

Changing the landscape for patient stratification

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Outline

- Diversifying discovery
 - 1,200 iPSC lines
 - Partnering with patient advocates
- Stratifying patients
 - Mixture of Gaussian process models
 - An ongoing metabolomic study
 - Accelerating discovery of novel biomarkers

What makes a biomarker reliable?

- The best biomarkers are
 - closely linked to disease mechanism

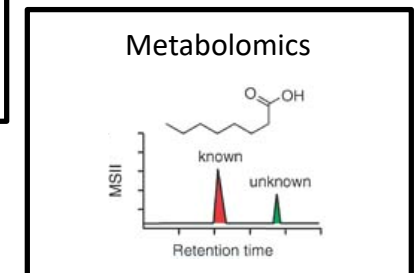
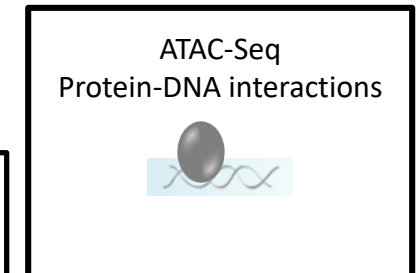
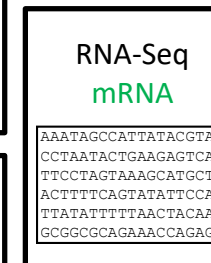
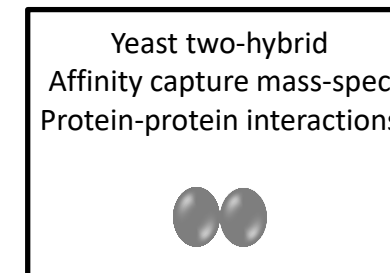
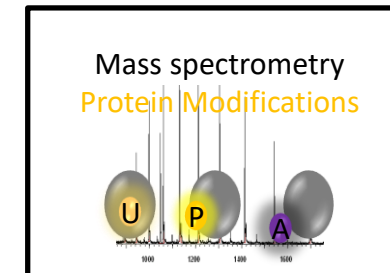
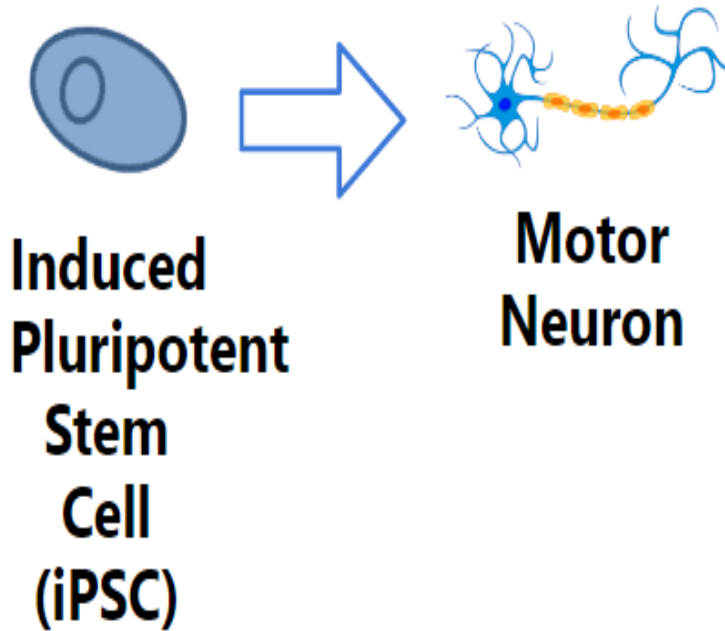
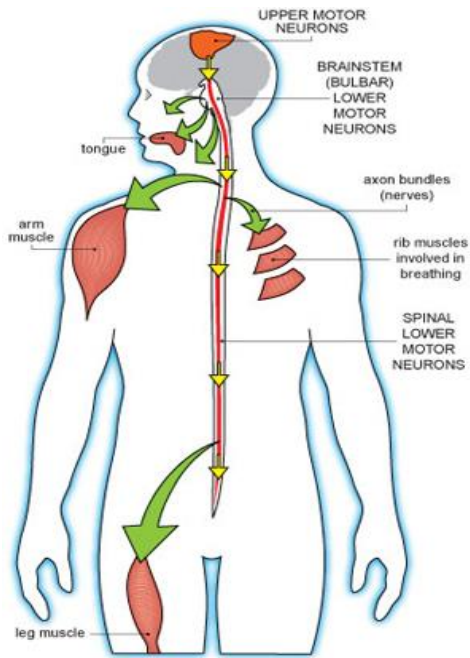
Challenge:
Mechanisms are poorly understood
and hard to model in animals

