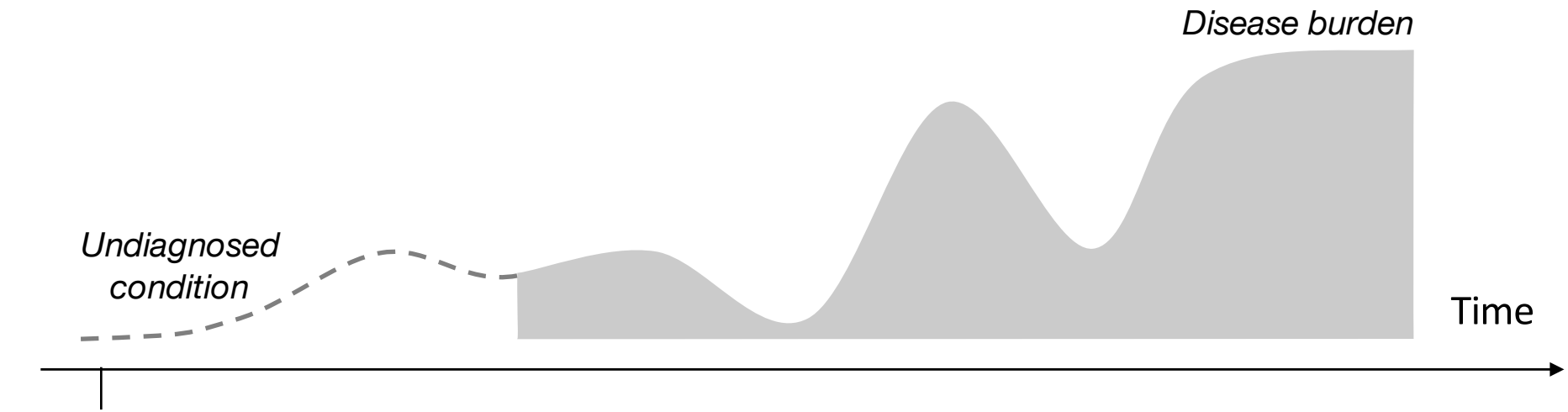
Machine Learning for Healthcare

HST.956, 6.S897

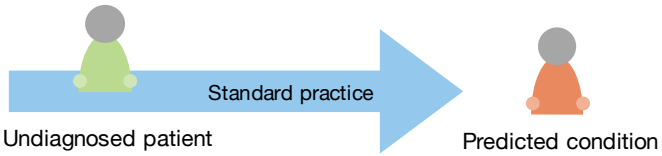
Lecture 18: Disease progression modeling & subtyping, Part 1

David Sontag

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

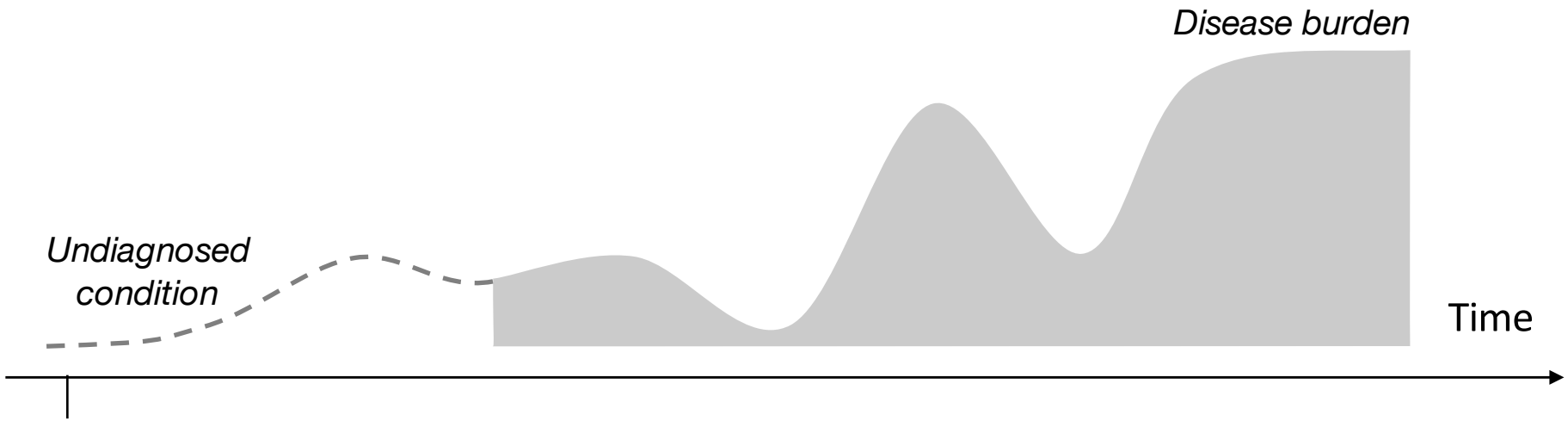
- Rare blood cancer
- MMRF CoMMpass Study has ~1000 patients

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

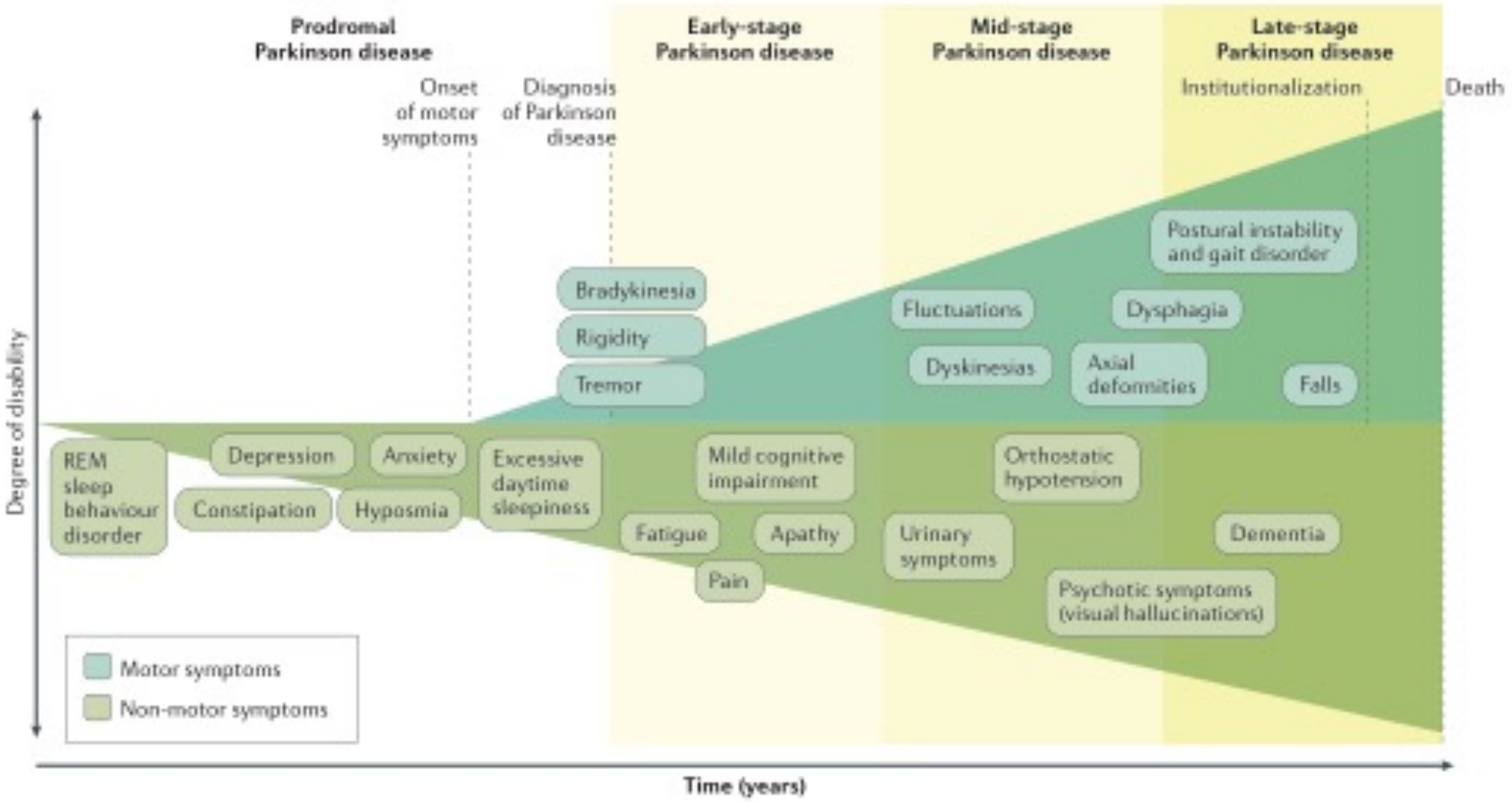
https://www.lls.org/disease-information/myeloma/diagnosis/myeloma-staging

Descriptive: What does a typical trajectory look like?



