Biomarkers and clinical trials in neurodegenerative diseases

Alice S. Chen-Plotkin, MD
Assistant Professor of Neurology
March 3, 2016

Penn
University of Pennsylvania

Outline

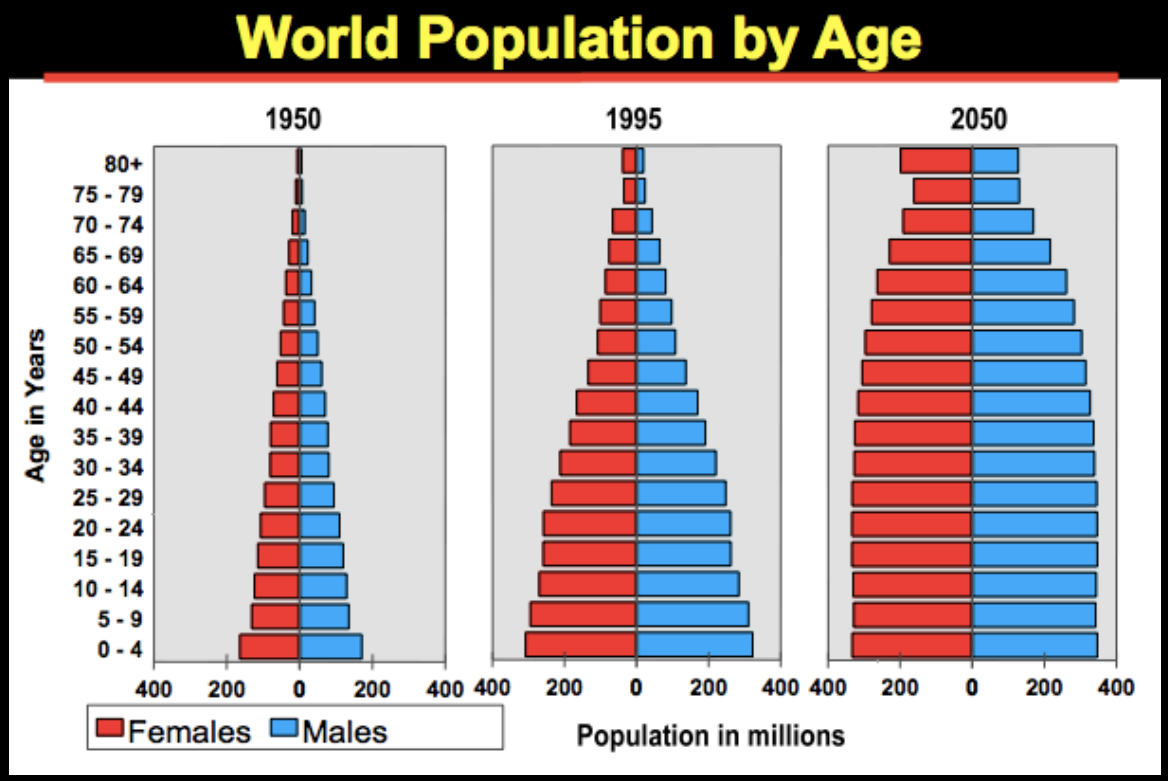
Experience in Alzheimer's Disease

On the ground in Parkinson's Disease

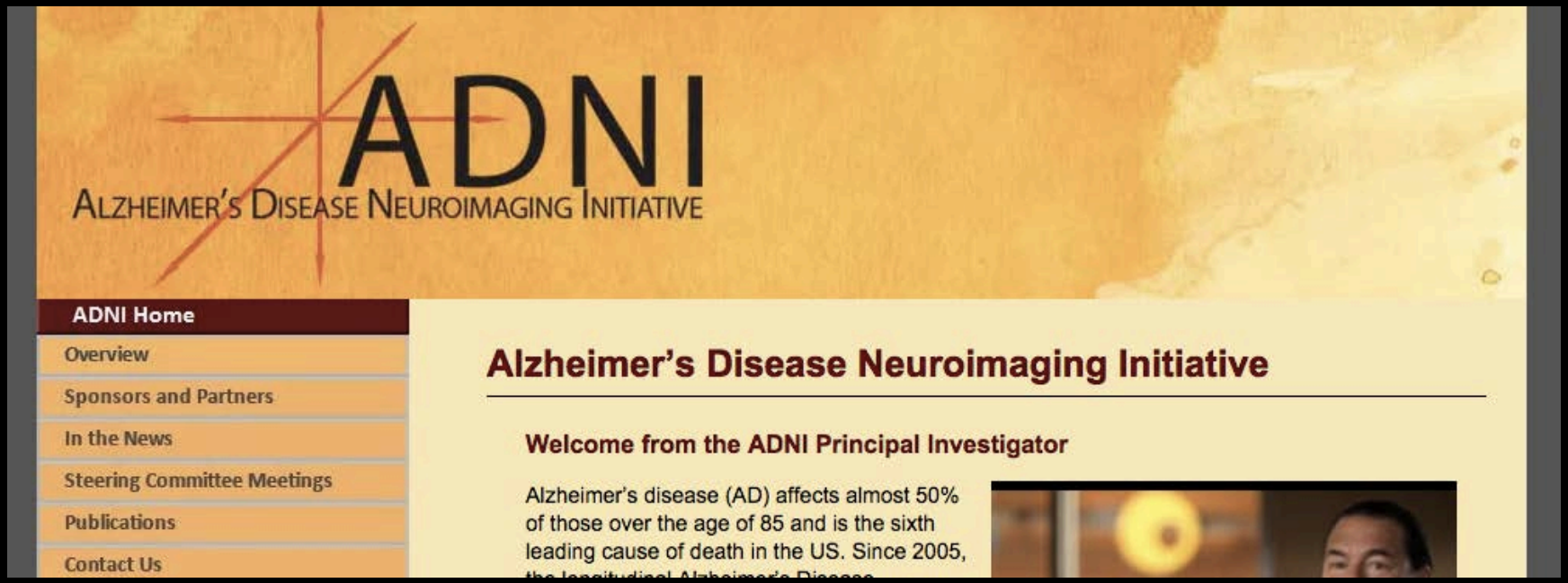
Any lessons learned?