- discovered from representative populations

Challenge:
Participation in clinical studies
are not fully representative

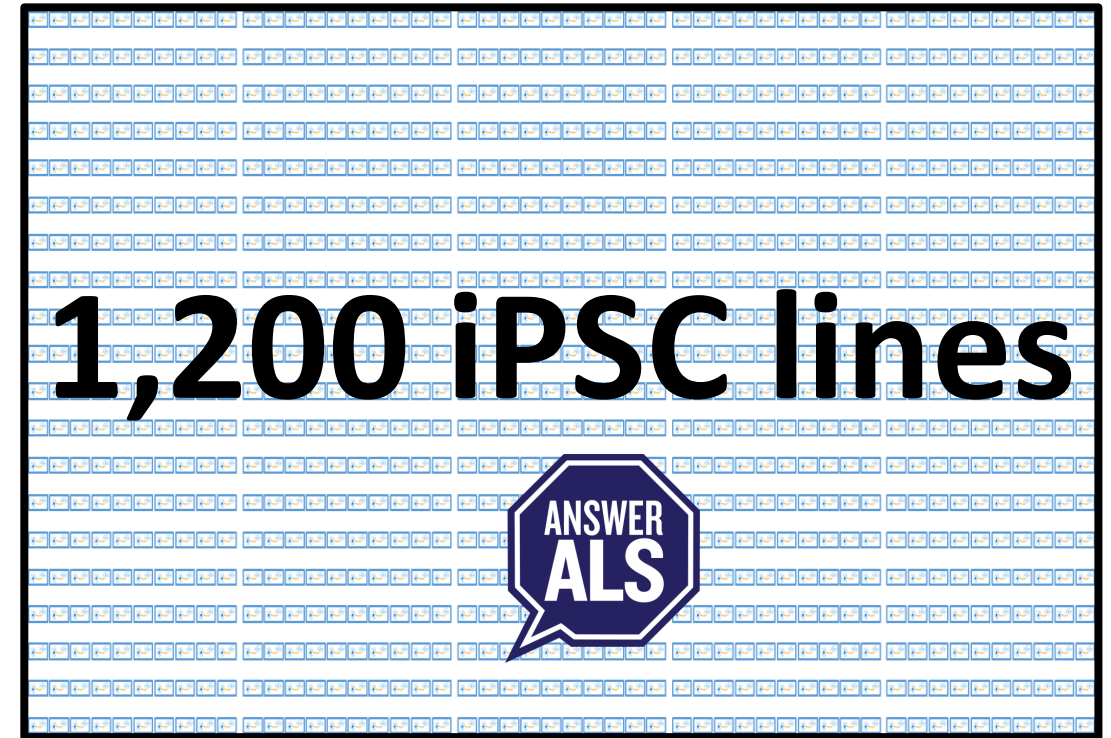
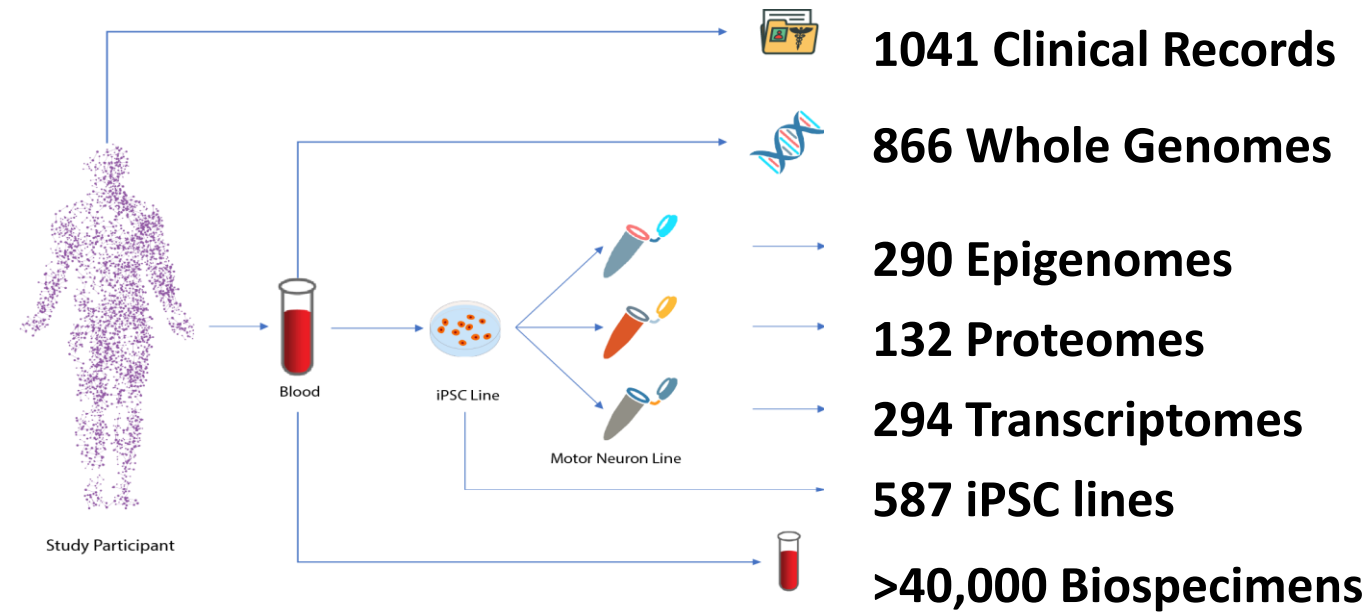
Challenge:
Mechanisms are poorly understood
and hard to model in animals