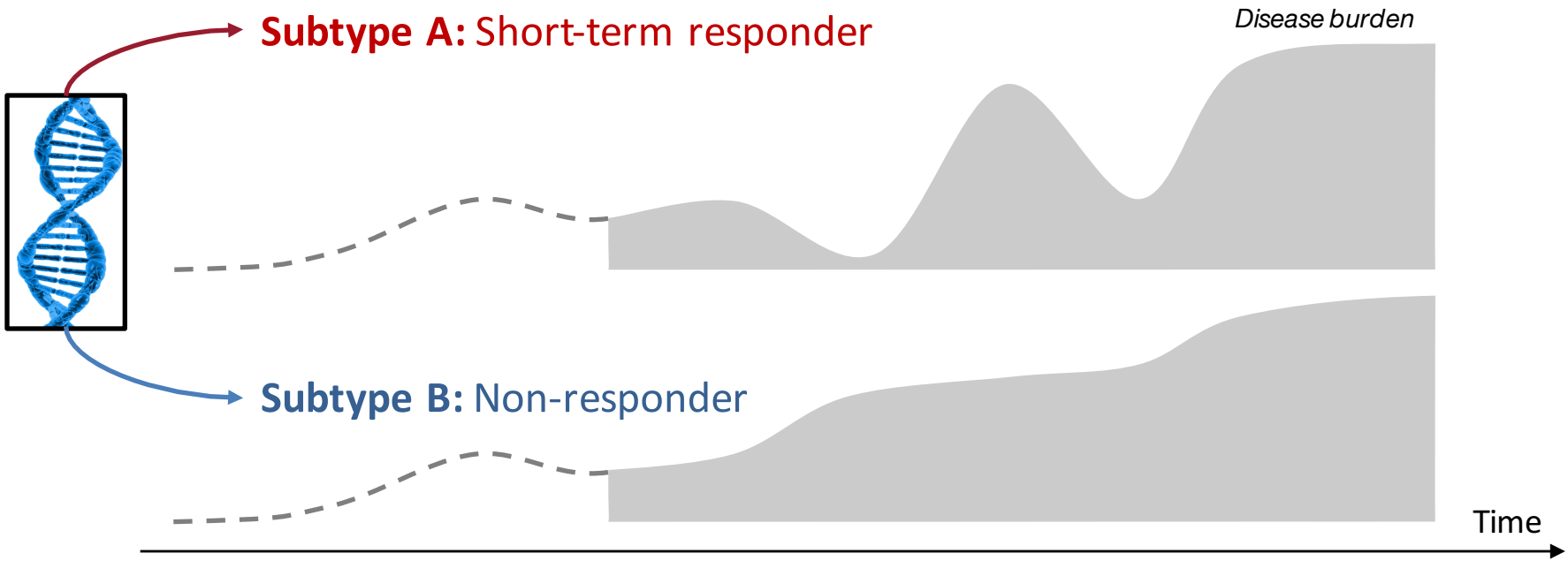
Example: Parkinson's

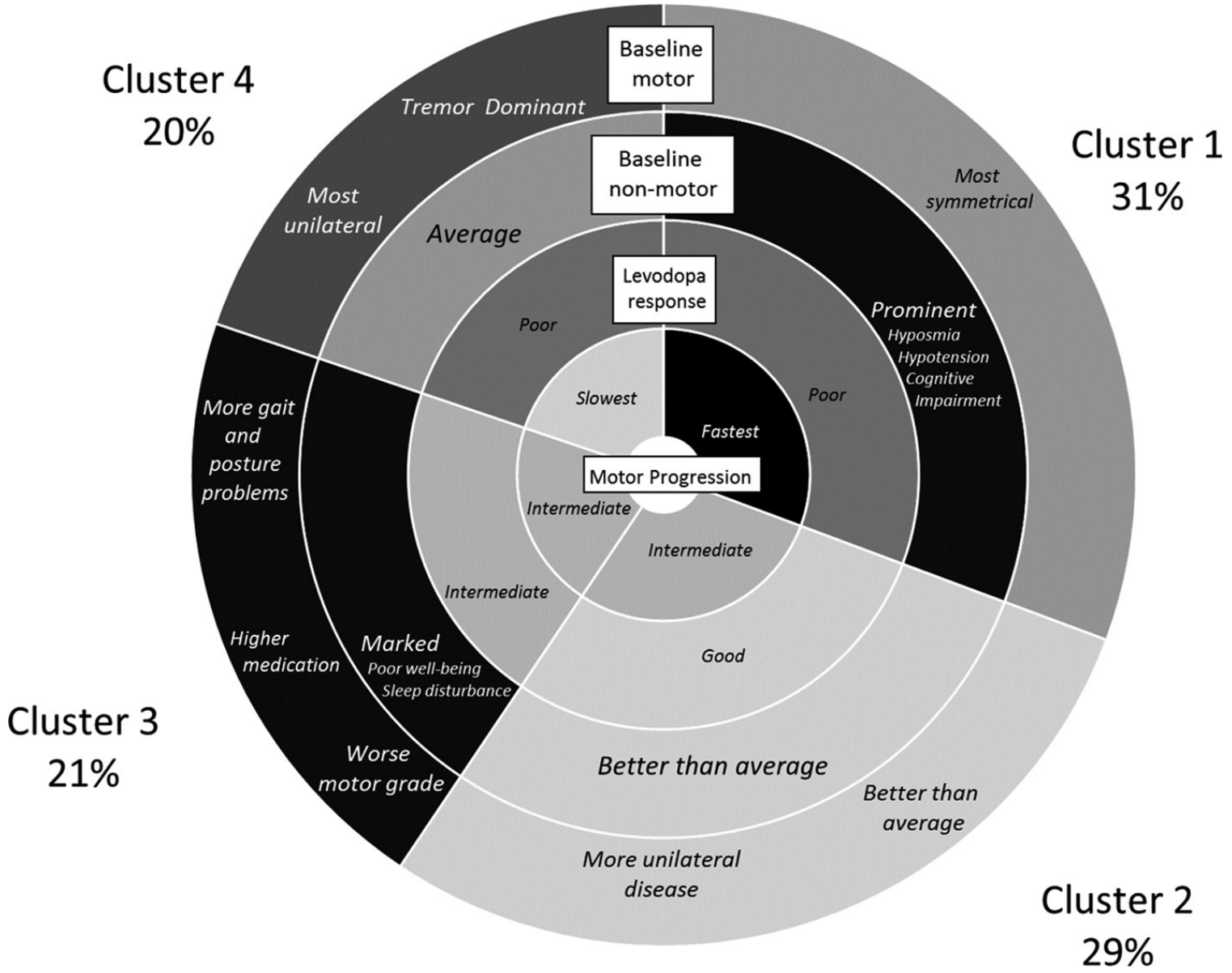
- Progressive nervous system disorder
- Affects 1 in 100 people over age 60
- PPMI dataset follows patients across time



