Machine Learning for Healthcare

HST.956, 6.S897

Lecture 18: Disease progression modeling & subtyping, Part 1

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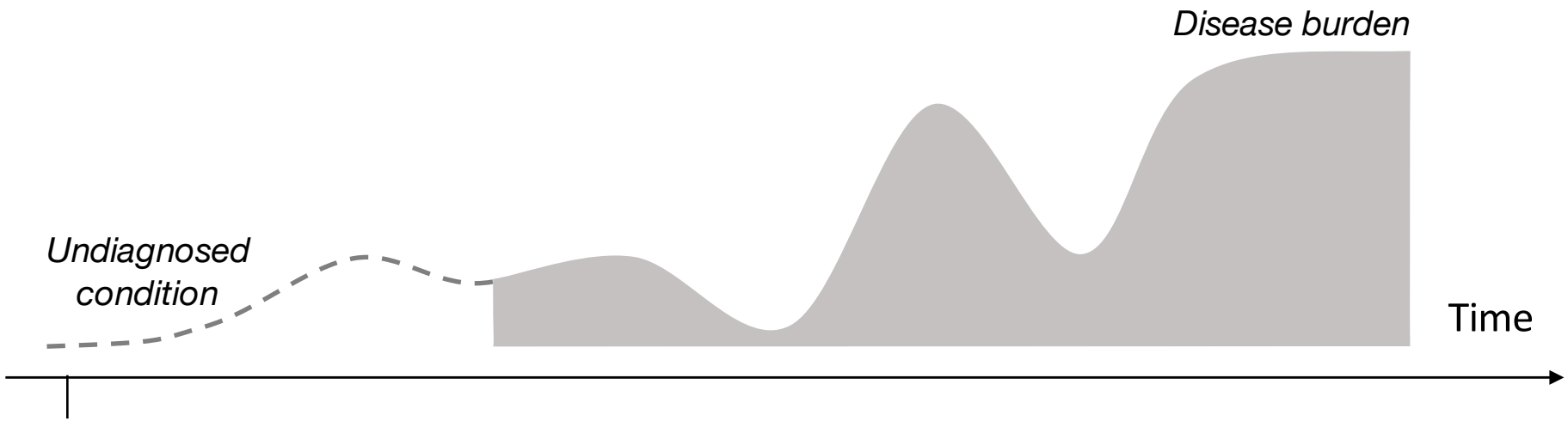
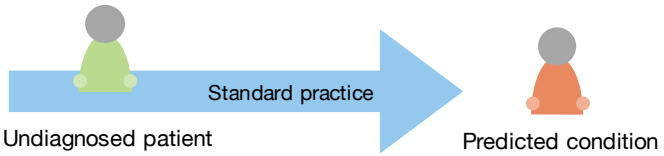
HEALTH SCIENCES
& TECHNOLOGY

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

Myeloma Staging Systems

Stage	Durie-Salmon Staging System	Revised International Staging System
I	All of the following: ○ Hemoglobin >10.5 g/dL ○ Serum calcium value normal or ≤12 mg/dL ○ X-ray studies of bone, normal bone structure (scale 0) or solitary bone plasmacytoma only ○ Low M-component production rate IgG value <5 g/dL; IgA value <3 g/dL ○ Urine light chains <4g/24 hours	○ Serum albumin >3.5 g/dL ○ Serum β_2-microglobulin <3.5 mg/L ○ No high-risk cytogenetics ○ Normal serum lactate dehydrogenase level
II	Neither stage I nor stage III ○ A—No renal failure (creatinine ≤2 mg/dL) ○ B—Renal failure (creatinine >2 mg/dL)	Neither stage I nor stage III
III	○ Hemoglobin value <8.5 g/dL ○ Serum calcium value >12 mg/dL ○ X-ray studies of bone, >3 lytic bone lesions ○ High M-component production rate IgG value >7 g/dL; IgA value >5 g/dL ○ Urine light chains >12 g/24 hours	○ Serum β_2-microglobulin >5.5 mg/L ○ High-risk cytogenetics t(4;14) t(14;16) del(17p) ○ Elevated serum lactate dehydrogenase level

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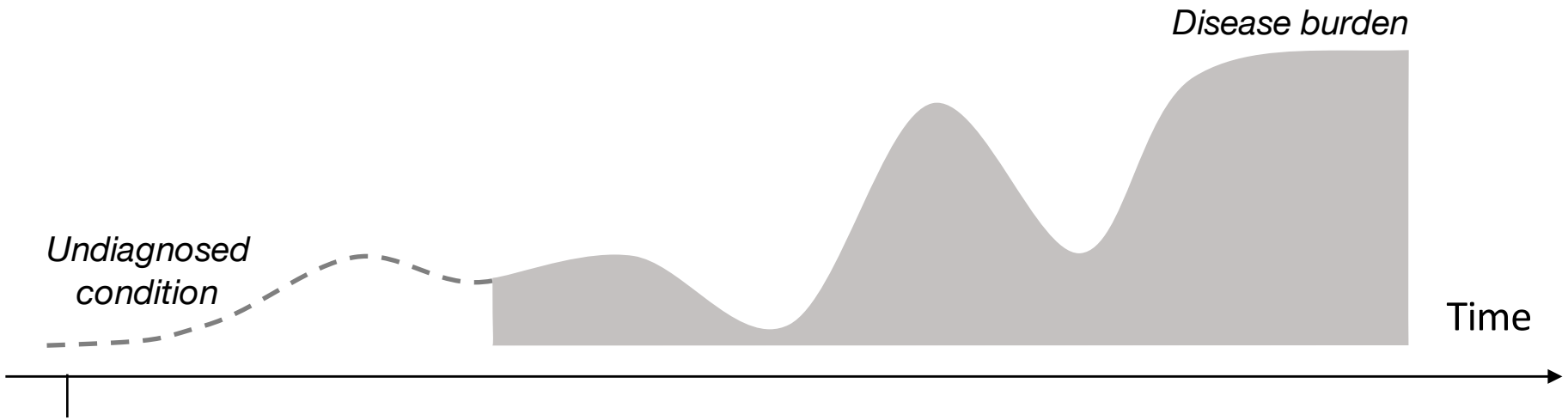
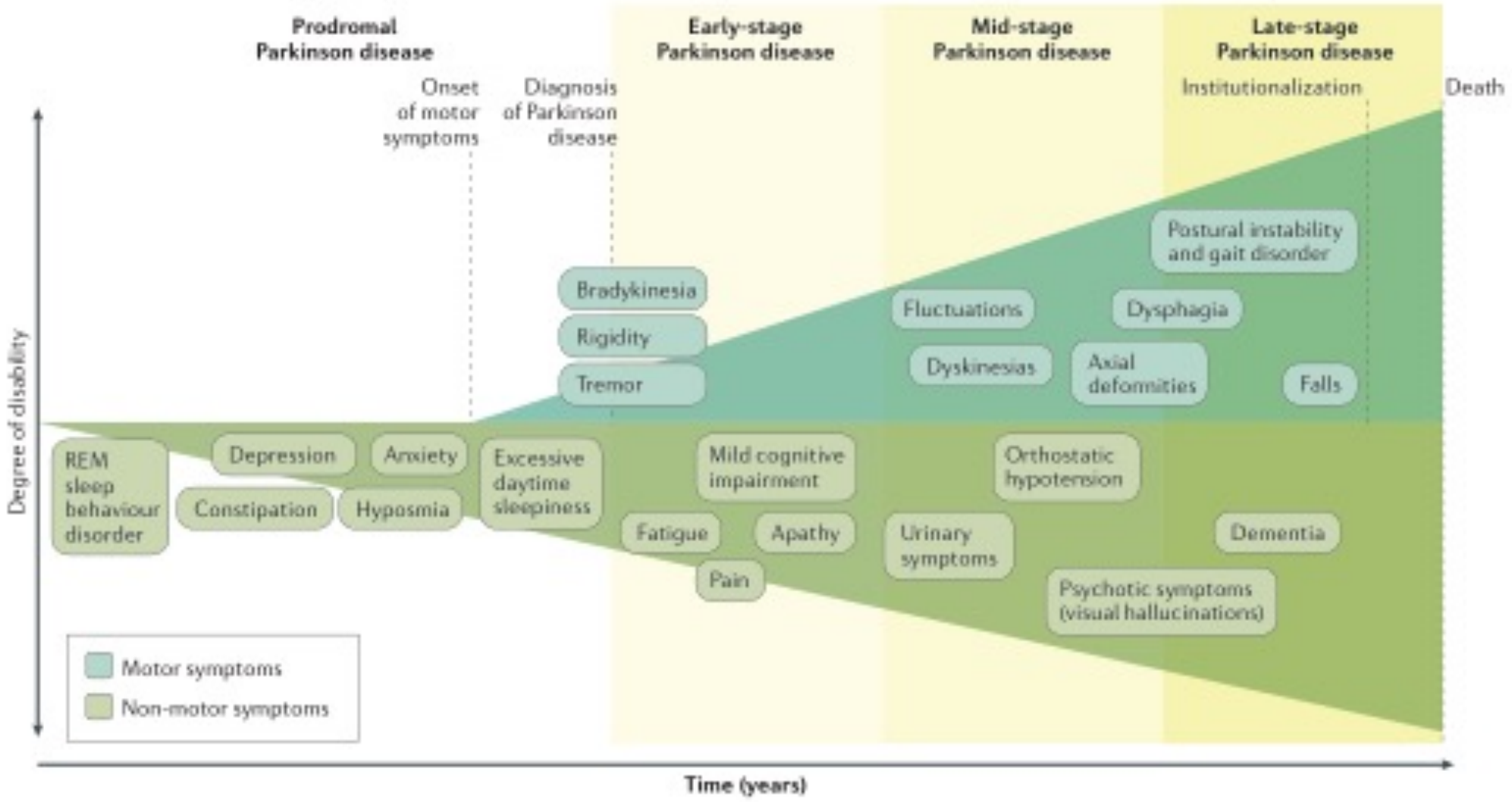
Descriptive: What does a typical trajectory look like?