Alzheimer's Disease and Parkinson's Disease

5 million in US with AD now
1 million in US with PD now



The Alzheimer's Disease Neuroimaging Initiative (ADNI)



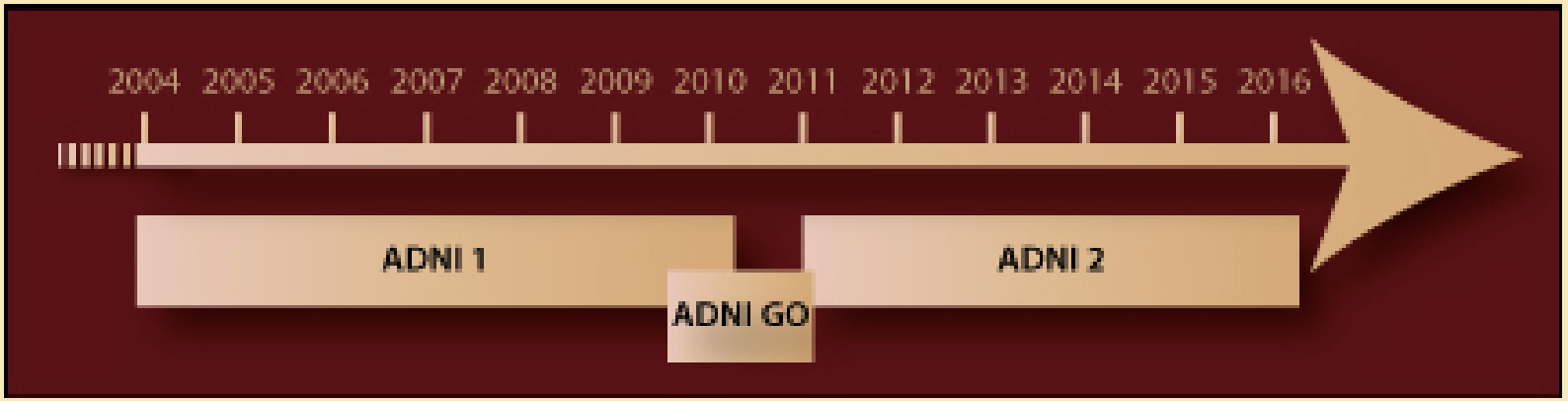
Launched in 2004.

Goal was to develop imaging and biochemical biomarkers for

- earlier detection of AD.
- use in clinical trials.

Set precedent for open data sharing in the neurodegenerative disease space.

The Alzheimer's Disease Neuroimaging Initiative (ADNI)

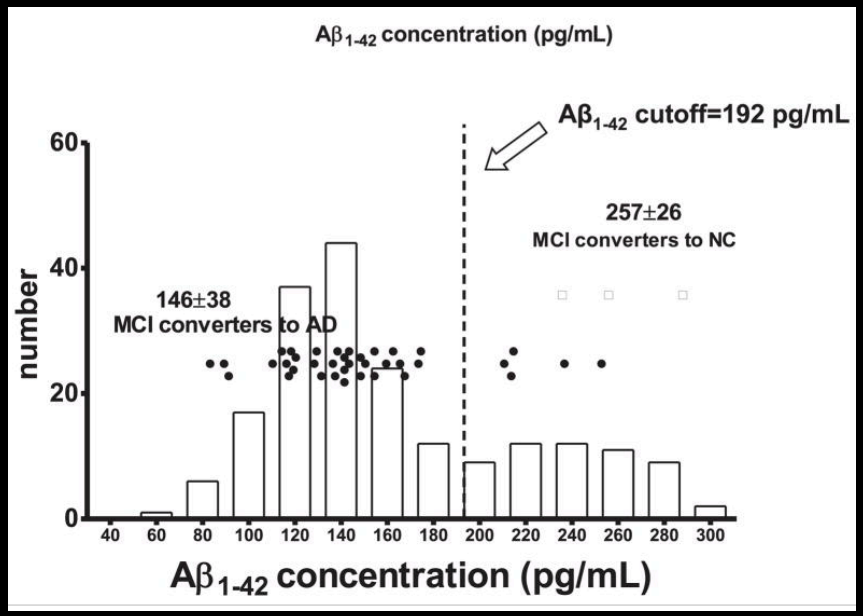


Original cohort = 200 normal controls, 200 AD, 400 amnestic MCI.
$67M from public/private sources (NIH, pharma, foundation).
Longitudinally followed.

Additional 550 enrolled participants with ADNI GO + ADNI 2, focusing on earliest phases of AD process.