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

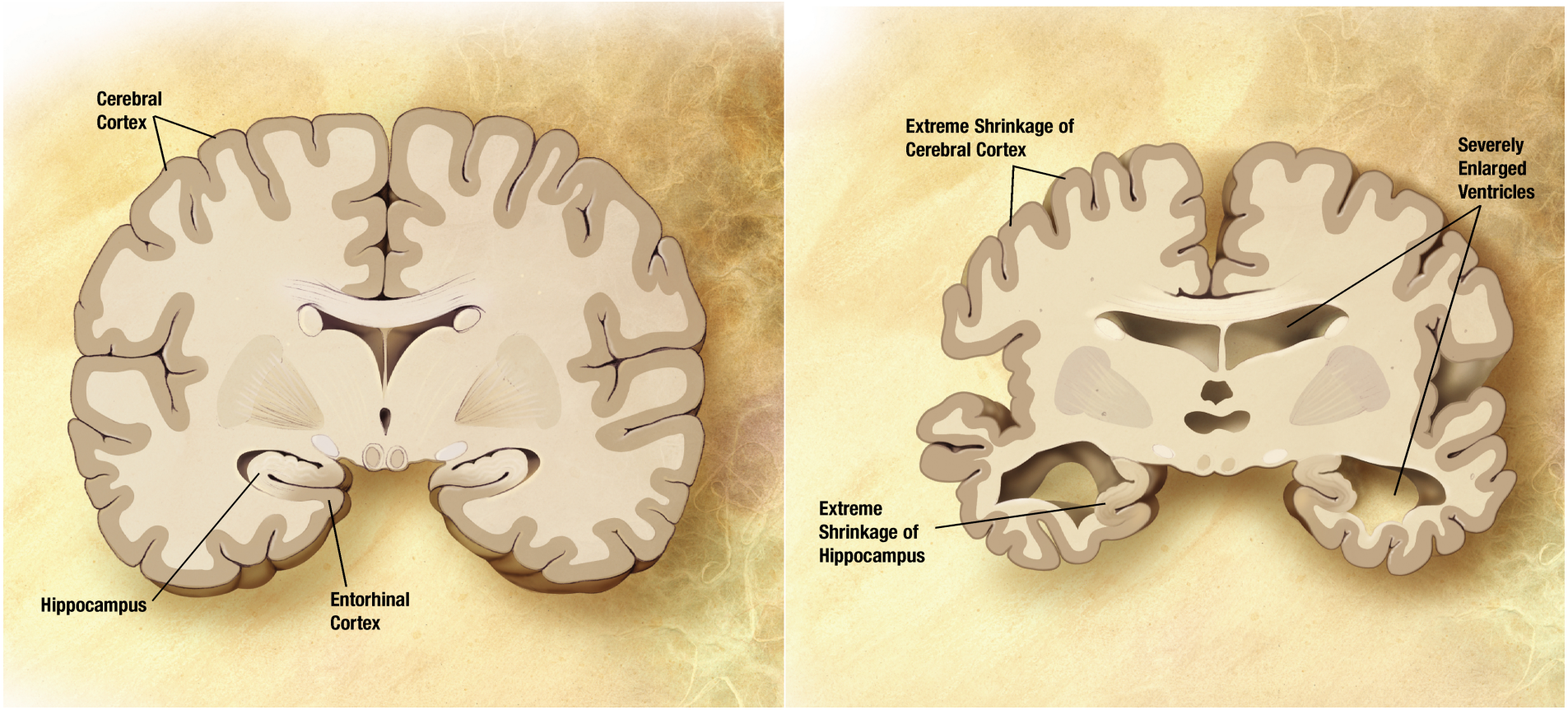
Subtyping: Can we re-define the disease altogether?





[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."]

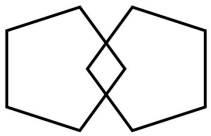
Disease status quantified by cognitive score (continuous valued)