Example: Parkinson's

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



[Poewe et al., Parkinson's disease. *Nature Reviews Disease Primers*, 2017]

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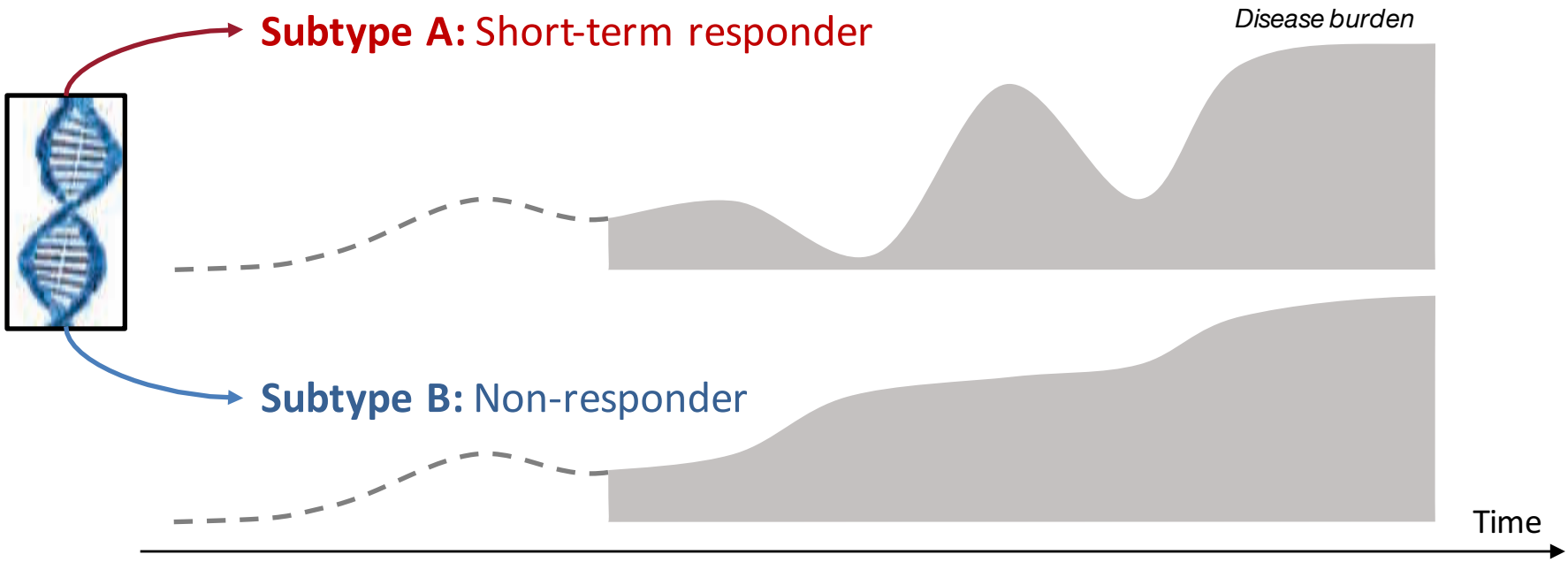
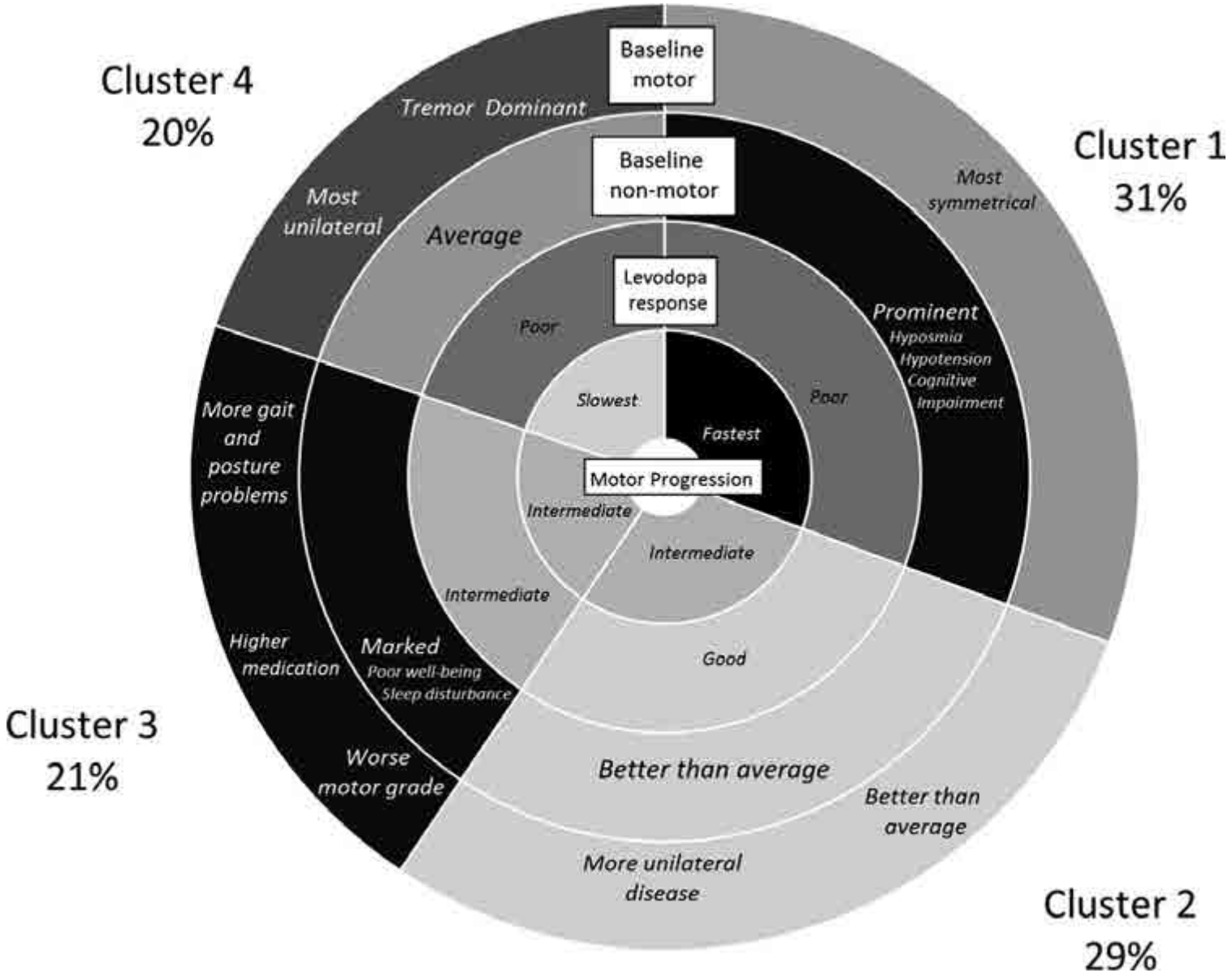
Subtyping: Can we re-define the disease altogether?