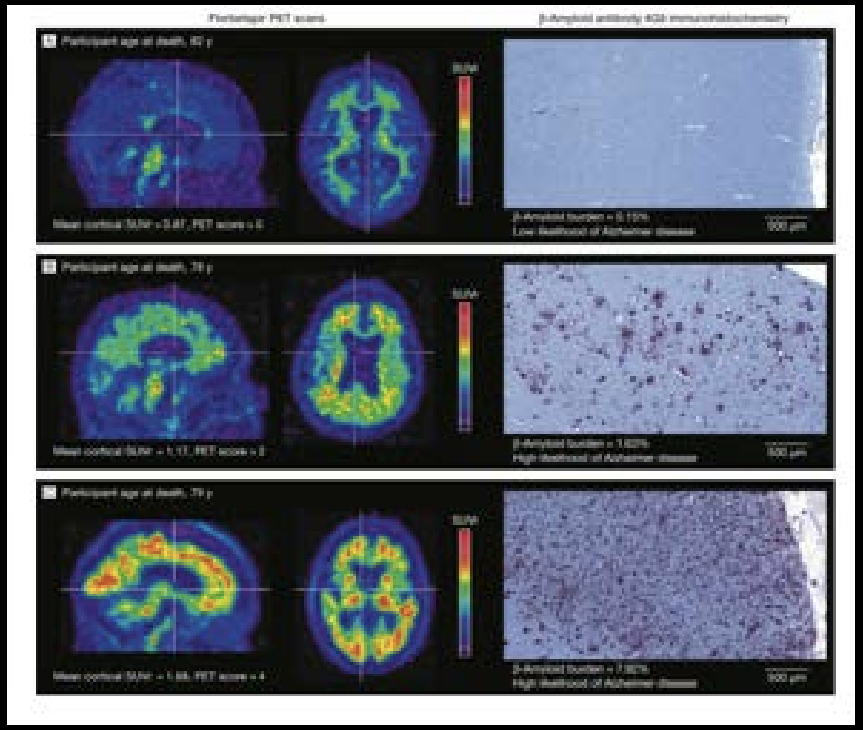
What was learned?

CSF biochemical biomarkers might discriminate who would convert to AD.



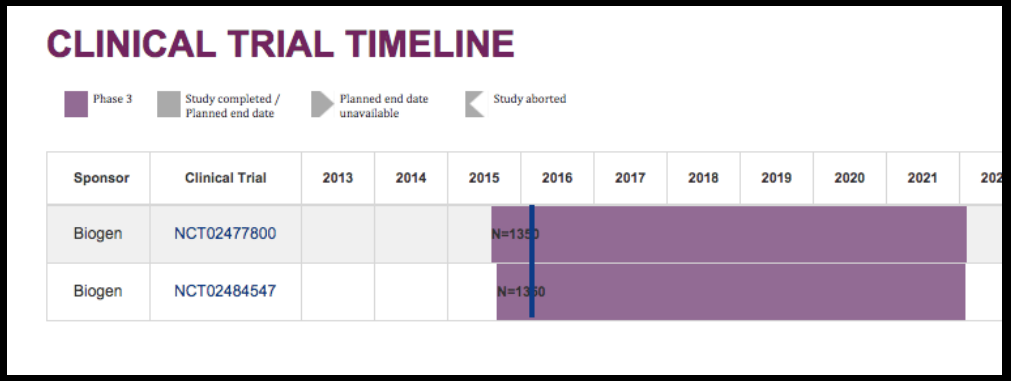
Shaw et al, Ann Neurol 2009

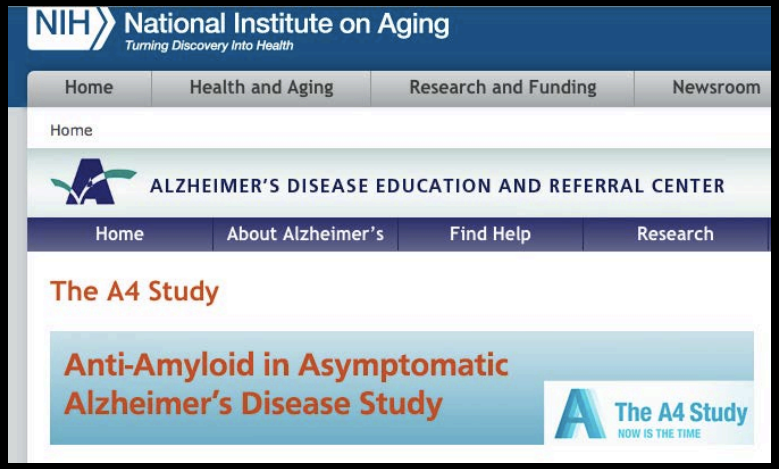
Specific PET ligands might detect amyloid pathology in vivo.



Clark et al, JAMA, 2011

What does this mean for AD trials?





Current Phase 3 AD trials (amyloid immunotherapy) are using amyloid imaging as entry criteria and enrolling MCI individuals, as well as asymptomatic people. Plans for new study to use CSF biochemical biomarkers as entry criteria.

What does this mean for AD trials?