Approach:
Use iPSC models to develop
mechanistic insights



Critical to study a diverse population

Many iPSC studies focus on a few “representative” lines



Data and cell lines available at <https://data.answerals.org>

Clinical



James Berry



Nicholas Maragakis



Jonathan Glass



Stephen Kolb



Timothy Miller



Bob Baloh



Daragh Heitzman



Senda Arjoud-Driss



Ernest Fraenkel

Jenny Van Eyk

Clive Svendsen



Research

Leslie Thompson



Jeff Rothstein



Steve Finkbeiner



\$45 Million Program
Rigorous Oversight by
Independent Board

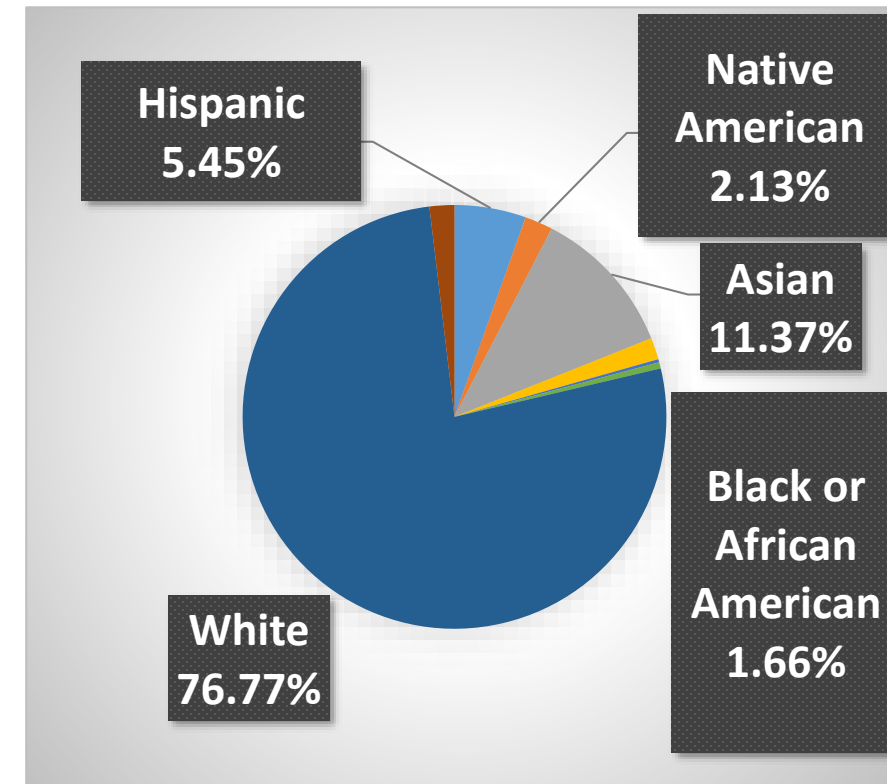


Ed Rapp

Former Caterpillar Group
President
Diagnosed with ALS 11/5/15
Answer ALS patient, funder and
Chairman of the Advisory Board

Challenge:
Participation in clinical studies
are not fully representative

Approach:
Partner with
patient advocacy groups



Indu Navar

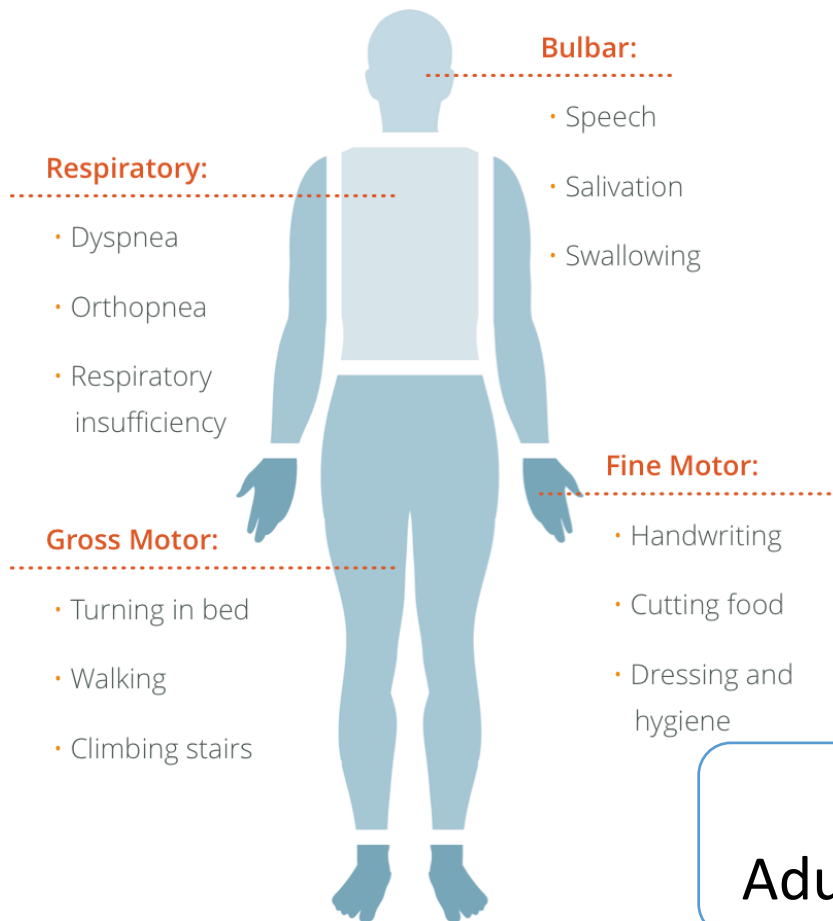


Aria Anvar

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Clinical symptoms monitored with ALSFRS-R



- 48 point scale
- Twelve questions assess functions at left:
SPEECH: Ask “How is your speech?”
SALIVATION: Ask “How is your saliva?”
SWALLOWING: Ask “How is your swallowing?”

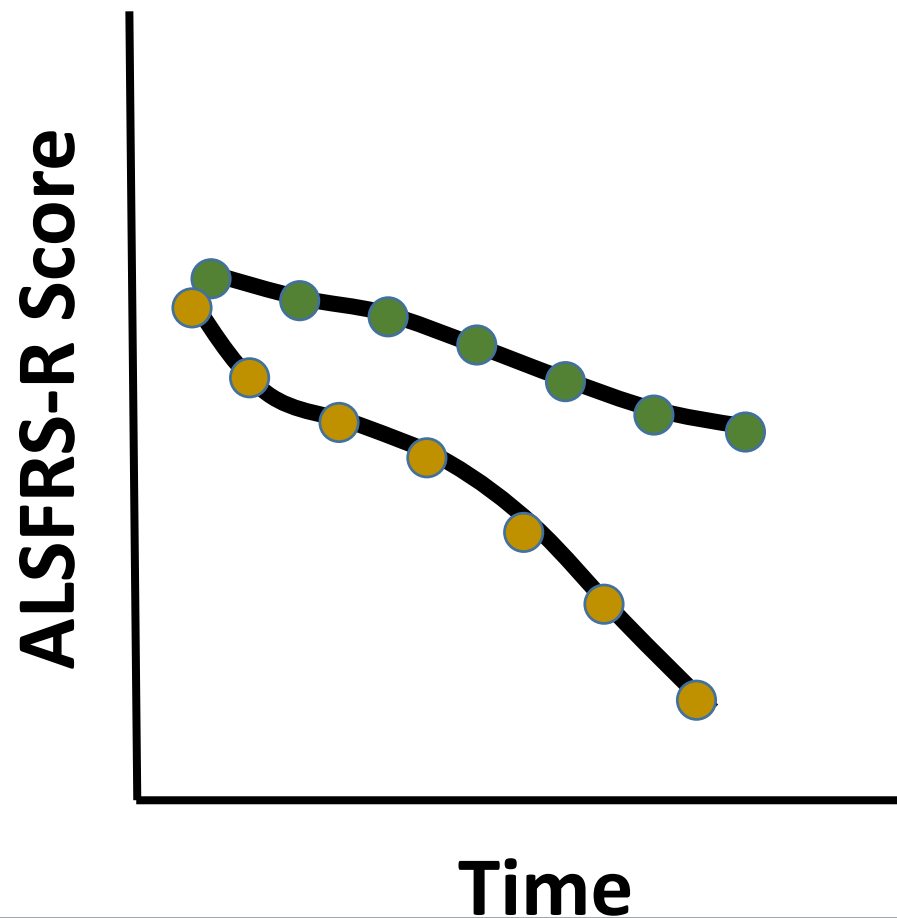
...