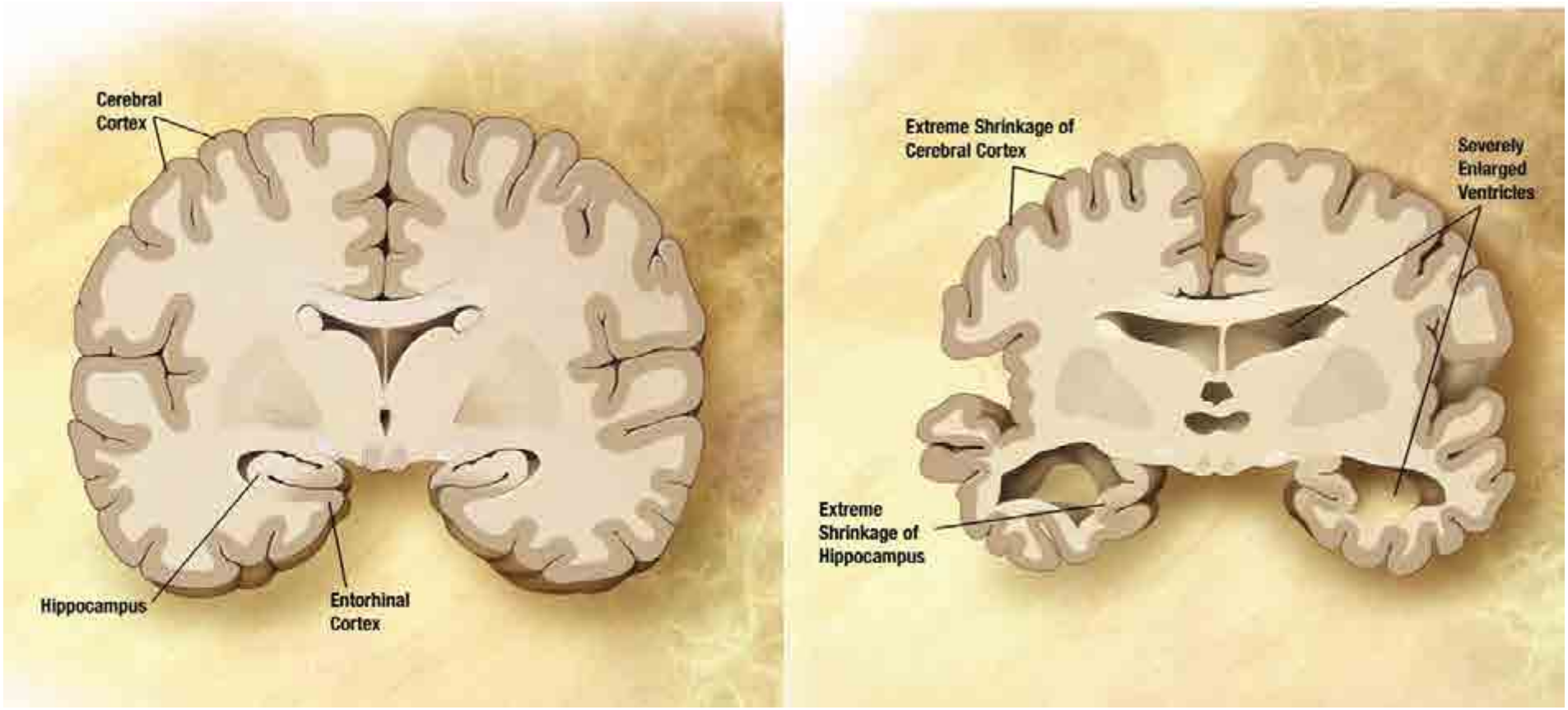




[Lawton et al., Developing and validating Parkinson's disease subtypes and their motor and cognitive progression. *J Neurol Neurosurg Psychiatry*, 2018]

Courtesy of Lawton et al. Used under CC BY.

Predicting disease progression in Alzheimer's disease



Courtesy of the NIH. Image is in the public domain.

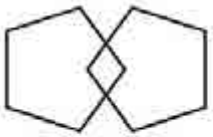
Disease status quantified by cognitive score (continuous valued)

MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

Hospital Number:

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).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
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").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 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

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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

[Zhou et al., KDD '12]