A rethinking of diagnostic criteria…

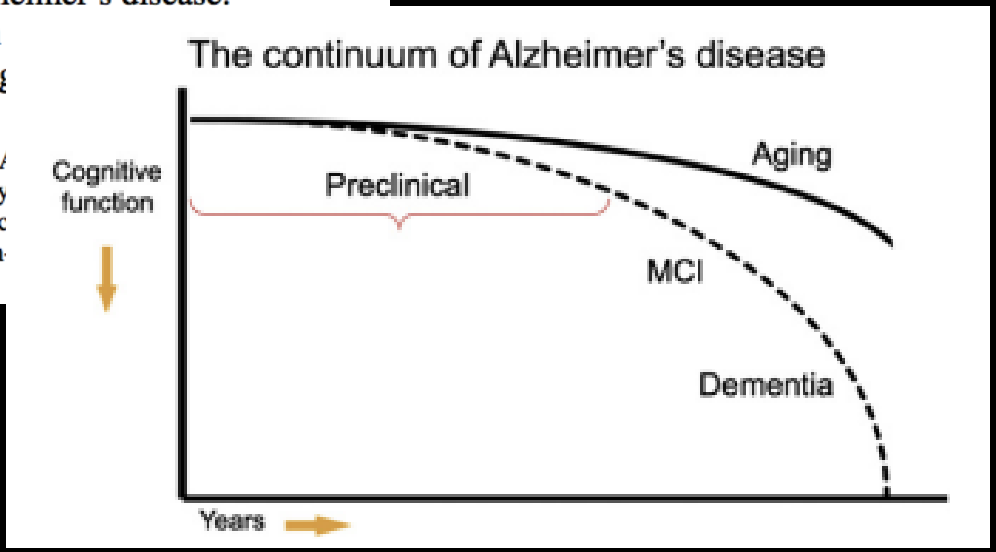
ELSEVIER

Alzheimer's & Dementia 7 (2011) 280–292

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Association workgroups on diagnostic g for Alzheimer's disease

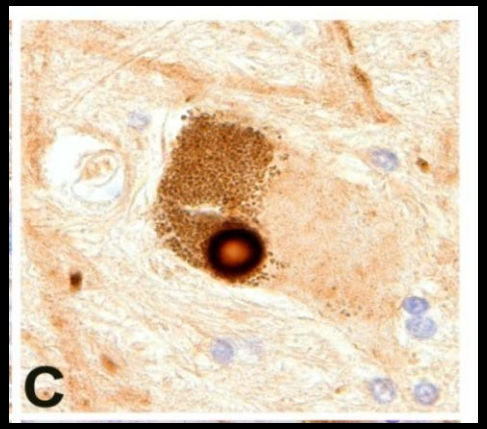
Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack, Jr.[h], Jeffrey Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison Creighton H. Phelps[r]

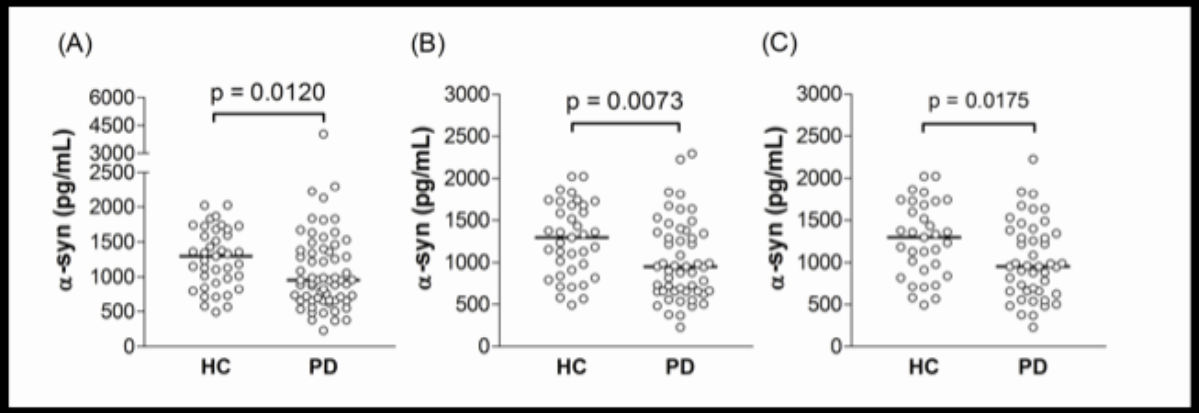


On the ground in PD

The candidate approach to biomarker development has not worked as well in PD.

- No specific imaging ligand.





Modified from Kang *et al.*, *JAMA Neurology*, 2013; 70(10):1277-87.