4 = normal

0 = complete loss of function

A similar approach is used in other diseases:
Aducanumab used the “Clinical Dementia Rating Sum of Boxes”

The challenge of identifying clinical patterns



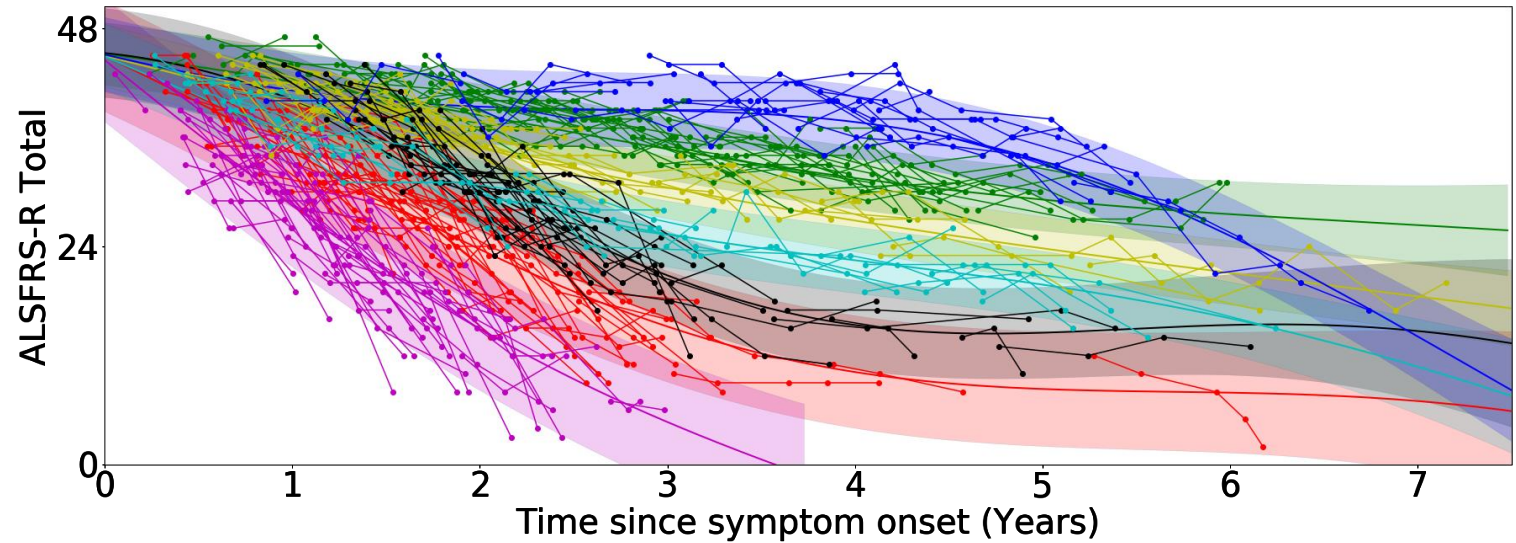
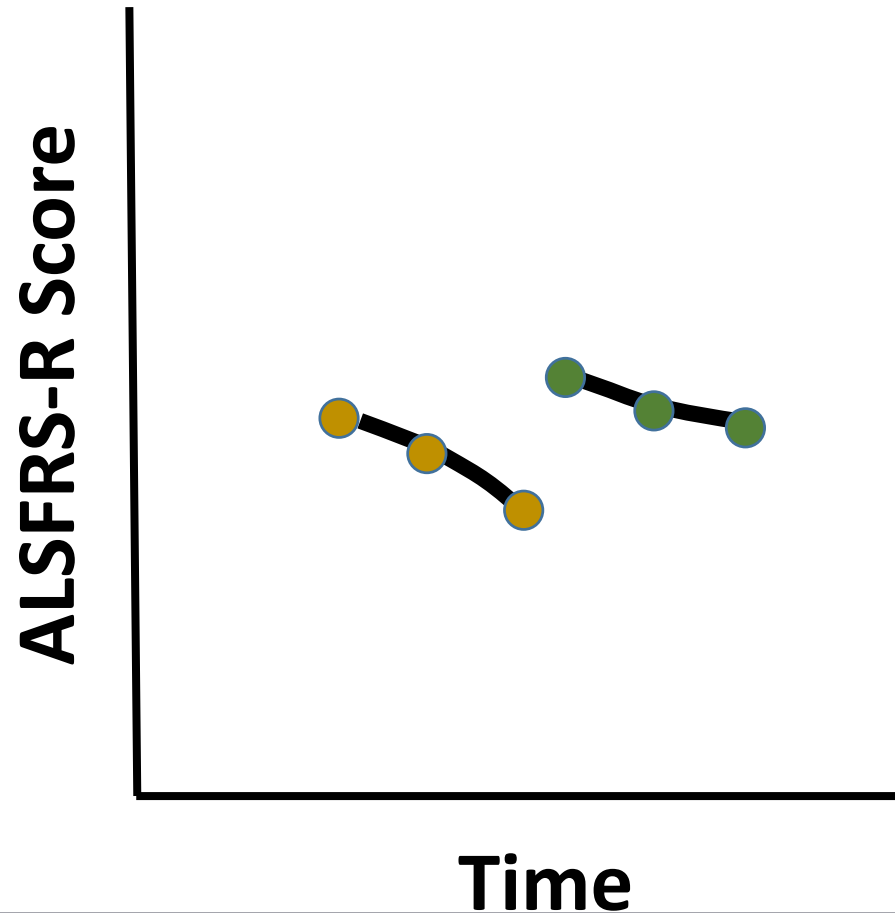
Divya
Ramamoorthy