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

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

M06	M12	M24	M36	M48
648	642	569	389	87

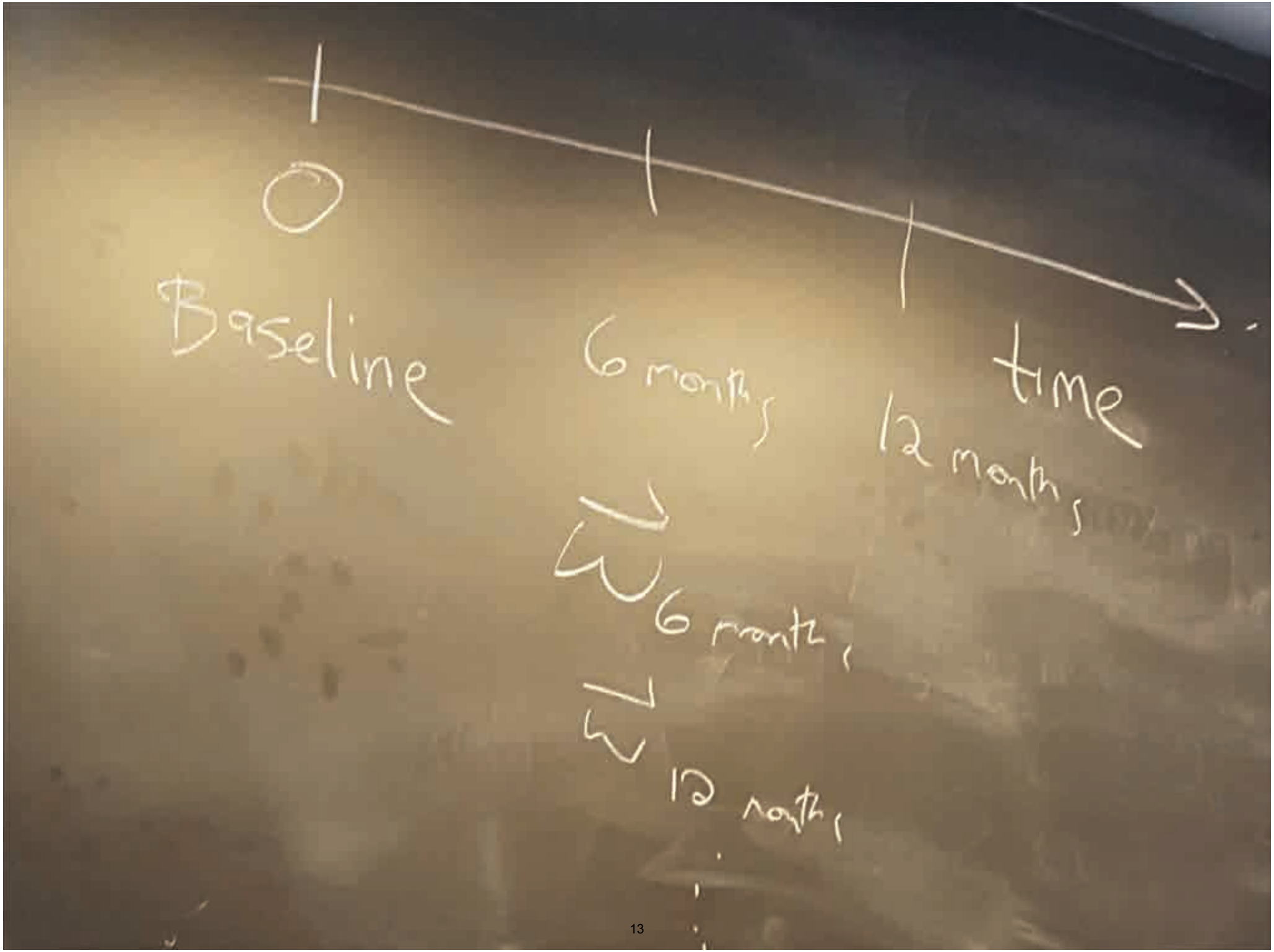
M06 = 6 months after baseline

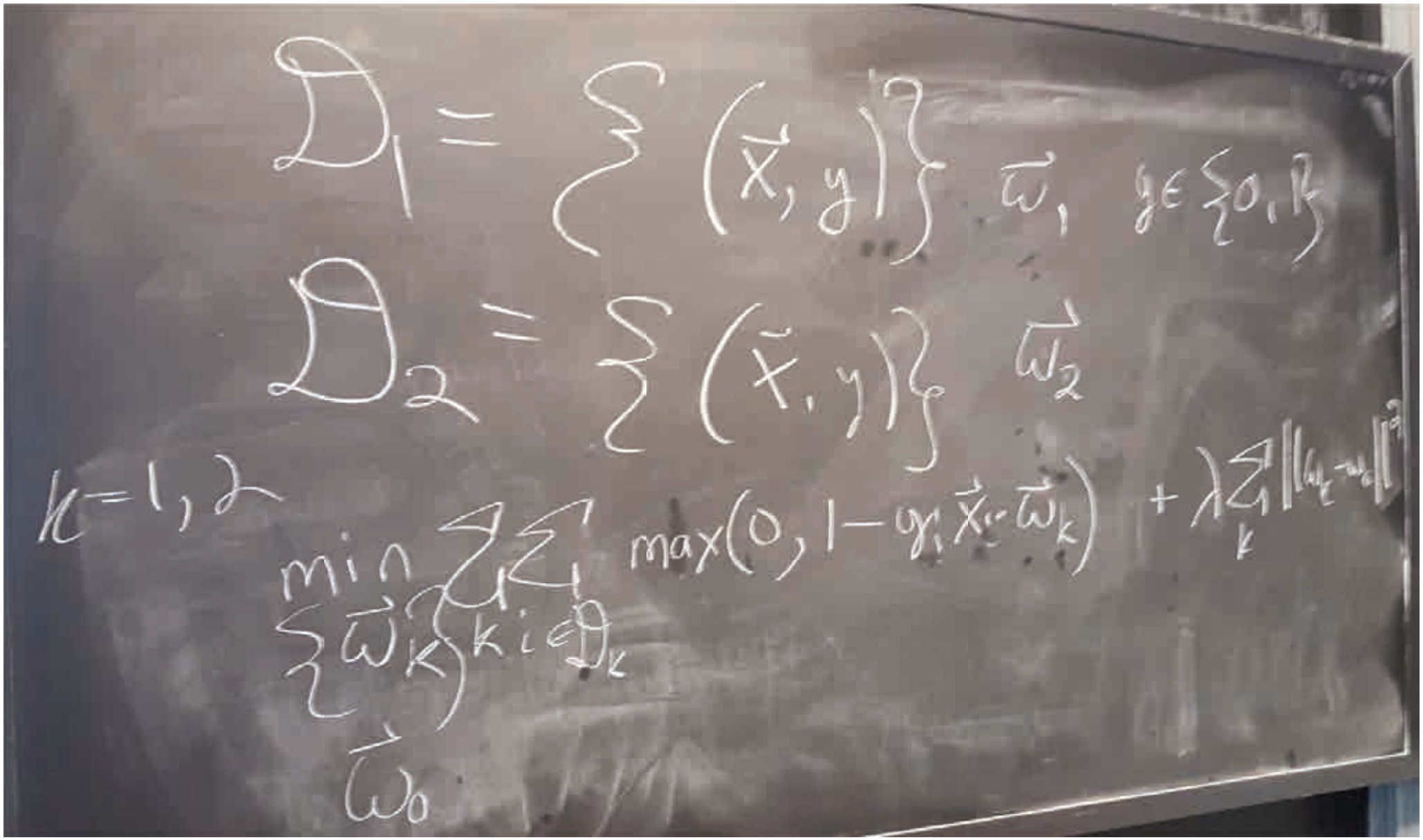
[Zhou et al., KDD '12]

