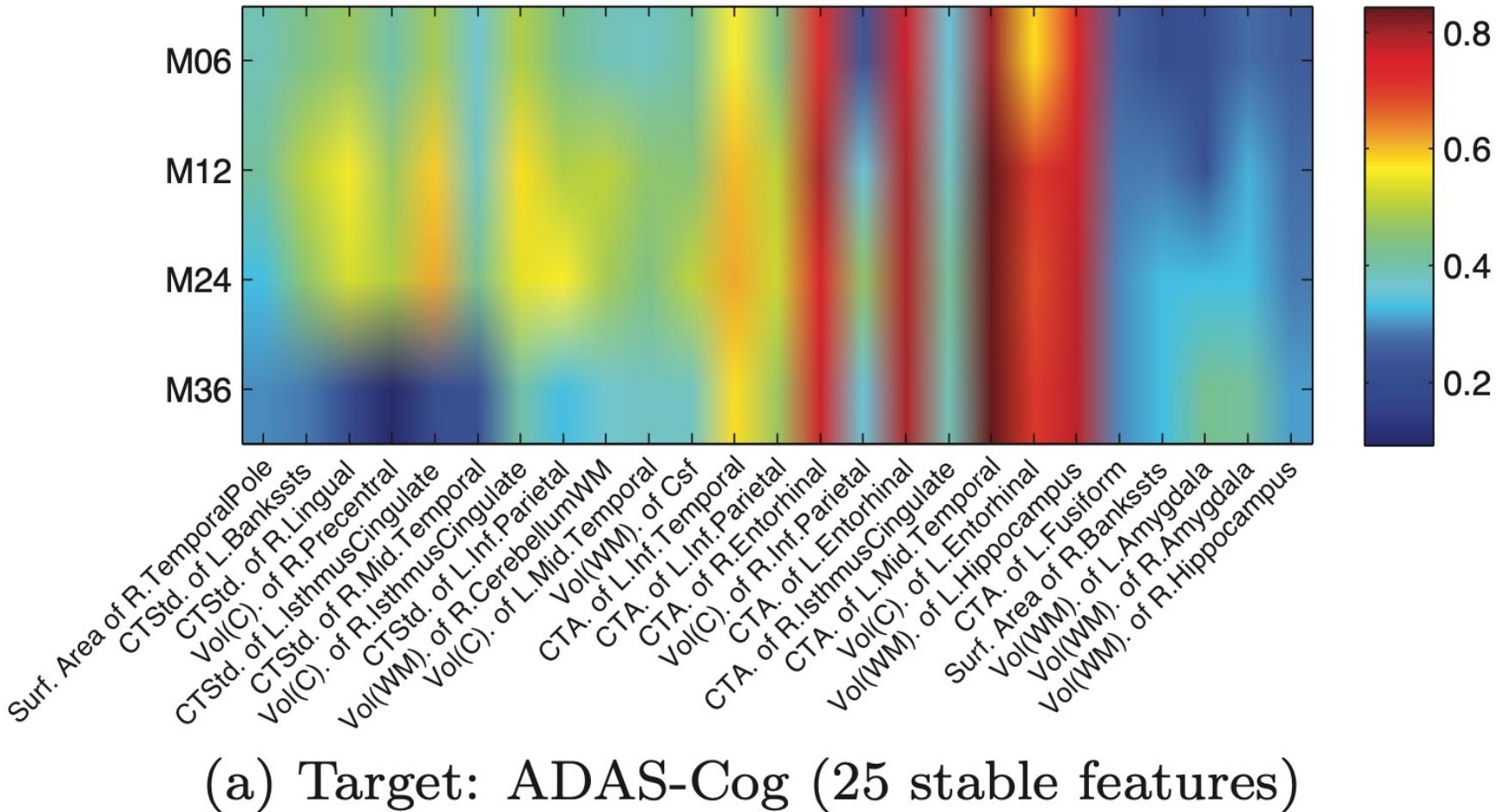
$$\lambda_2 = 100$$

	Ridge	cFSGL1	cFSGL2	cFSGL3
Target: MMSE				
nMSE	0.548 ± 0.057	0.428 ± 0.052	0.400 ± 0.053	0.395 ± 0.052
R	0.689 ± 0.030	0.772 ± 0.030	0.790 ± 0.032	0.796 ± 0.031

nMSE – normalized mean squared error. Smaller is better
R – average R^2 (correlation coefficient). Larger is better

$$\min_W L(W) + \lambda_1 \|W\|_1 + \lambda_2 \left\| RW^T \right\|_1 + \lambda_3 \|W\|_{2,1}$$

Results: Feature importance values vary by time



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