IBM Watson

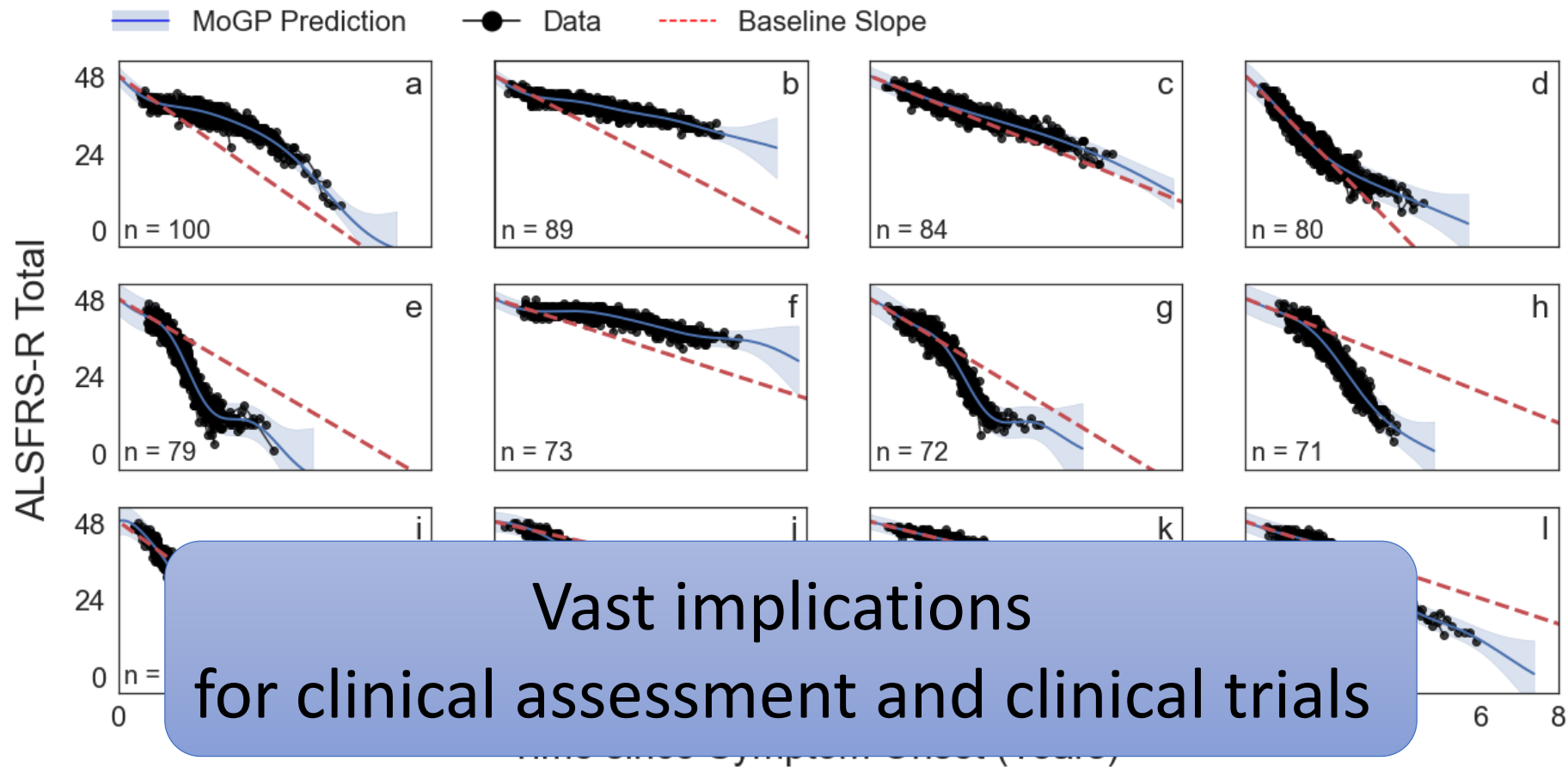


Kristen Severson, Soumya Ghosh, Kenney Ng

AI-based analysis finds clinical subtypes

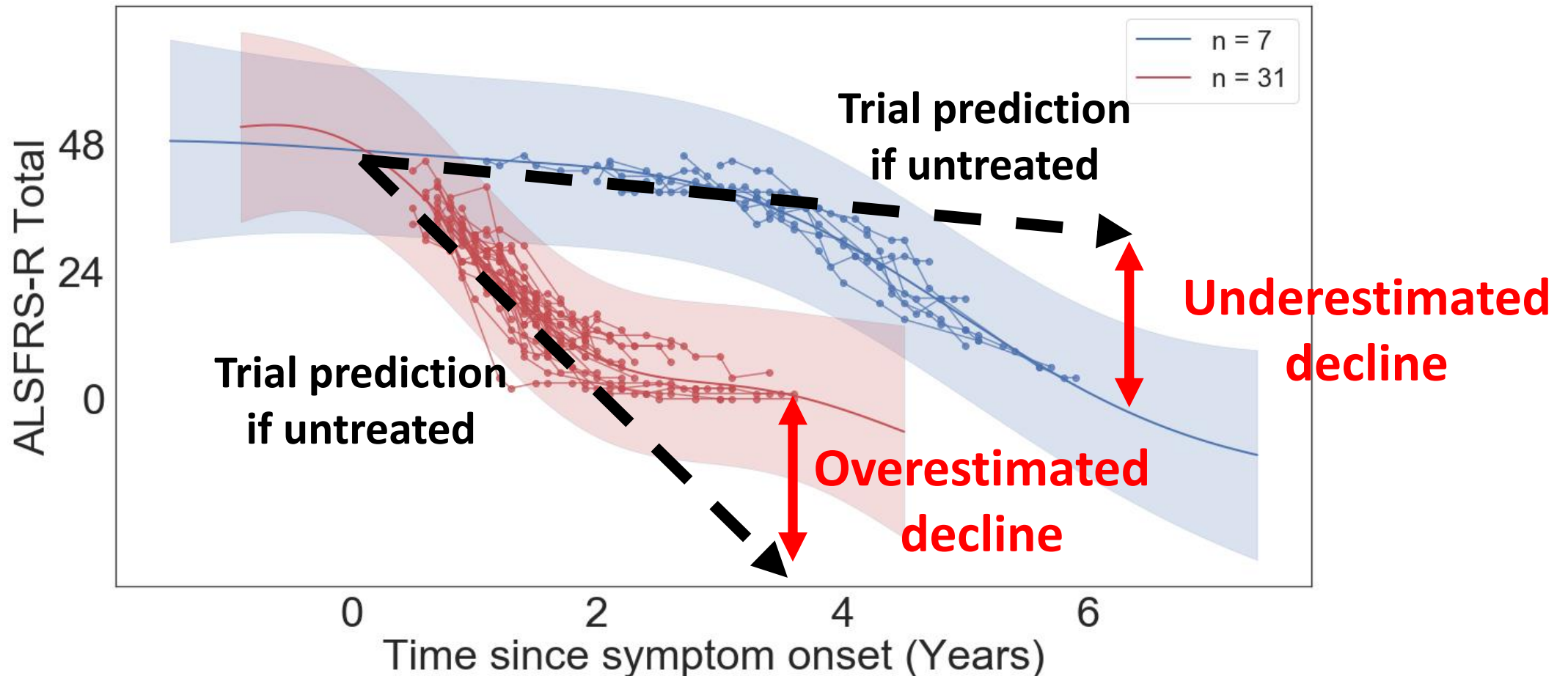


Consistent clinical patterns emerge



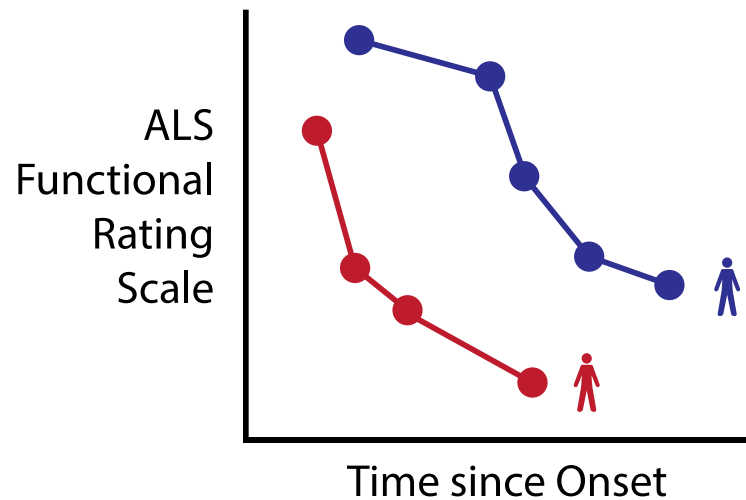
Did some “failed” trials actually work?

Data: Ceftriaxone (includes patients with 3+ALSFRS-R measurements, n=453)



Ongoing study: Are there blood biomarkers of clinical subtypes?

Longitudinal Blood Plasma



150 ALS patients
78 Non-neurological controls