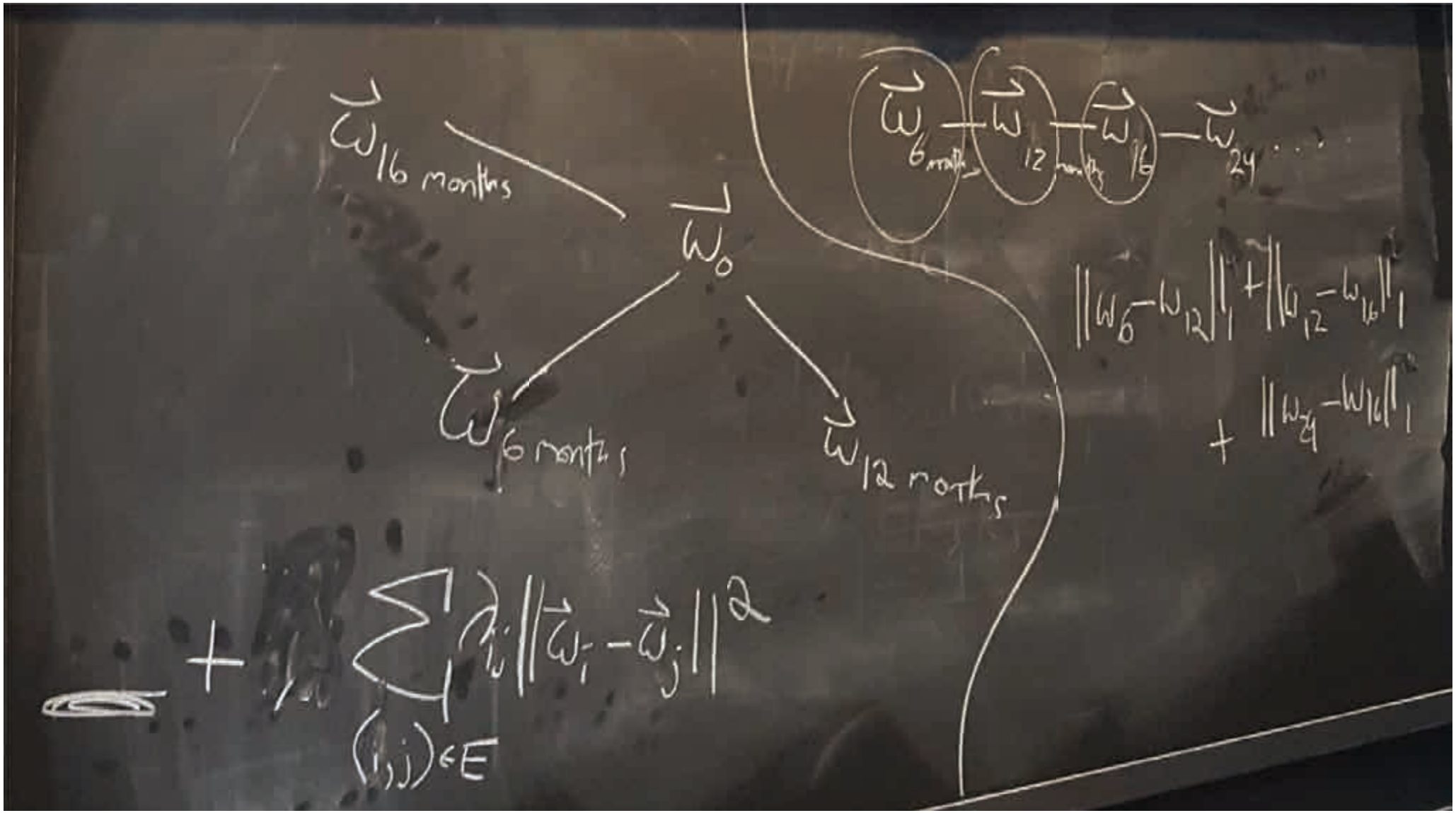
Multi-task learning

- Goal: Predict disease status in *6*, *12*, *24*, *36, and 48 months*
- Rather than learn several independent models, view as *multi-task* learning
  - Select common set of biomarkers for all time points
  - Also allow for specific set of biomarkers at different time points
  - Incorporate temporal smoothness in models

[Zhou et al., KDD '12]


0
1
1
Baseline
6 months
12 months
time
6 months
12 months


$D_1 = \{(\vec{x}, y)\}$ $\vec{w}_1$ $y \in \{0, 1\}$
$D_2 = \{(\vec{x}, y)\}$ $\vec{w}_2$
$k = 1, 2$
$\min_{\{\vec{w}_k\}} \sum_k \sum_{i \in D_k} \max(0, 1 - y_i \vec{x}_i \cdot \vec{w}_k) + \lambda \sum_k \|w_k - w_0\|^2$
$\vec{w}_0$


$\vec{w}_{16\ months}$
$\vec{w}_0$
$\vec{w}_{6\ months}$
$\vec{w}_{12\ months}$
$\vec{w}_{6\ months}$ — $\vec{w}_{12\ months}$ — $\vec{w}_{16}$ — $\vec{w}_{24}$ . . .
$\|w_6 - w_{12}\|_1 + \|w_{12} - w_{16}\|_1$
$+ \|w_{24} - w_{16}\|_1$
$+ \sum_{(i,j) \in E} \|\vec{w}_i - \vec{w}_j\|^2$

Convex fused sparse group lasso

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

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

- Squared loss: $L(W) = \|S \odot (XW - Y)\|_F^2$
  (*S* is a mask to account for labels missing in subset of tasks)

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

- R =

5

4

1	-1	
	1	-1
		1 -1

[Zhou et al., KDD '12]

Features

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

Demographic	age, years of education, gender
Genetic	ApoE-$\varepsilon 4$ information
Baseline cognitive scores	MMSE, ADAS-Cog, ADAS-MOD, ADAS sub-scores, 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

[Zhou et al., KDD '12]

Results (averaged over 5 time points)

Baseline – independent regressors

Temporal smoothing helps!

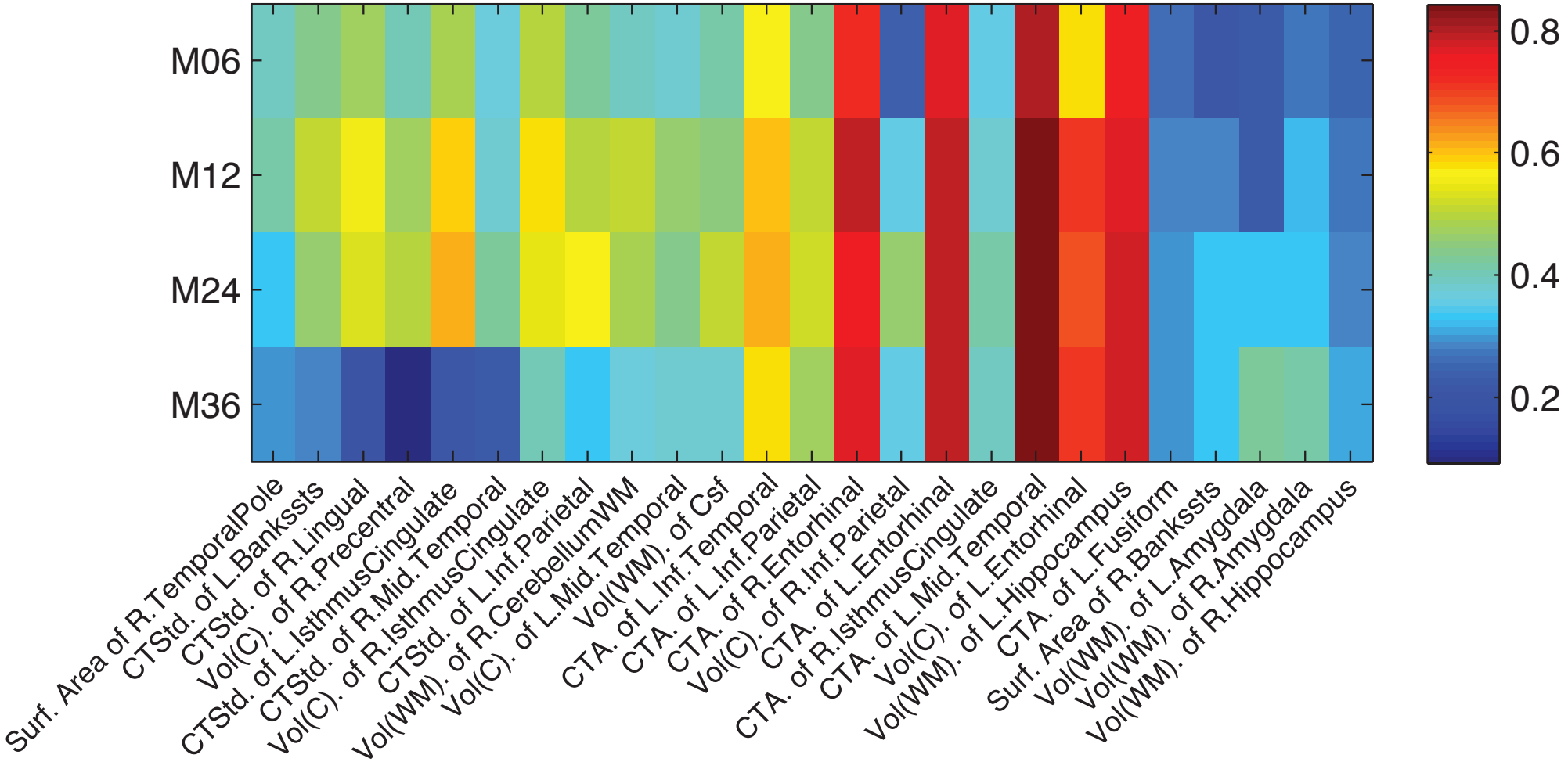
	Ridge	cFSGL1 $\lambda_2 = 20$	cFSGL2 $\lambda_2 = 50$	cFSGL3 $\lambda_2 = 100$
		Target: MMSE		
nMSE	0.548 ± 0.057	0.428 ± 0.052	0.400 ± 0.053	$\mathbf{0.395 \pm 0.052}$
R	0.689 ± 0.030	0.772 ± 0.030	0.790 ± 0.032	$\mathbf{0.796 \pm 0.031}$

nMSE – normalized mean squared error. Smaller is better

R – average R^2 (correlation coefficient). Larger is better

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

Feature importance varies by time



(a) Target: ADAS-Cog (25 stable features)

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Can we use an unsupervised approach?