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

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

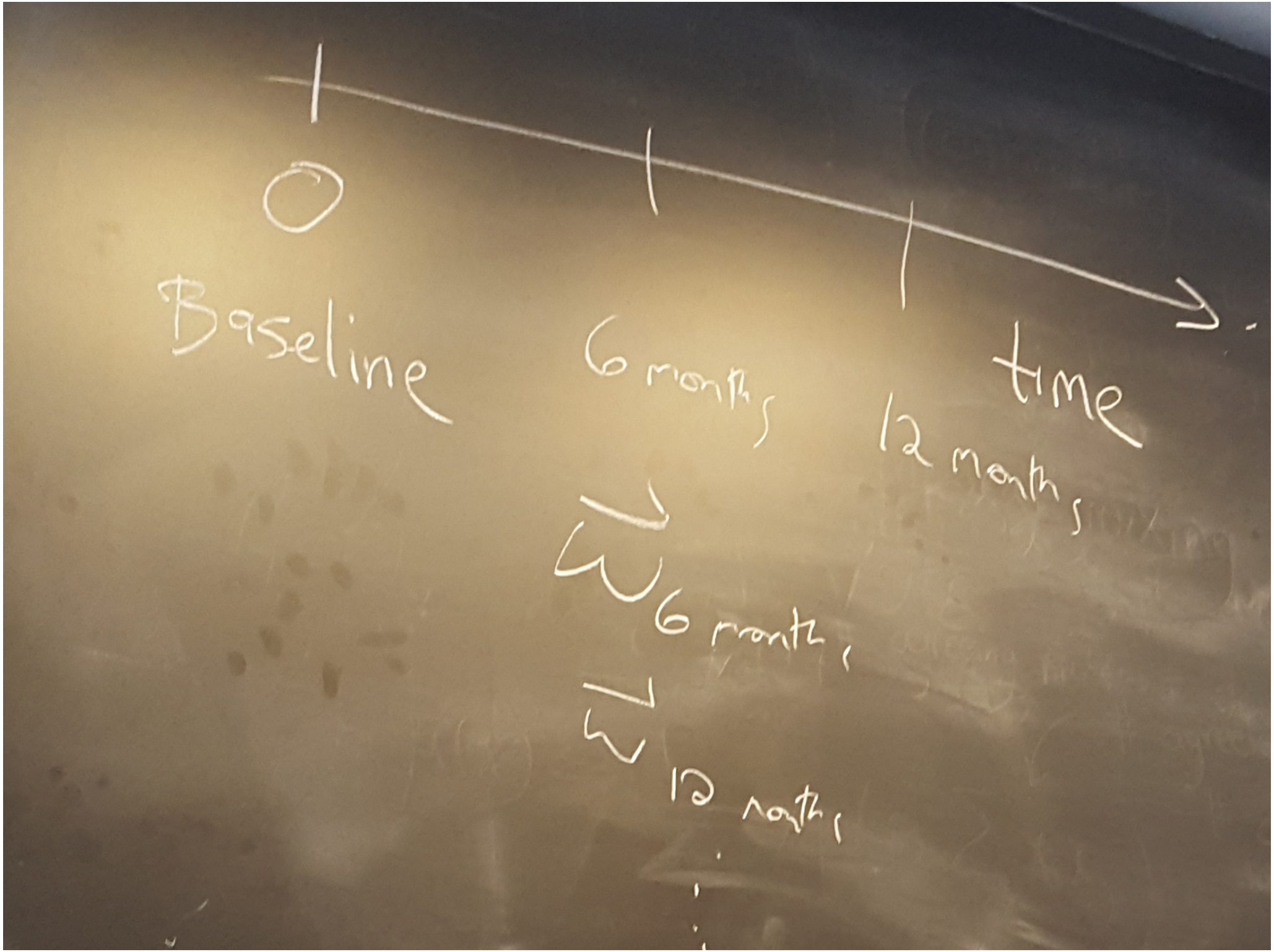
M06 = 6 months after baseline

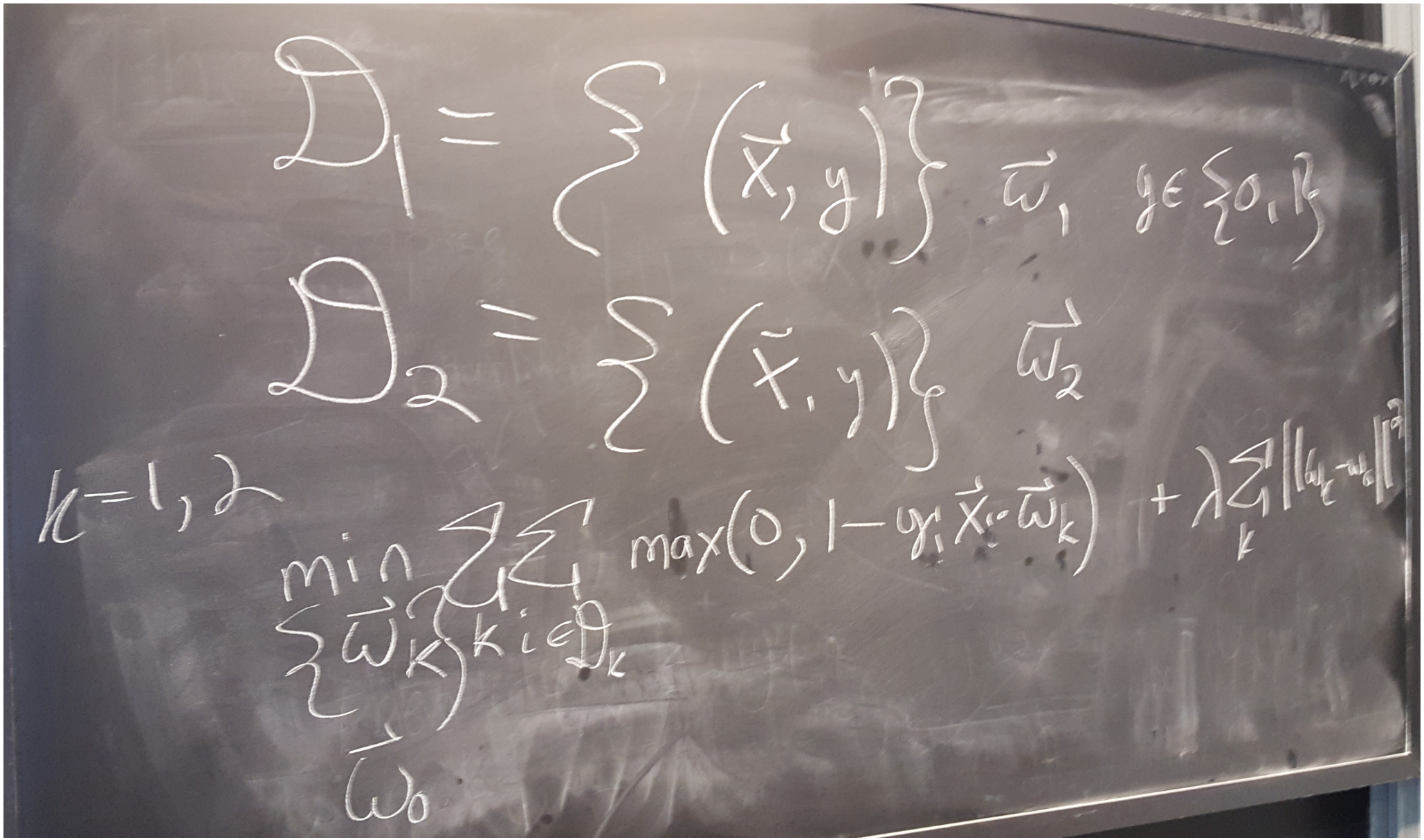
[Zhou et al., KDD '12]

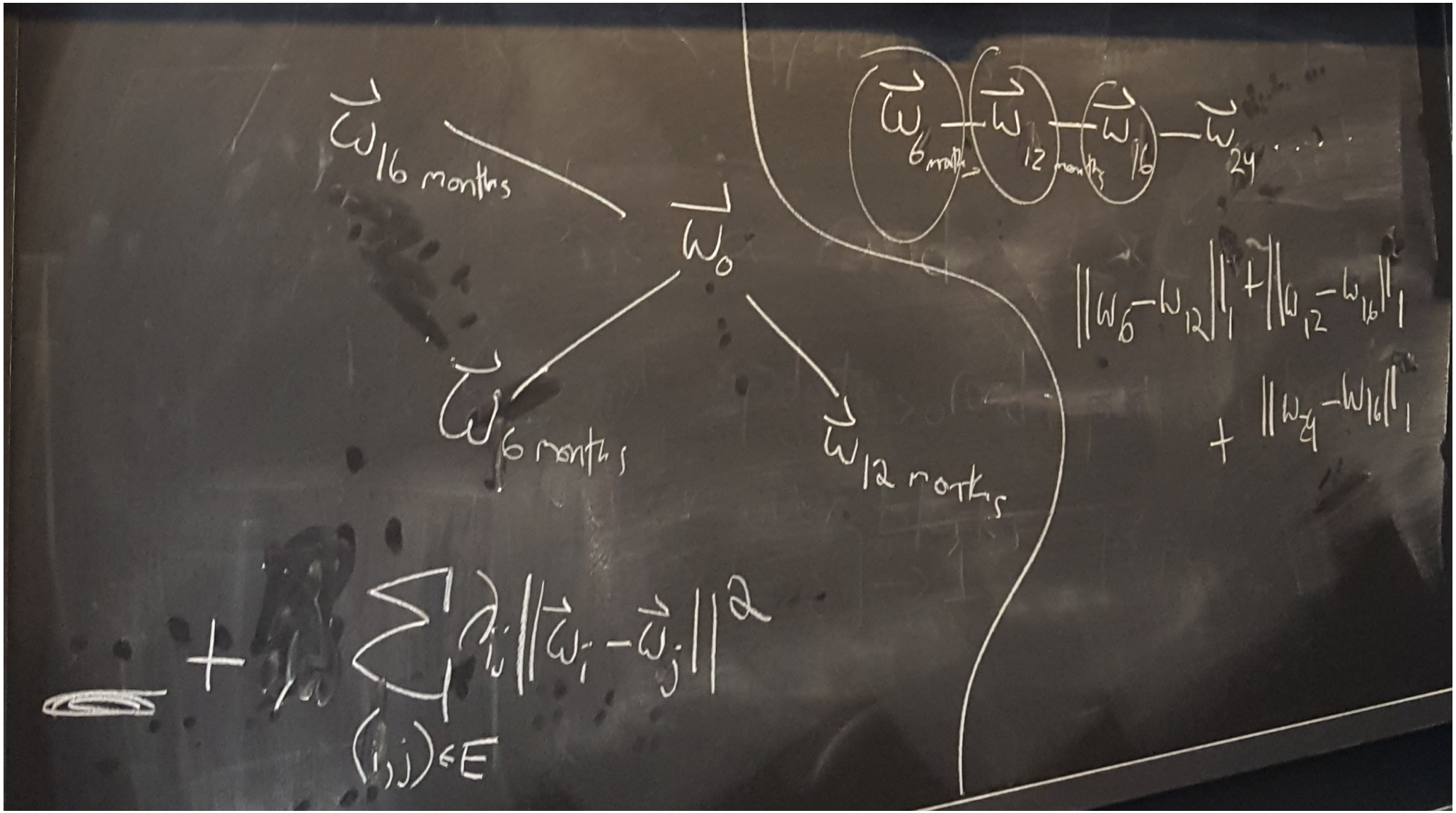
Multi-task learning

- 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


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


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

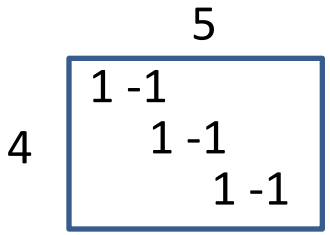
Convex fused sparse group lasso

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

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

- 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 =



[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!