40 Neurological controls

3 to 5 blood draws per ALS patient

Assays

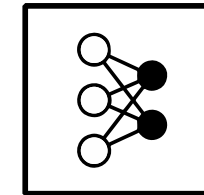
Untargeted
Metabolomics

Phosphorylated
neurofilament
heavy chain

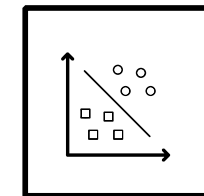
LC-MS: C8-pos, C18-neg,
HILIC-pos, HILIC-neg

> 15,000 metabolites measured

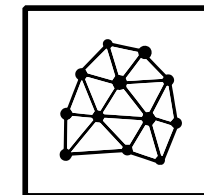
Machine Learning



Classifiers

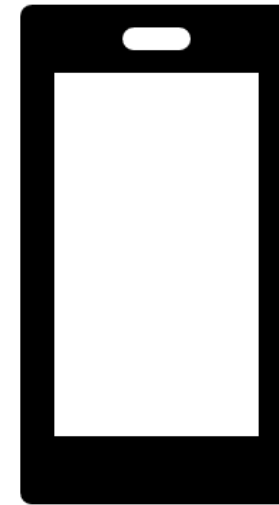
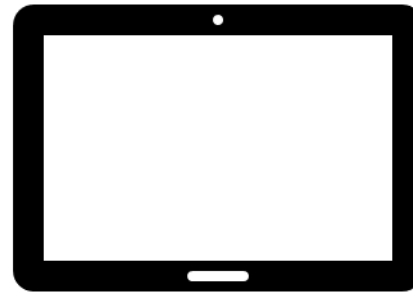
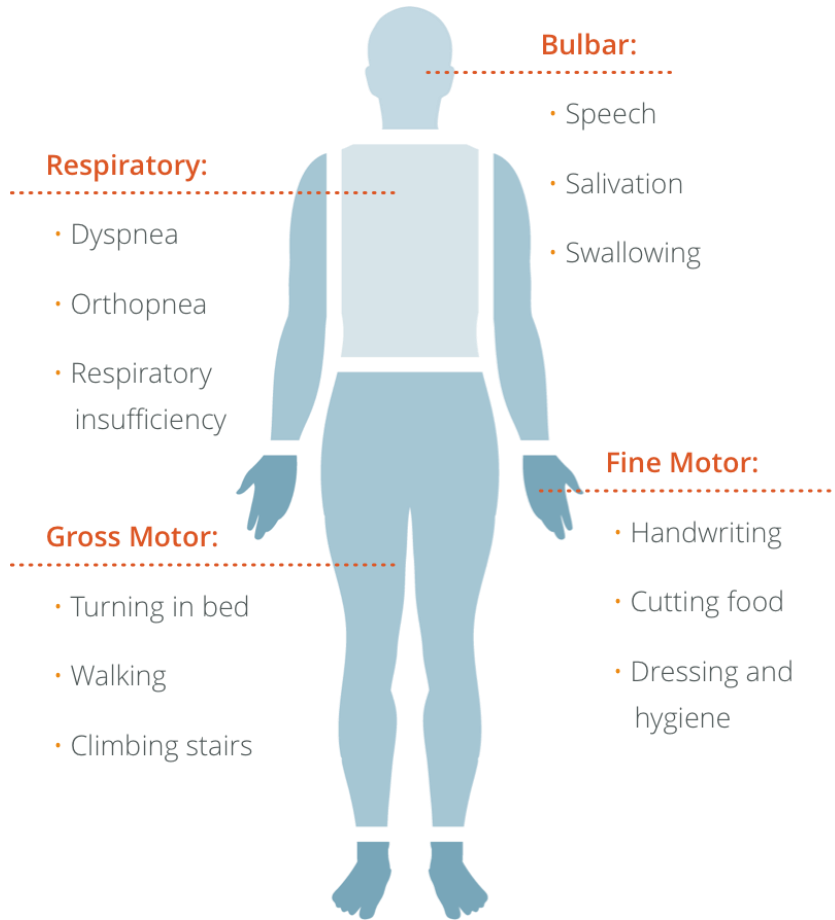