The traditional approach: Specific genes and proteins

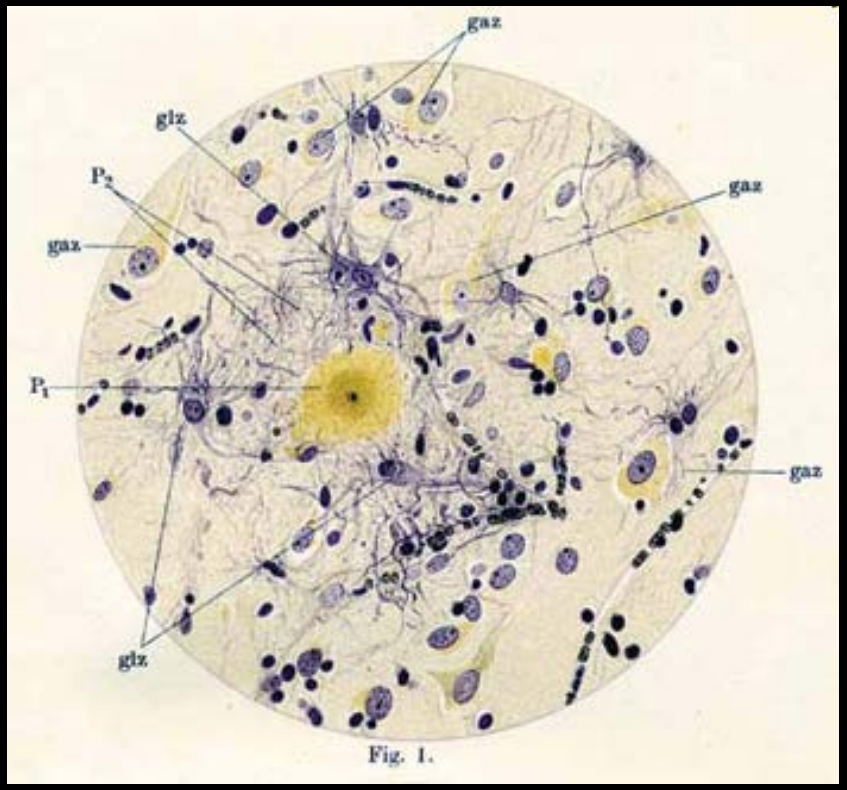
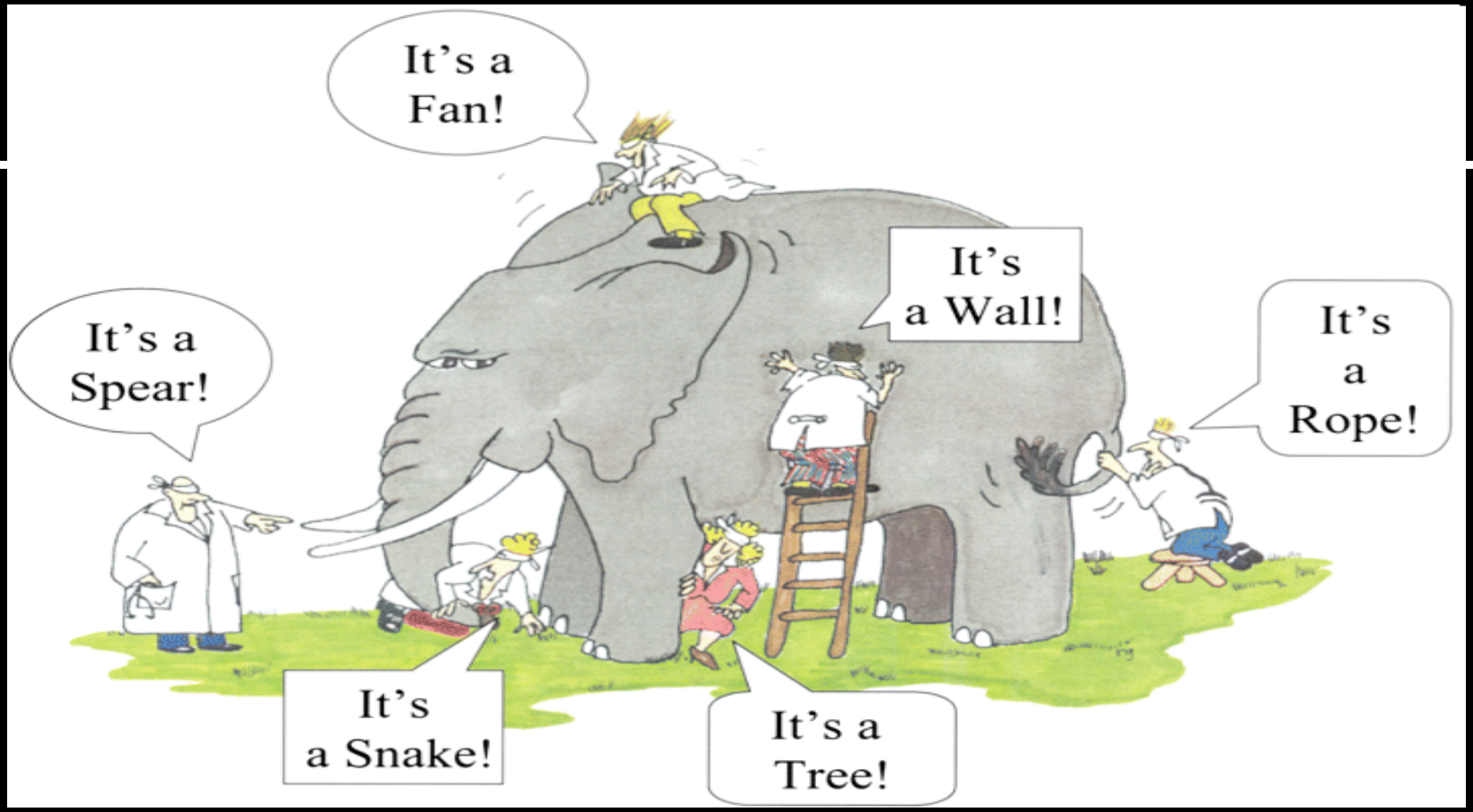


Fig. 1.

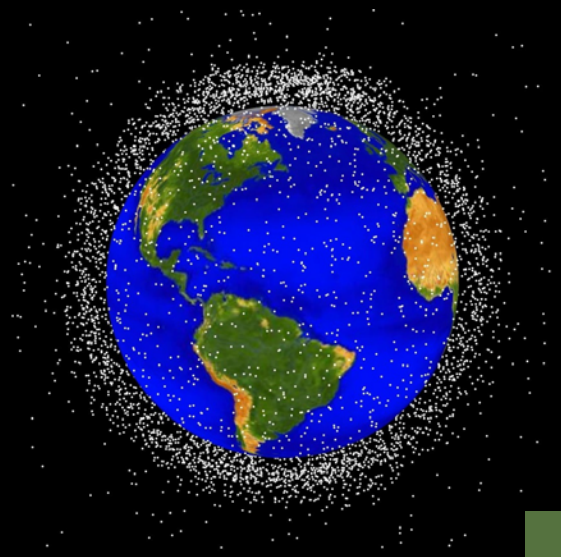
Decide *a priori* what genes or proteins are likely to lead to central processes in a disease → pursue experiments based on them.