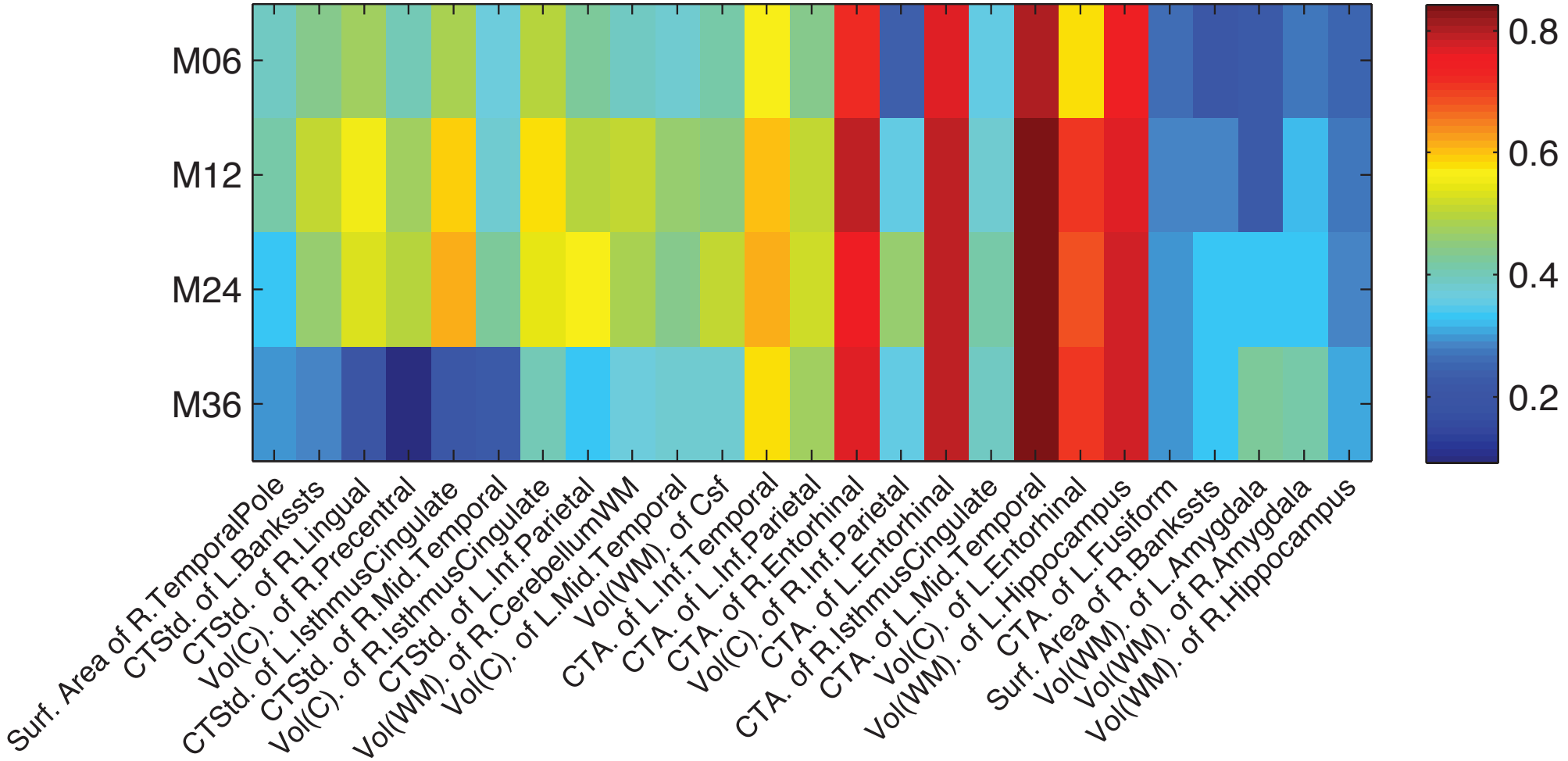
	Ridge	cFSGL1 $\lambda_2 = 20$	cFSGL2 $\lambda_2 = 50$	cFSGL3 $\lambda_2 = 100$
		Target: MMSE		
nMSE	0.548 ± 0.057	0.428 ± 0.052	0.400 ± 0.053	$\mathbf{0.395 \pm 0.052}$
R	0.689 ± 0.030	0.772 ± 0.030	0.790 ± 0.032	$\mathbf{0.796 \pm 0.031}$

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)

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)

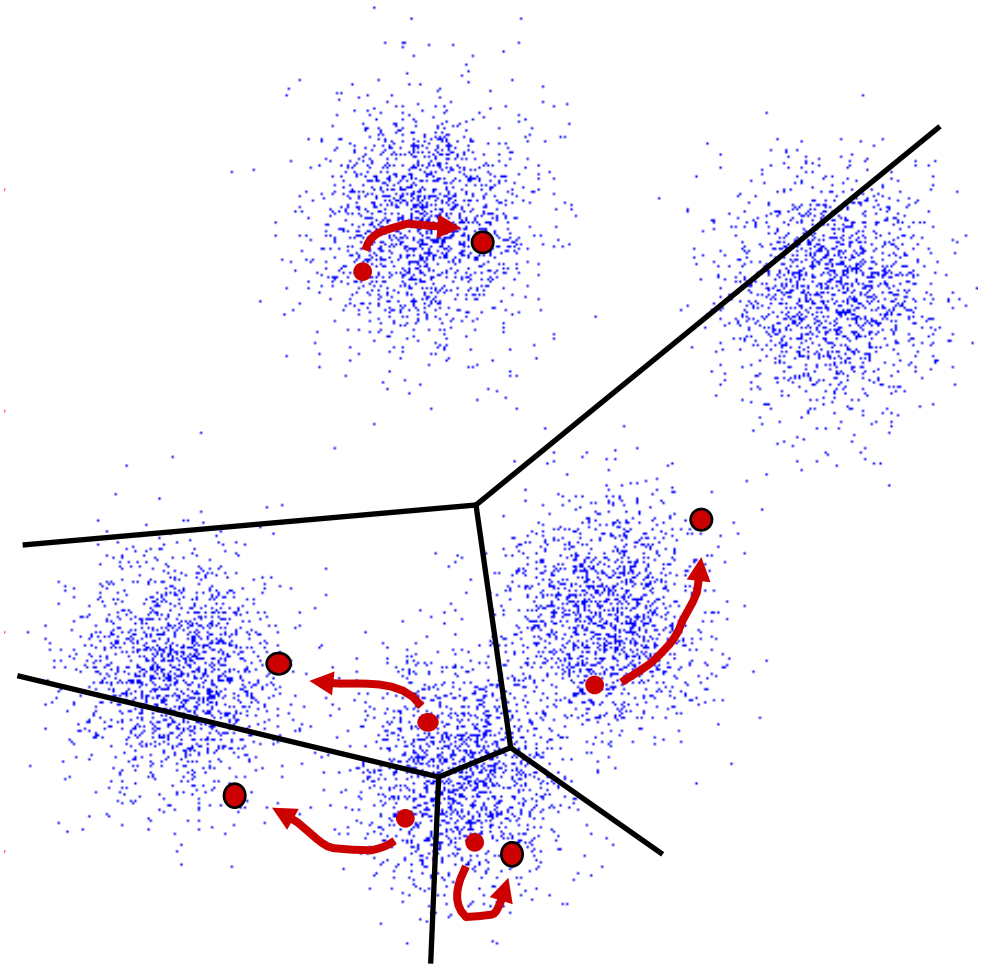
    Not *just* interested in prediction – rather, identify cohorts for clinical trials, better understand disease mechanism

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

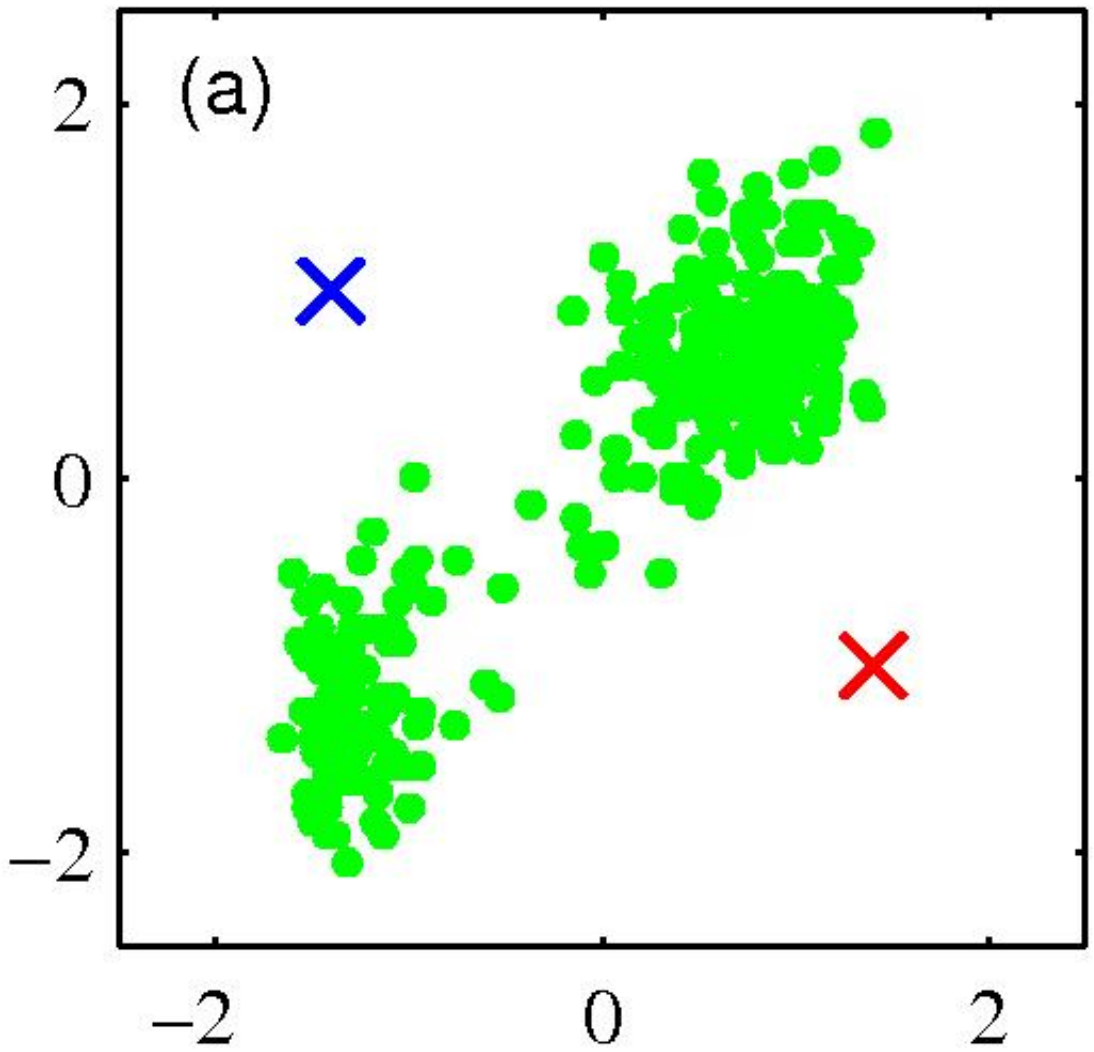
    Dimensionality reduction to prevent overfitting