- Twin goals:
  - **Discover disease subtypes:**

    Want to describe heterogeneity in a way that can be easy to act on (i.e., interpretable)

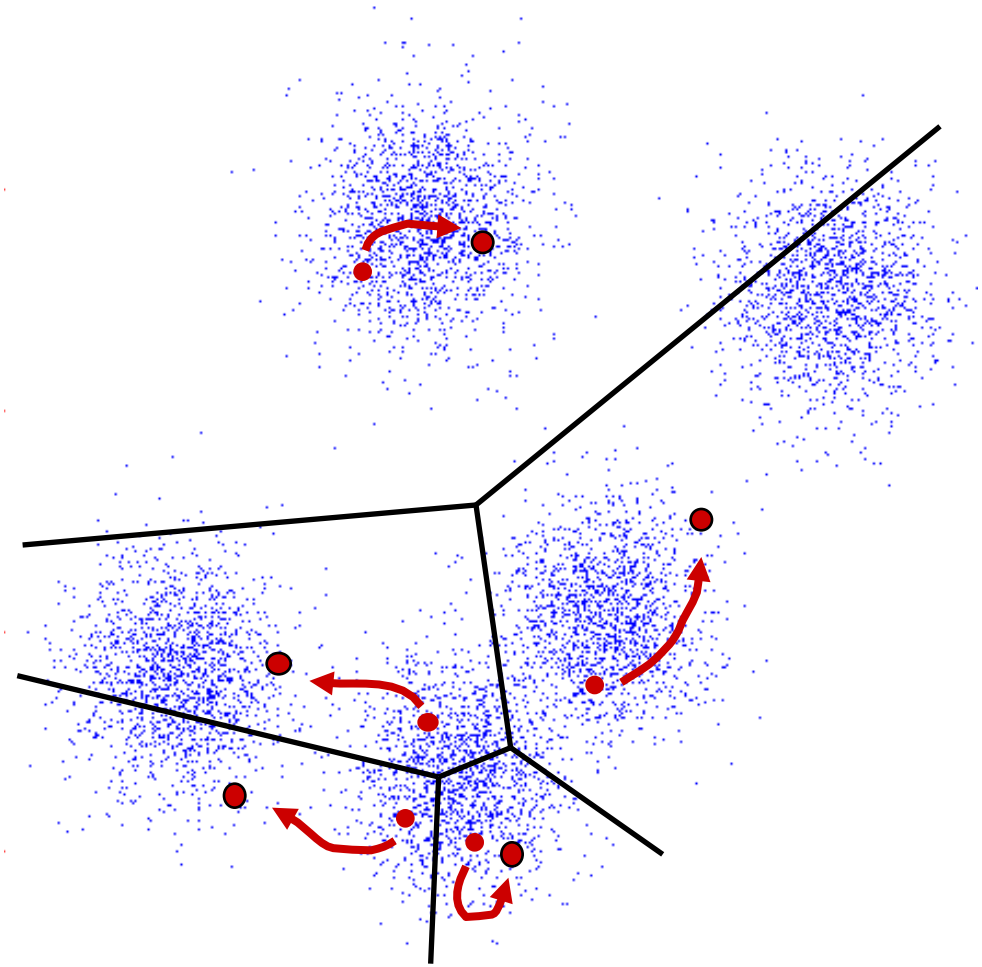
    Not *just* interested in prediction – rather, identify cohorts for clinical trials, better understand disease mechanism

  - **Make use of similarity of individuals at baseline**

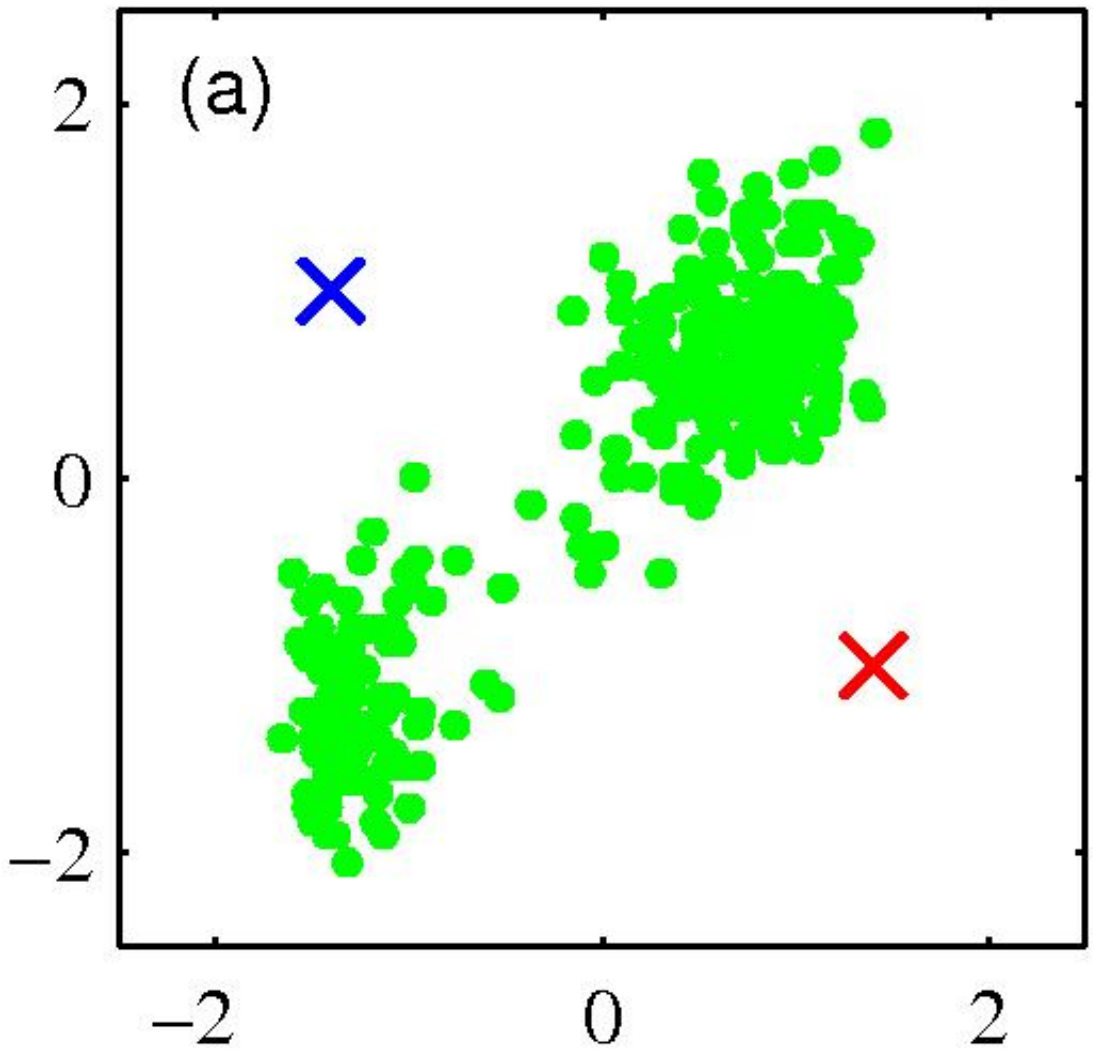
    Dimensionality reduction to prevent overfitting