Sometimes you're right…



...but sometimes you're wrong.

Another approach: Assay gene/protein expression, genetic variation at a genomic/proteomic scale



Made possible by recent technologies.

Whole picture may be a little fuzzier, but:

1. You're getting a whole picture.
2. You're not biased…and may make unexpected discoveries.

CellPress

Neuron

Perspective

Unbiased Approaches to Biomarker Discovery in Neurodegenerative Diseases

Alice S. Chen-Plotkin[1,*]
[1]Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, 3 West Gates, 3400 Spruce Street, Philadelphia, PA 19104, USA
*Correspondence: chenplot@mail.med.upenn.edu
http://dx.doi.org/10.1016/j.neuron.2014.10.031

On the ground in PD

Community is organizing around a pipeline for

discovery
replication
further development

of novel biomarkers.

TRANSLATION

Our experience with PPMI samples: Plasma ApoA1 as a correlate of PD severity.

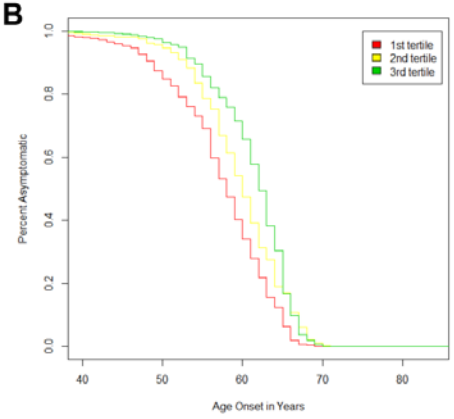
We showed in 2013 (Qiang et al, Ann Neurol, 2013) that higher plasma levels of ApoA1 were correlated with:
(1) older age at PD onset, and
(2) less severe PD.

This relationship replicated beautifully in >1000 people from around the world, including 154 PD patients from PPMI (Swanson et al, Mov Disord, 2015).

A

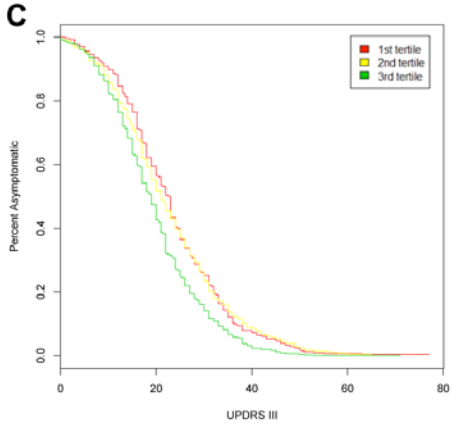
Cohort	N	Yrs of PD	Measurement	Age at Onset			UPDRS III		
				Beta	SE	*P*	Beta	SE	*P*
UPenn Cohort 1	152	7	Luminex Assay	11.22	3.37	**0.001**	-21.98	7.12	**0.003**
U. Washington	187	9.45	ELISA	2.72	0.79	**<0.001**	-3.75	1.38	**0.008**
UPenn Cohort 2	288	7	ELISA	48.11	24.23	**0.048**	14.54	16.66	0.385
Columbia U.	237	6	Immunoturbidimetry	2.39	1.61	0.139	-3.39	2.41	0.161
PPMI	154	1	Immunoturbidimetry	0.41	0.18	**0.023**	-3.54	2.01	0.080
COMBINED	1018	-	-	0.86		**<0.001**	-1.57		**<0.001**

B



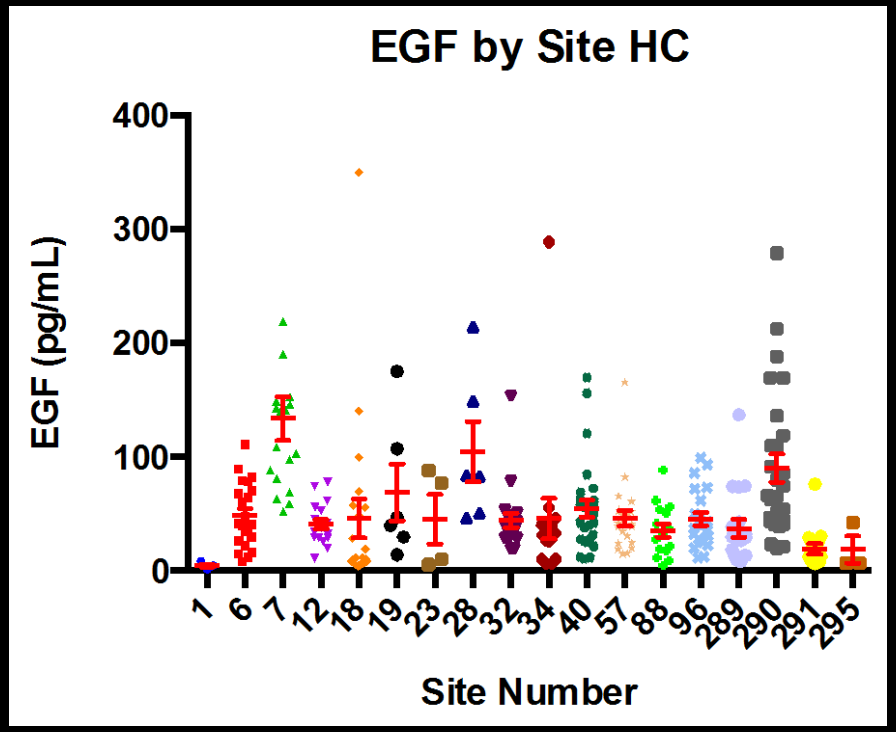
Hazard Ratio	0.86
95% CI	0.79-0.94
P-value	**0.0004**