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



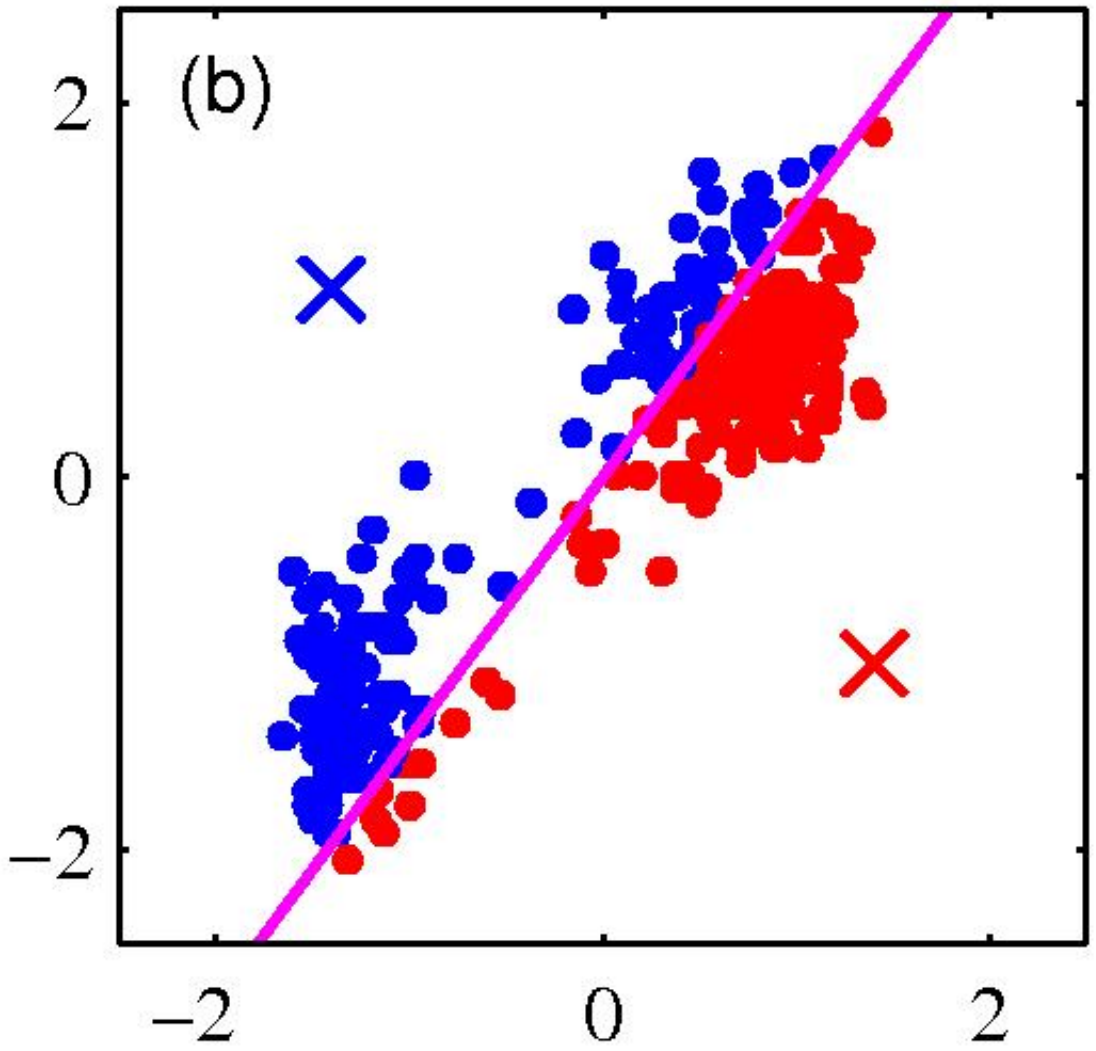
K-means clustering: Example



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

Shown here for *K*=2

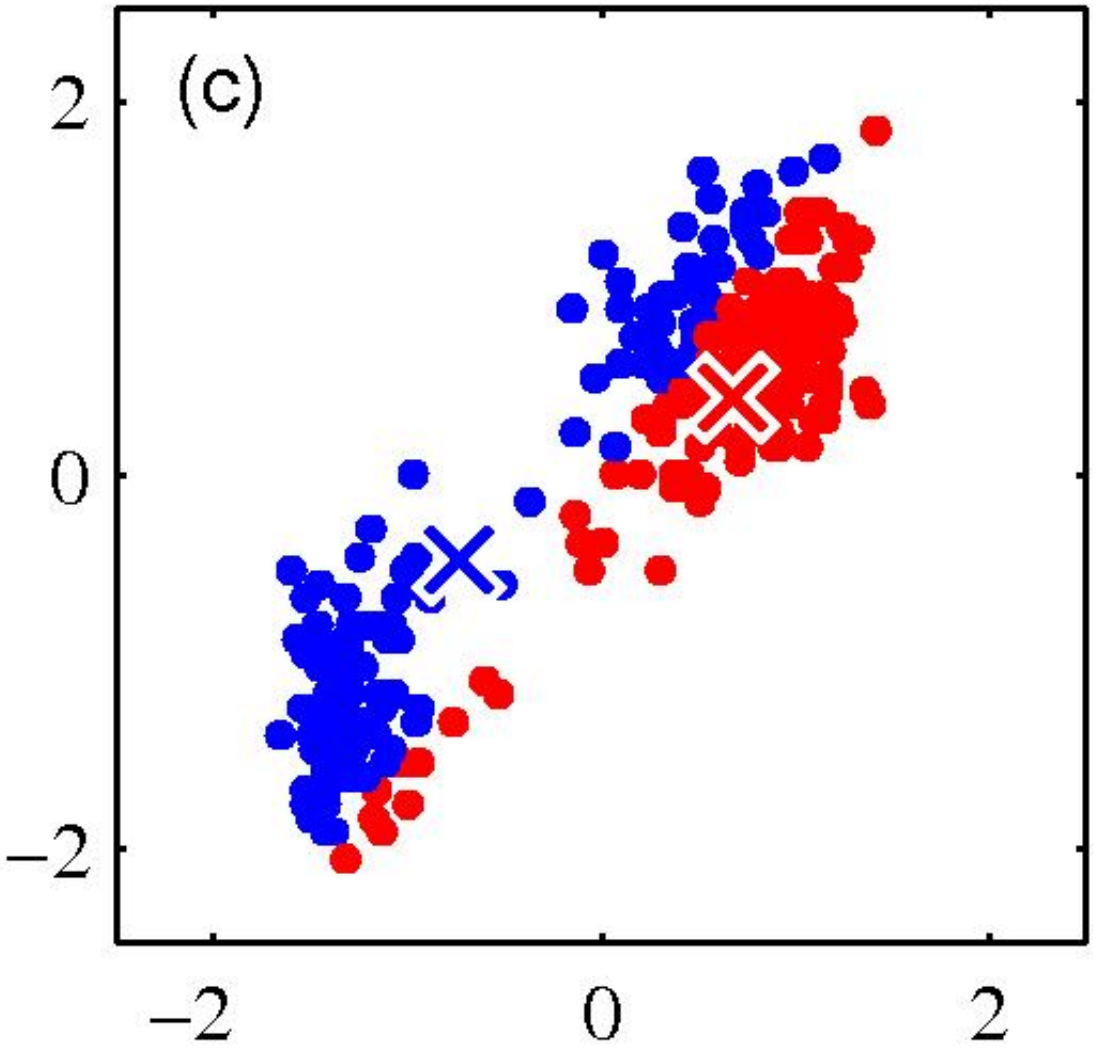
K-means clustering: Example



Iterative Step 1

- Assign data points to closest cluster center

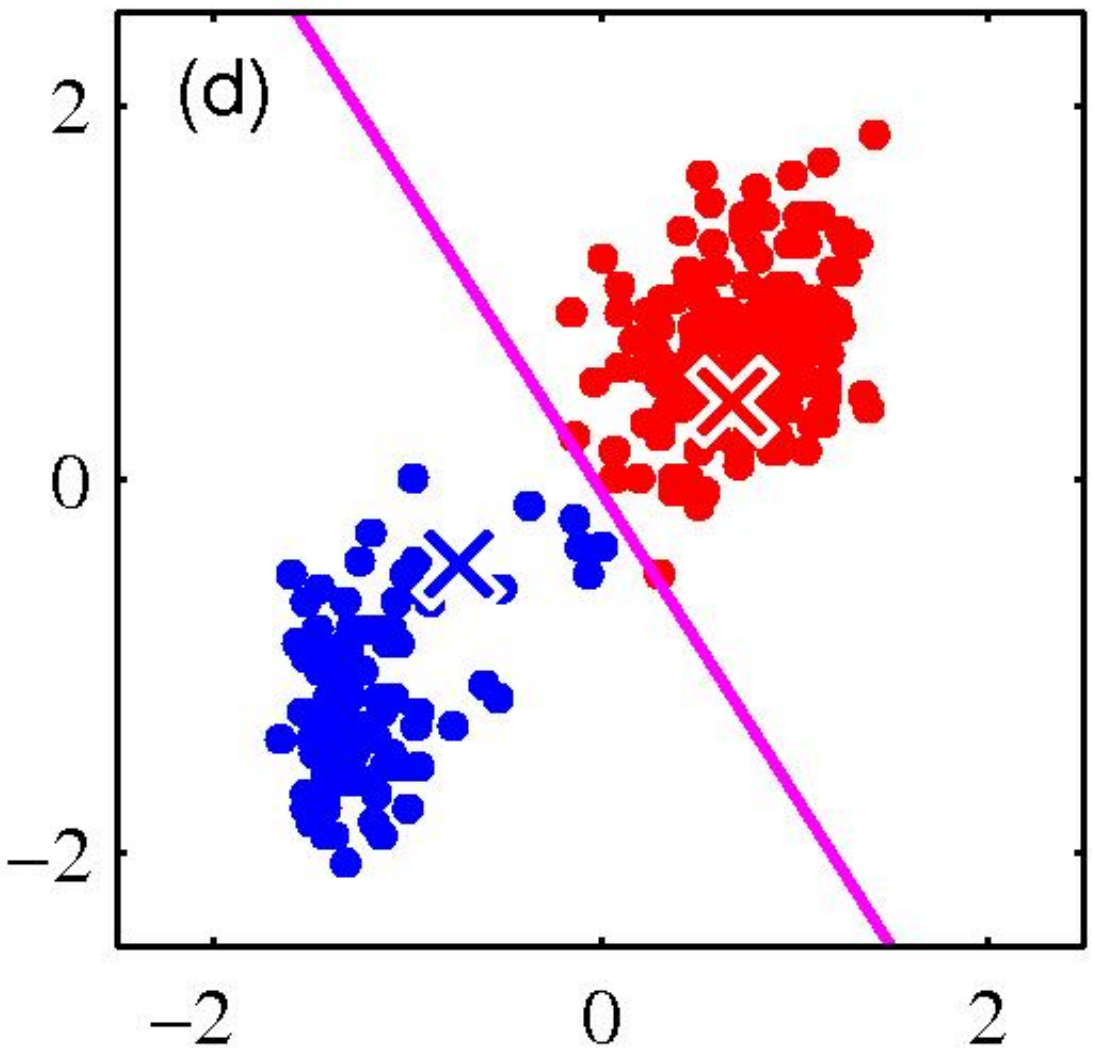