K-Means

- An iterative clustering algorithm
  - Initialize: Pick *K* random points as cluster centers
  - Alternate:
    1. Assign data points to closest cluster center
    2. Change the cluster center to the average of its assigned points
  - Stop when no points' assignments change



K-means clustering: Example



- Pick *K* random points as cluster centers (means)

Shown here for *K*=2

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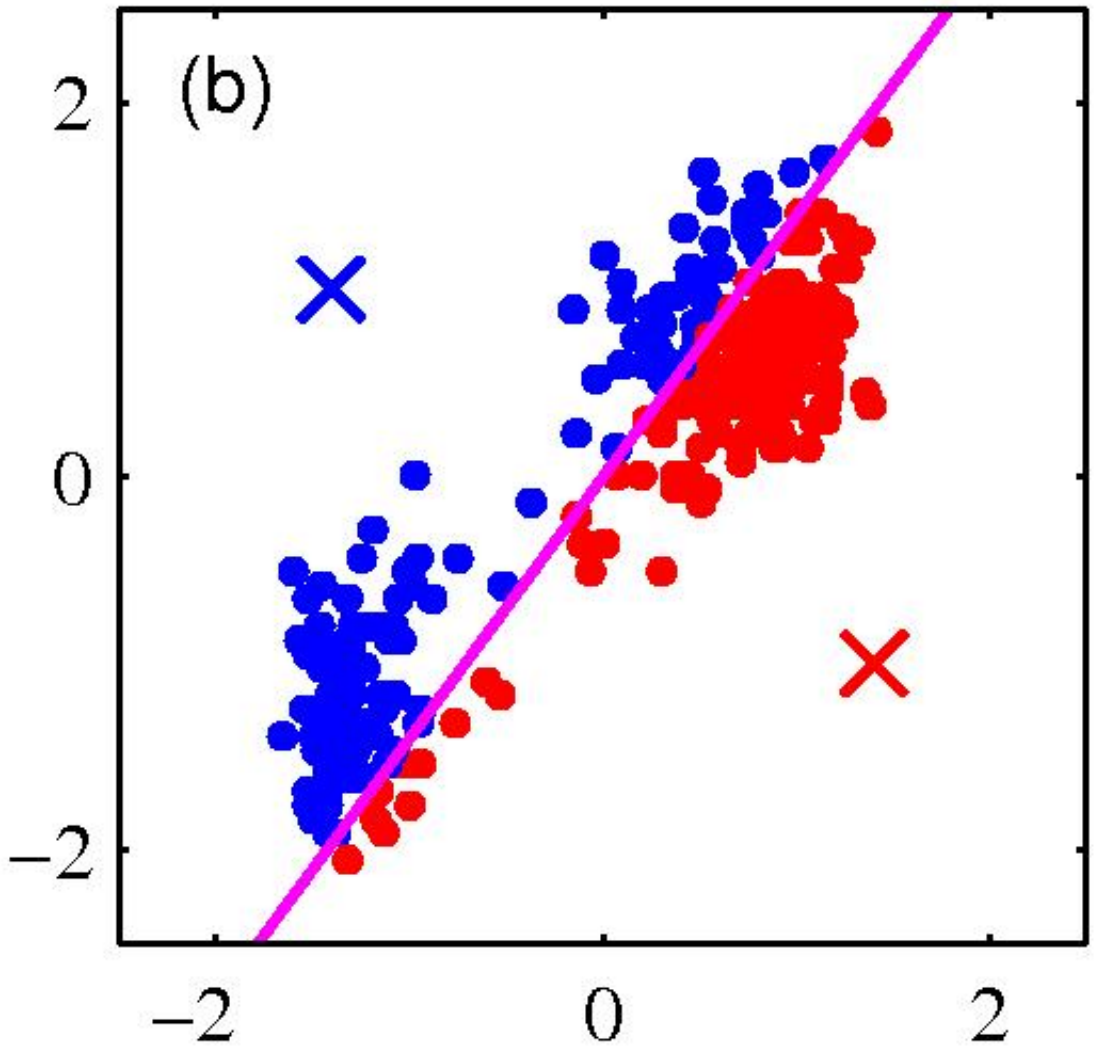
K-means clustering: Example



Iterative Step 1

- Assign data points to closest cluster center

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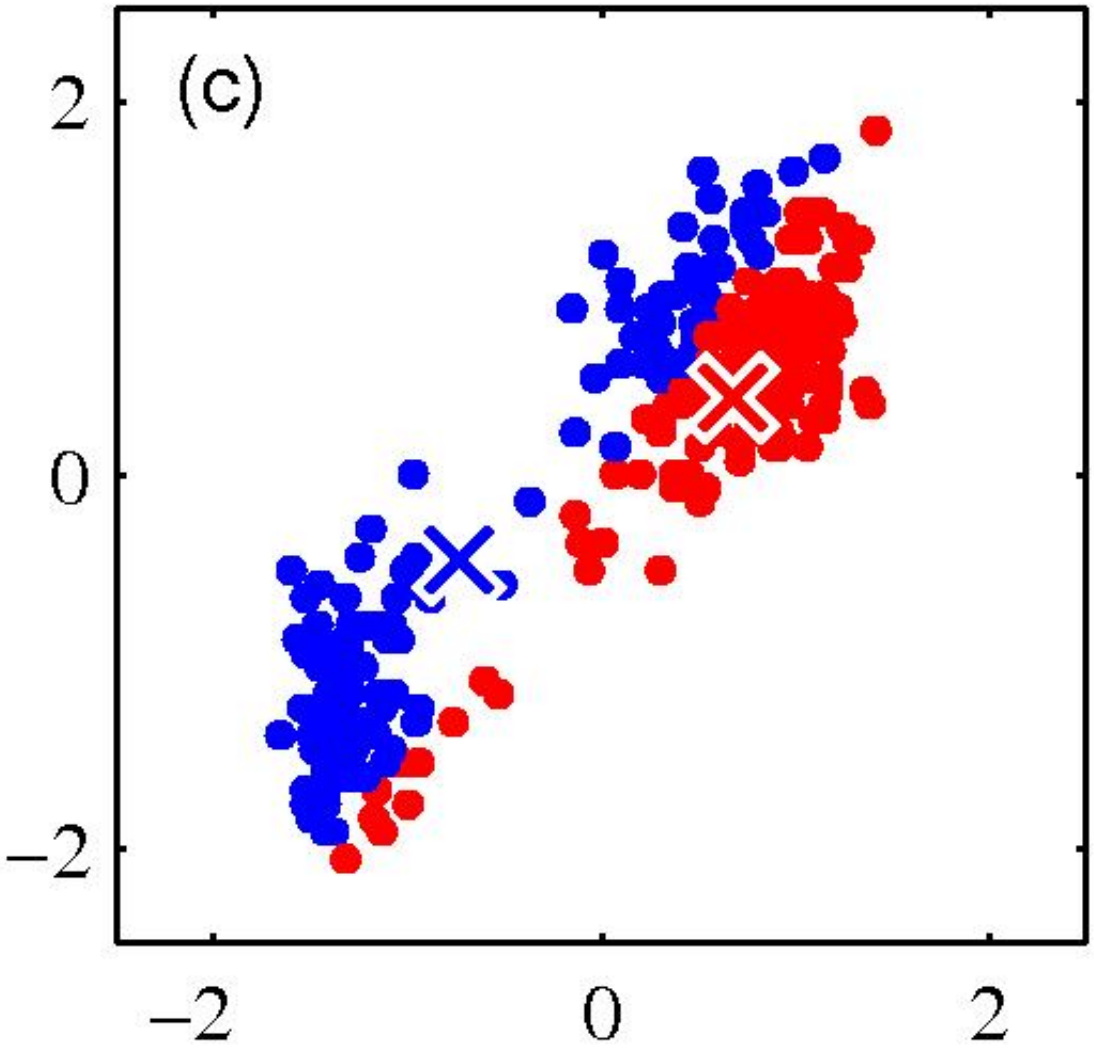
K-means clustering: Example