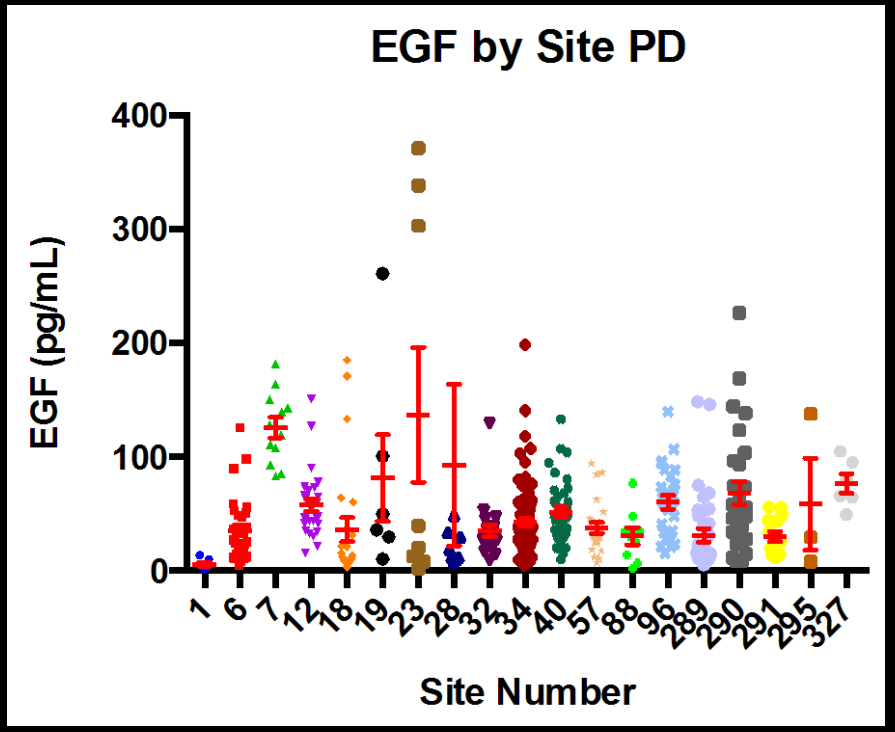
C



Hazard Ratio	0.85
95% CI	0.77-0.92
P-value	**0.0004**

Our experience with PPMI samples: EGF as a correlate of clinical site.





Summary

In AD, a candidate biomarker approach produced imaging (PET ligand specific for beta-amyloid) and CSF biochemical biomarkers (beta-amyloid and tau).
In use now for clinical trial enrollment.

In PD, candidate approaches have not worked as well. We may need an unbiased approach for biomarker discovery.

Permissive to the development of biomarkers:

- Biorepositories with strict protocols for sample collection.
- Data sharing (including databases).
- Partnerships (academia, industry, foundation, government).

Acknowledgements

Current members

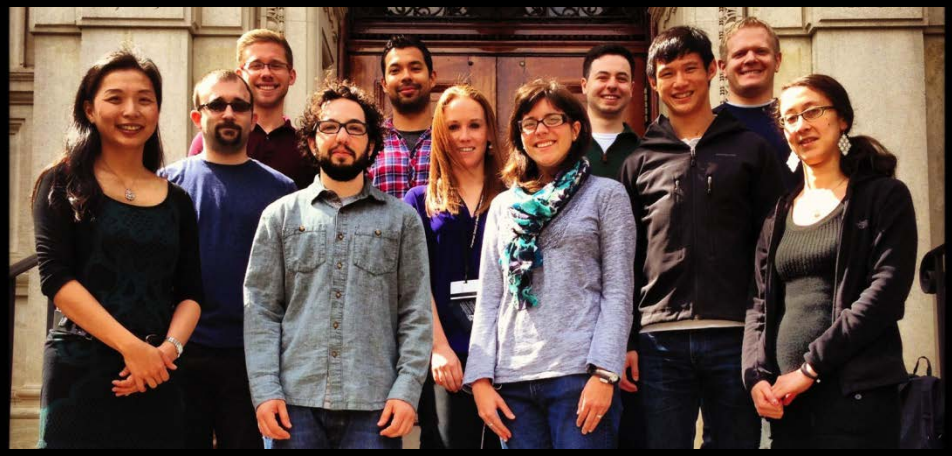
Defne Amado
Johanna Busch
Rakshita Charan
Ryan Cherng
Fortunay Diatta
Mike Gallagher
Nimansha Jain
Ben Liu
Jordan Mak
Pierce Nathanson
Tyler Skrinak
Travis Unger

Past members

Katherine Li
Judy Qiang
Christine Swanson

University of Pennsylvania

John Trojanowski
Virginia Lee
Howard Hurtig
Matt Stern
Dan Weintraub
Sharon Xie
Leslie Shaw
Vivianna Van Deerlin