K-means clustering: Example



Iterative Step 2

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

K-means clustering: Example



- Repeat until convergence

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]

[whatasthmais.com]

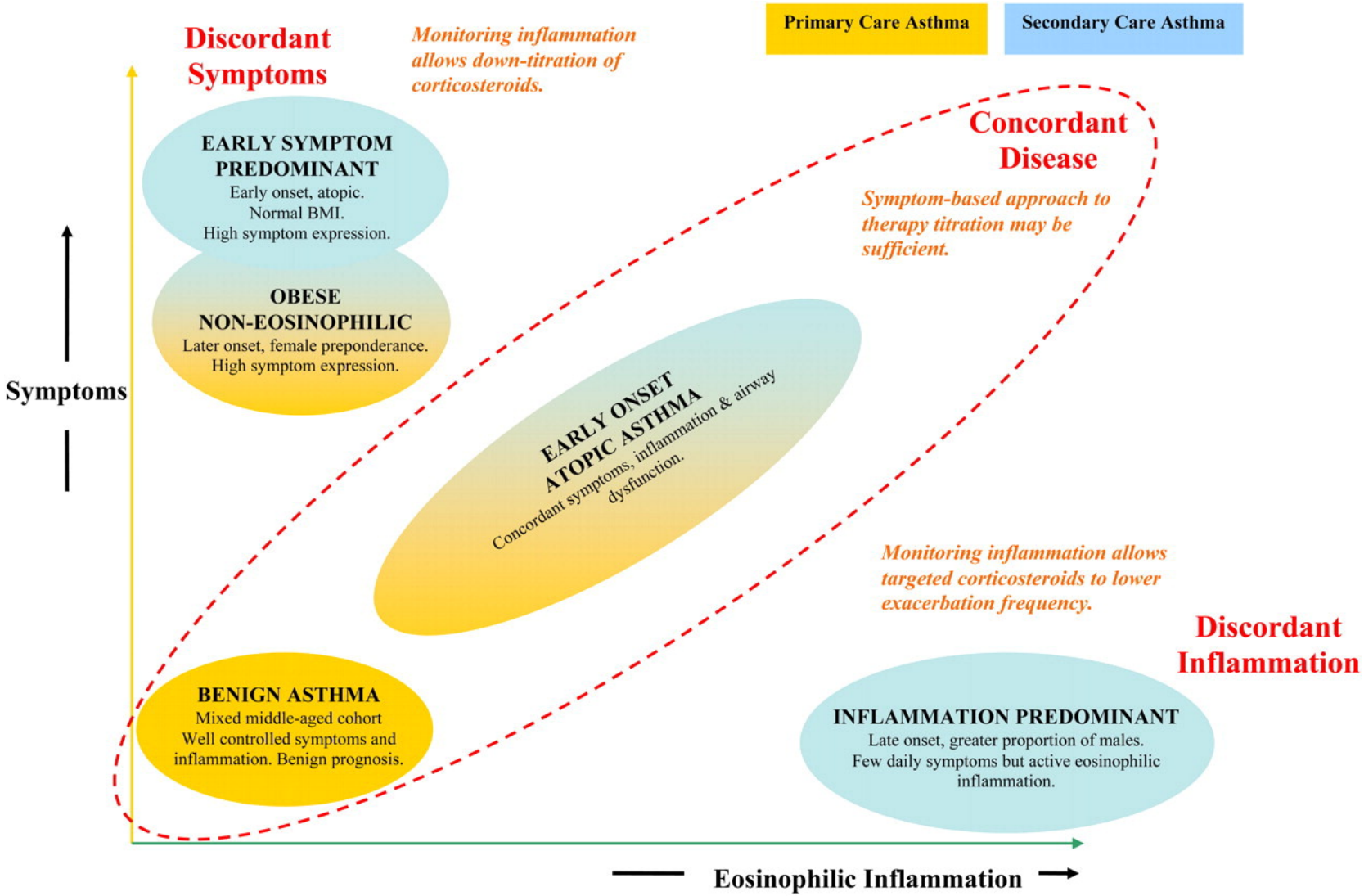
Asthma: the question

"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]