Clustering



Network
Analysis

Can digital monitoring capture disease progression?

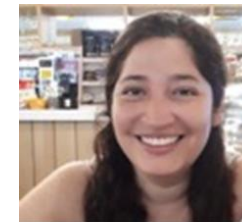


Clinical and behavioral data collected with phone apps

Picture description, reading, counting and fine motor.



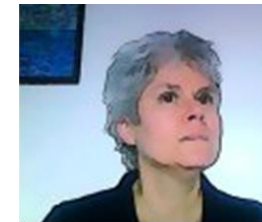
Individual signals are only weekly predictive.
Combined signal from acoustic, fine motor and cognitive tasks predicts ALSFRS-R



Carla Agurto



Guillermo Cecchi



Raquel Norel



Mary Pietrowicz

C. Agurto, M. Pietrowicz, E. K. Eyigoz, E. Mosmiller, E. Baxi, J. D. Rothstein, P. Roy, J. Berry, N.J. Maragakis, O. Ahmad, G.A. Cecchi, R. Norel, "Analyzing progression of motor and speech impairment in ALS", EMBC 2019.

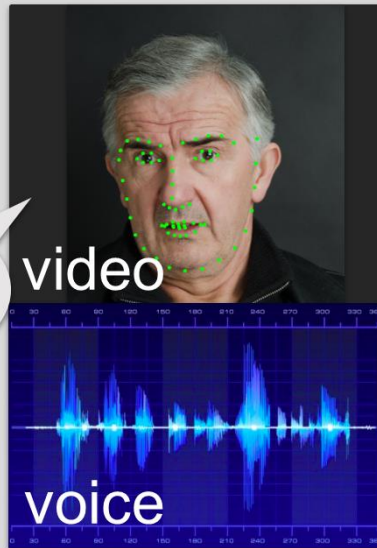
Everything ALS Voice Study

Lead by
Modality Platform Patient Advocates

virtual agent

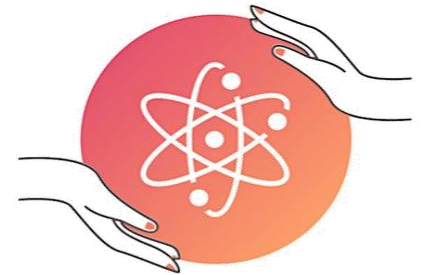


multimodal



metrics

facial	d=6.3s
	a=908mm ²
	v=4.2mm/s
speech	l=43mm
	s=133/min
	r=145/min



EVERYTHING ALS
C A R E T O C U R E

Acoustic features distinguish patients from controls before onset of bulbar symptoms

Very Preliminary Results from Modality

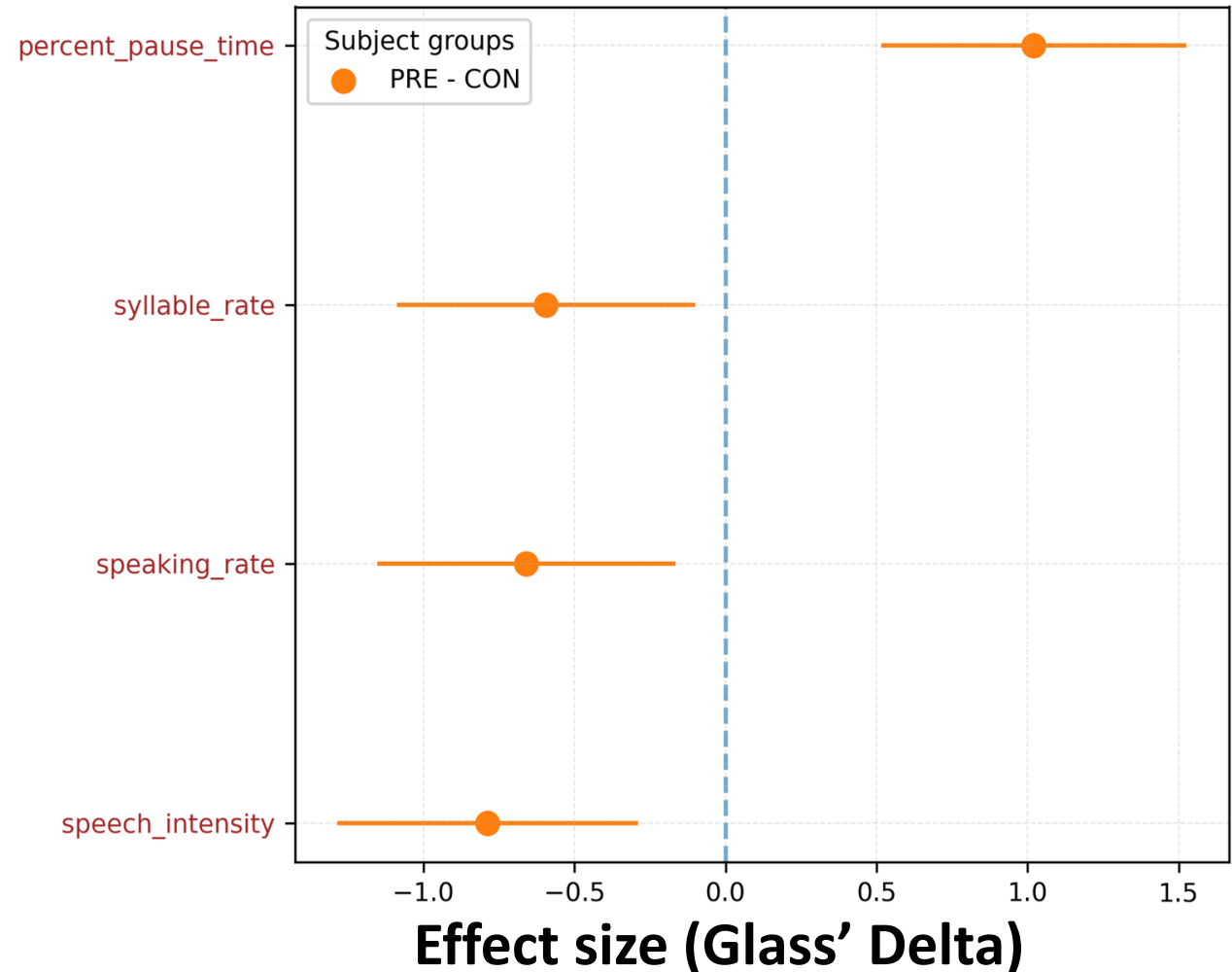
*David Suendermann-Oeft,
Vikram Ramanarayanan et al.*