PPMI

Ken Marek
Mark Frasier
Katie Kopil

PARS

Ken Marek
Danna Jennings
Susan Mendick

University of Washington

Cyrus Zabetian
Dora Yearout
James Leverenz
Tom Montine

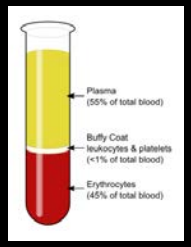
Columbia University

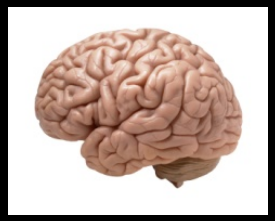
Roy Alcalay
Oren Levy
Cheryl Waters
Stanley Fahn
Adina Wise

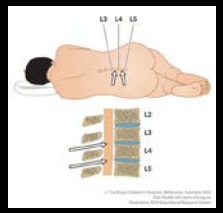
Funding

Doris Duke Charitable Foundation CSDA
NIH-NINDS: UO1-NS082134, RO1-NS082265, P50 NS053488
Burroughs Wellcome Fund CAMS
Benaroya Fund, BAND (MJFF/AA/Weston)

Aspects of biochemical biomarker discovery studies







Collection protocol matters A LOT

Multiple potential things to measure

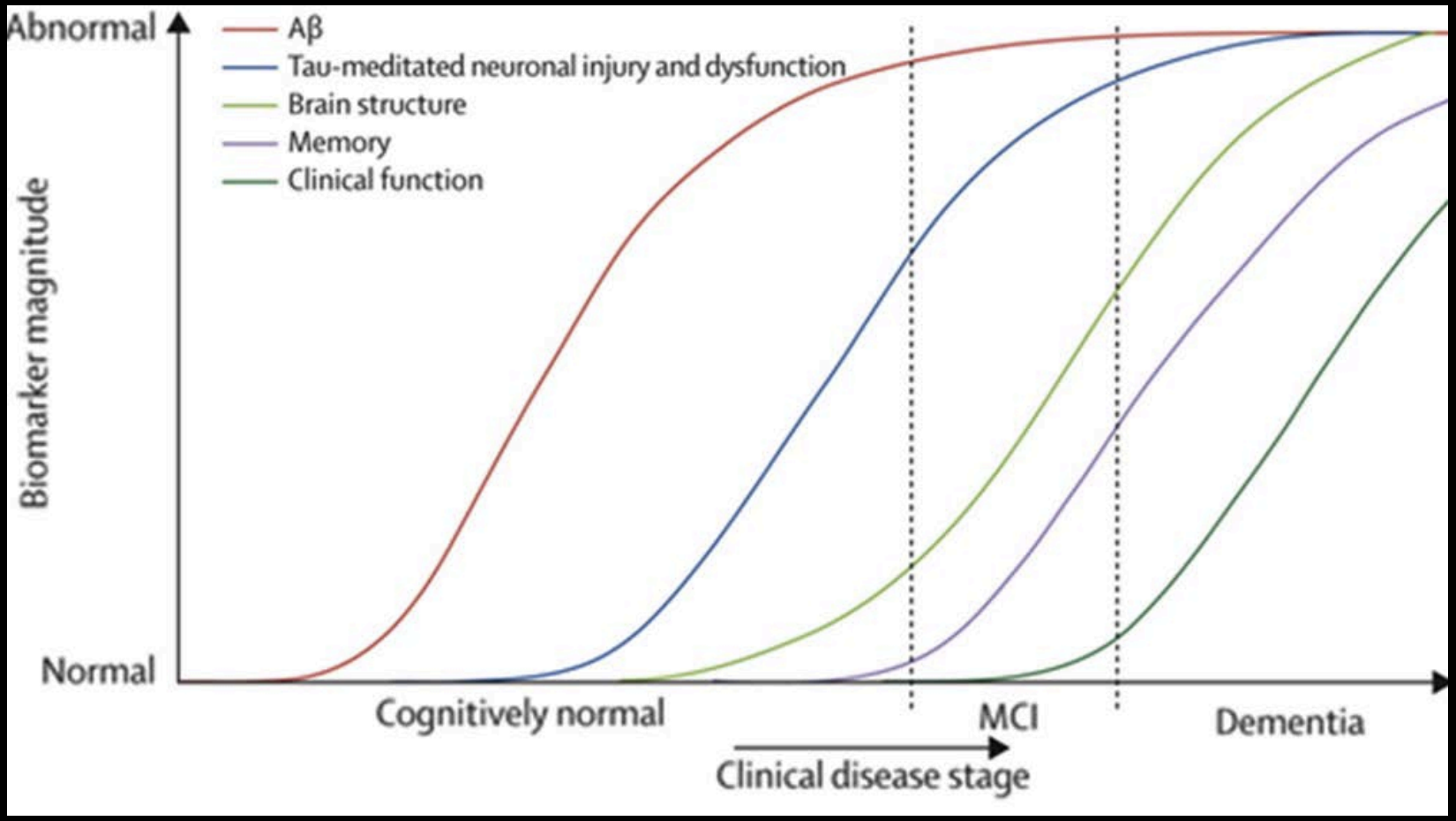
Proteins
Lipids
Others (RNA)

Multiple potential ways to measure them

Targeted: usually immunoassay-based

Unbiased:
(1) Multiplex immunoassays
(2) Mass spect
(3) Others (like aptamers)

What was learned?



Jack et al, Lancet Neurol 2010