Discovering subtypes from data



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

Comparison of Baseline Characteristics in the three Asthma Populations

Variable	Primary Care (*n = 184*)	Secondary Care (*n = 187*)	Longitudinal Cohort (*n = 68*)
Sex, % female	54.4	65.8	47.1
Age, yr (SD)	49.2 (13.9)	43.4 (15.9)	52.4 (14.6)
Age of onset, yr (SD)	24.7 (19)	20.3 (18.4)	31.1 (23.7)
Atopic status, % positive	72.8	73.8	57.4
Body mass index, kg/m^2 (SD)	27.5 (5.4)	28.5 (6.5)	28.0 (5.9)
PC_{20} methacholine†, mg/ml	1.04 (1.13)	†	0.67 (0.68)
Peak flow variability, amp % mean	17 (0.38)	32.2 (0.48)	13.8 (0.29)
FEV_1 change with bronchodilator, %	1.63 (1.16)	12.8 (0.41)	3.2 (1.04)
Post-bronchodilator FEV_1, % predicted	91.4 (21)	82.1 (21.1)	80.2 (20.6)
Sputum eosinophil count, %	1.32 (0.62)	2.9 (0.99)	2.4 (0.81)
F_{ENO}‡, ppb	31.6 (0.33)	43 (0.32)	4.32 (0.64)‡
Sputum neutrophil count, %	55.09 (0.31)	46.7 (0.32)	41.1 (0.35)
Modified JACS§ (SD)	1.36 (0.74)	2.02 (1.16)	1.42 (1.26)
Dose of inhaled corticosteroid, BDP equivalent/μg (SD)	632 (579)	1,018 (539)	1,821 (1,239)
Long-acting bronchodilator use, %	40.2	93	86.7

Definition of abbreviations: amp = amplitude; BDP = beclomethasone dipropionate; JACS = Juniper Asthma Control Score

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

Clusters in primary care

(found by K-means)

Variable	Primary Care (*n* = 184)	Cluster 1 Early-Onset Atopic Asthma (*n* = 61)	Cluster 2 Obese Noneosinophilic (*n* = 27)	Cluster 3 Benign Asthma (*n* = 96)	Significance (*P* Value)*
Sex†, % female	**54.4**	45.9	81.5	52.1	0.006
Age, yr (SD)	**49.2 (13.9)**	44.5 (14.3)	53.9 (14)	50.8 (13)	0.003
Age of onset†, yr (SD)	**24.7 (19)**	14.6 (15.4)	35.3 (19.6)	28.2 (18.3)	<0.001
Atopic status†, % positive	**72.8**	95.1	51.9	64.6	<0.001
Body mass index†, kg/m^2 (SD)	**27.5 (5.4)**	26.1 (3.8)	36.2 (5.5)	26 (3.6)	<0.001
PC_{20} methacholine†‡, mg/ml	**1.04 (1.13)**	0.12 (0.86)	1.60 (0.93)	6.39 (0.75)	<0.001
PC_{20} >8 mg/ml, n (%)	**64 (34.7)**	2 (3.3)	6 (22.2)	56 (58.3)	<0.001
Peak flow variability†‡, amp % mean	**17 (0.38)**	20 (0.47)	21.9 (0.32)	14.8 (0.32)	0.039
FEV_1 change with bronchodilator‡, %	**1.63 (1.16)**	4.5 (0.91)	1.82 (1.16)	0.83 (1.22)	<0.001
Post-bronchodilator FEV_1, % predicted	**91.4 (21)**	86.9 (20.7)	91.5 (21.4)	94.2 (20.7)	0.107
Sputum eosinophil count†‡, %	**1.32 (0.62)**	3.75 (0.64)	1.55 (0.51)	0.65 (0.44)	<0.001
F_{ENO}‡§, ppb	**31.6 (0.33)**	57.5 (0.27)	25.8 (0.29)	22.8 (0.27)	<0.001
Sputum neutrophil count‡, %	**55.09 (0.31)**	45.87 (0.24)	72.71 (0.13)	57.56 (0.36)	0.038
Modified JACS† (SD)	**1.36 (0.74)**	1.54 (0.58)	2.06 (0.73)	1.04 (0.66)	<0.001
Dose of inhaled corticosteroid, BDP equivalent/μg (SD)	**632 (579)**	548 (559)	746 (611)	653 (581)	0.202
Long-acting bronchodilator use, %	**40.2**	34.4	48.2	41.7	0.442
Previous hospital admission or emergency attendance, no. per patient	**0.60 (1.57)**	1.04	0.26	0.20	0.037
Previous outpatient attendance, % attended	**15%**	22%	19%	6%	0.121
Severe asthma exacerbations (requiring oral corticosteroids) in past 12 mo, no. per patient	**1.25 (1.94)**	1.86 (0.32)	1.07 (0.32)	0.39 (0.18)	0.002

Clusters in secondary care

Variable	Secondary Care (*n = 187*)	Cluster 1 Early Onset, Atopic (*n = 74*)	Cluster 2 Obese, Noneosinophilic (*n = 23*)	Cluster 3 Early Symptom Predominant (*n = 22*)	Cluster 4 Inflammation Predominant (*n = 68*)	Significance (*P* Value)*
Sex†, % female	**65.8**			68.2	47.1	<0.001
Age, yr (SD)	**43.4 (15.9)**			35.5 (15.5)	50.6 (15.1)	<0.001
Age of onset†, yr (SD)	**20.3 (18.4)**			12.6 (15)	32.6 (19.1)	<0.001
Atopic status†, % positive	**73.8**			81.8	63.2	0.024
Body mass index†, kg/m^2 (SD)	**28.5 (6.5)**			23.6 (3.1)	27 (3.9)	<0.001
Peak flow variability‡, amp % mean	**32.2 (0.48)**			24.2 (0.65)	27.6 (0.36)	0.002
FEV_1 change with bronchodilator‡, %	**12.8 (0.41)**	24.5 (0.31)	9.3 (0.35)	4.5 (0.33)	9.8 (0.34)	<0.001
Post-bronchodilator FEV_1, % predicted (SD)	**82.1 (21.1)**	79.0 (21.9)	79.0 (18.5)	79.5 (26.1)	87.2 (18.5)	0.093
Sputum eosinophil count†‡, %	**2.9 (0.99)**	4.2 (0.76)	1.3 (1.01)	0.1 (0.9)	8.4 (0.64)	<0.001
F_{ENO}‡§, ppb	**43 (0.32)**	51.2 (0.36)	24.2 (0.27)	22.6 (0.30)	53.1 (0.32)	<0.001
Sputum neutrophil count, %‡	**46.7 (0.32)**	45.4 (0.39)	49.3 (0.22)	51.3 (0.23)	45.9 (0.29)	0.892
Modified JACS† (SD)	**2.02 (1.16)**	2.63 (0.93)	2.37 (1.09)	2.11 (1.11)	1.21 (0.95)	<0.001
Dose of inhaled corticosteroid, BDP equivalent/μg (SD)	**1,018 (539)**	1,168 (578)	1,045 (590)	809 (396)	914 (479)	0.008
Long-acting bronchodilator use, %	**93.0**	91.9	95.4	90.9	94.1	0.999

Resembled clusters from primary care – i.e., these are common across spectrum of severity

Objective measures of disease severity show more advanced disease

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)

Cluster (found using *baseline* data)	Outcomes	Treatment strategy: Clinical (*n* = *10*)	Treatment strategy: 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?