Iterative Step 2

- Change the cluster center to the average of the assigned points

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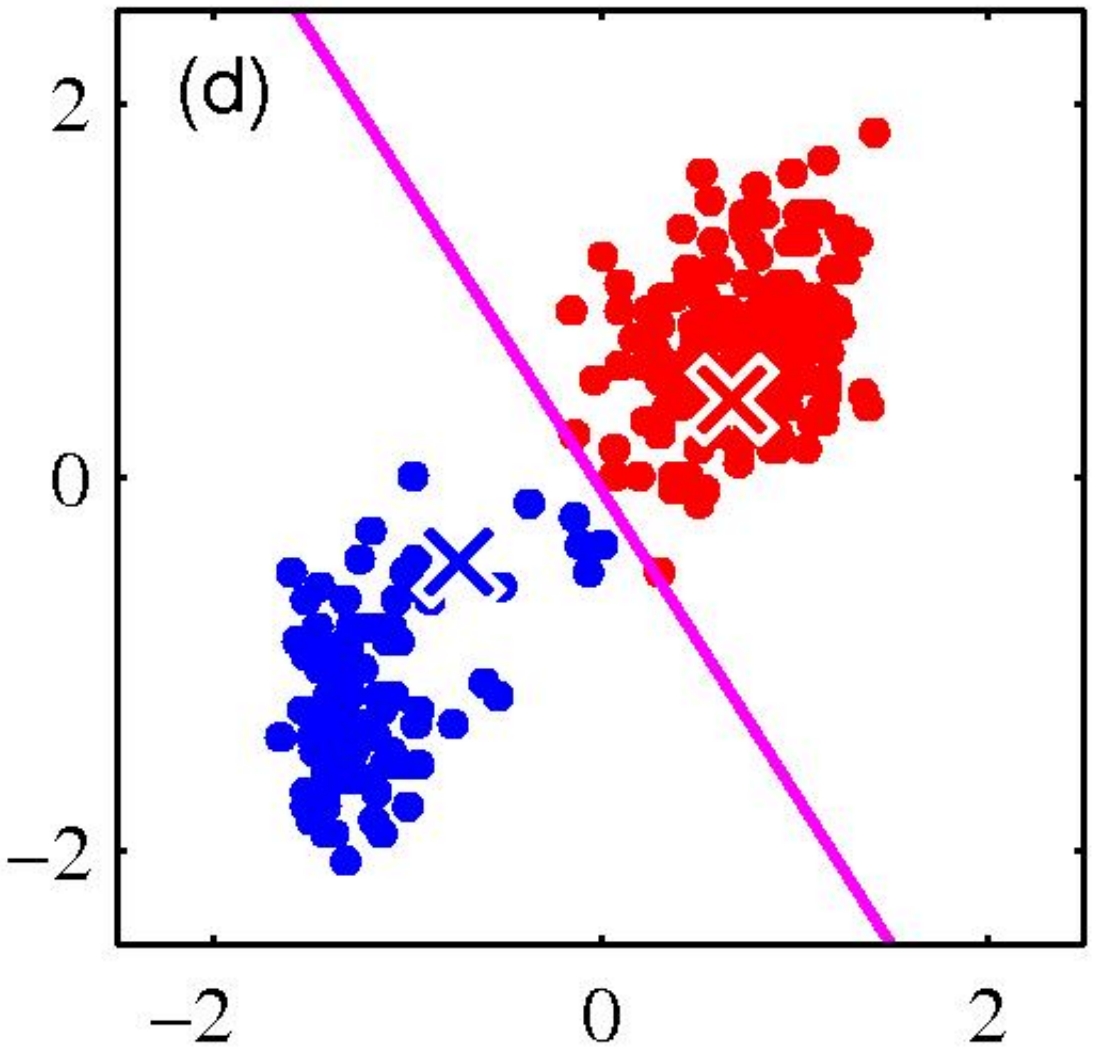
K-means clustering: Example



- Repeat until convergence

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Asthma: the problem

- 5 to 10% of people with severe asthma remain poorly controlled despite maximal inhaled therapy

[Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet. 2006; 368:780–793]

Asthma: the question

"It is now recognised that there are distinct asthma phenotypes and that distinct therapeutic approaches may only impinge on some aspects of the disease process within each subgroup"

- What are the processes (genetic or environmental) that underlie different subtypes of asthma?
- Which aspects of airway remodelling are important in disease subtypes?
- What are the best biomarkers of disease progression or treatment response?
- Why are some patients less responsive to conventional therapies than others?

[Adcock et al., "New targets for drug development in asthma". The Lancet, 2008]

The data

- All patients had physician diagnosis of asthma and at least one recent prescription for asthma therapy
- All were current nonsmokers
- *Data set #1*: 184 patients recruited from primary-care practices in the UK
- *Data set #2*: 187 patients from refractory asthma clinic in the UK
- *Data set #3*: 68 patients from 12 month clinical study
- Features: *z* scores for continuous variables, 0/1 for categorical
  - Some of the continuous variables log-transformed to approximate a normal distribution

[Haldar et al., *Am J Respir Crit Care Med*, 2008]

How should we treat asthma?

- Now we use 3rd dataset – 68 patients over 12 months
- Randomized control trial with two arms:
  - Standard clinical care ("clinical")
  - Regular monitoring of airway inflammation using induced sputum, to titrate steroid therapy to maintain normal eosinophil counts ("sputum")
- Original study found no difference in corticosteroid usage
  - But, this could have been explained by heterogeneity in treatment response!

[Haldar et al., *Am J Respir Crit Care Med*, 2008]

Patients in different clusters respond differently to treatment! (analysis using 3rd dataset from 12 month study)

Treatment strategy

Cluster (found using *baseline* data)

Cluster	Outcomes	Study Group: Clinical (*n* = *10*)	Study Group: Sputum (*n* = *8*)	Significance
1: Obese female	Δ Inhaled corticosteroid dose*/μg per day (SEM)	−400 (328)	−462 (271)	0.89
	Severe exacerbation frequency over 12 mo (SEM)	1.40 (0.78)	1.50 (0.80)	0.93
	Number commenced on oral corticosteroids	2	1	0.59
		Clinical (*n* = *15*)	Sputum (*n* = *24*)	
2: Inflammation predominant	Δ Inhaled corticosteroid dose*/μg per day (SEM)	+753 (334)	+241 (233)	0.22
	Severe exacerbation frequency over 12 mo (SEM)	3.53 (1.18)	0.38 (0.13)	0.002
	Number commenced on oral corticosteroids	2	9	0.17
		Clinical (*n* = *7*)	Sputum (*n* = *4*)	
3: Early symptom predominant	Δ Inhaled corticosteroid dose*/μg per day (SEM)	+1,429 (429)	−400 (469)	0.022
	Severe exacerbation frequency over 12 mo (SEM)	5.43 (1.90)	2.50 (0.87)	0.198
	Number commenced on oral corticosteroids	6	0	Undefined

[Haldar et al., *Am J Respir Crit Care Med*, 2008]

Summary – two approaches

- **Supervised:**
  predict future disease status
- **Unsupervised:**
  which patients look similar / different? Do clusters have different outcomes?

Limitations that we'll address in the next lecture

- Can't differentiate between *stage* and *subtype*
  - Patients assumed to be aligned at baseline
- Only make use of one time point per patient
- Assumes single factor (cluster) explains all variation
- Distance function is particularly simplistic
- Either supervised or unsupervised, but not both – how to combine?

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