82 controls

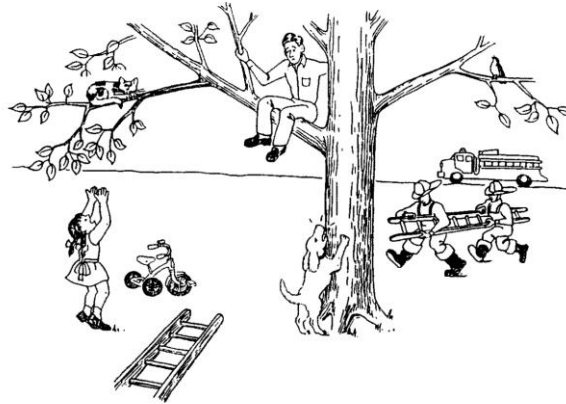
54 ALS patients

32 with bulbar score < 12

22 with bulbar score = 12
(asymptomatic)



Analyze how people describe pictures



- Word choice

- Frequency and dispersions in a corpus of texts (Corpus of Contemporary American English; COCA)

- Types of words

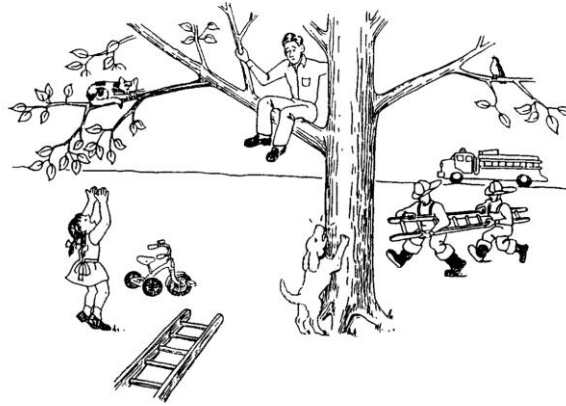
- Linguistic Inquiry and Word Count (LIWC)
 - Global Vectors for Word Representation (GloVe)



IBM Research

Carla Agurto, Guillermo
Cecchi & Kely Norel

Encouraging Early Findings



- Patient speech is less analytic ($P < 0.04$)
- Patient speech has a narrower emotional range ($P < 0.02$)
- Pre-manifest patients are more focused on the present ($P < 8e-3$)

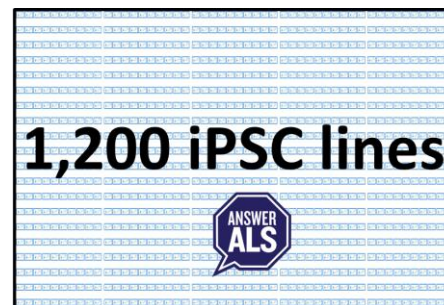
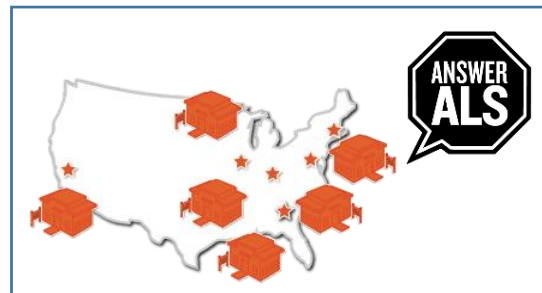


IBM Research

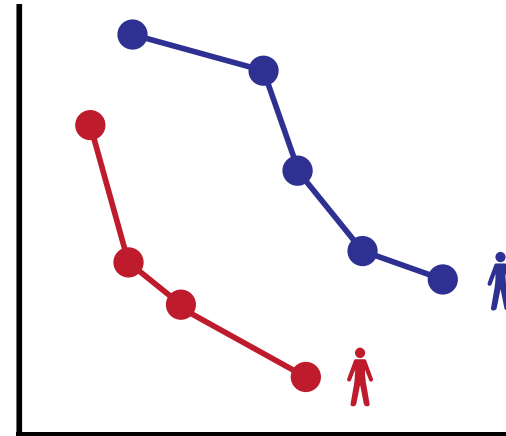
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Summary

Diversifying discovery



Stratifying patients



Blood/CSF biomarkers

