



# Dementia research

– Prevention of dementia and  
why early detection is important

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# The Problem

- More than 36m people with dementia
- Consumes 1% global GDP
- Serial trials failure



ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Reischl, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Roth, M.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D. for the Alzheimer's Disease Cooperative Study Investigators

CONCLUSIONS

Bapineuzumab did not improve cognition or functional ability in patients with mild-to-moderate Alzheimer's disease. The results of these trials are consistent with the observed lack of benefit in the Alzheimer's Disease Cooperative Study Immunotherapy with Bapineuzumab in Mild-to-Moderate Alzheimer's Disease ClinicalTrials.gov number NCT00574132, and the Alzheimer's Disease Cooperative Study EudraCT number 2009-016193-01.

Too little!

Too late!

Wrong people!

January 2014

ORIGINAL ARTICLE

A Correction Has Been Published

Solanezumab for Mild-to-Moderate Alzheimer's Disease

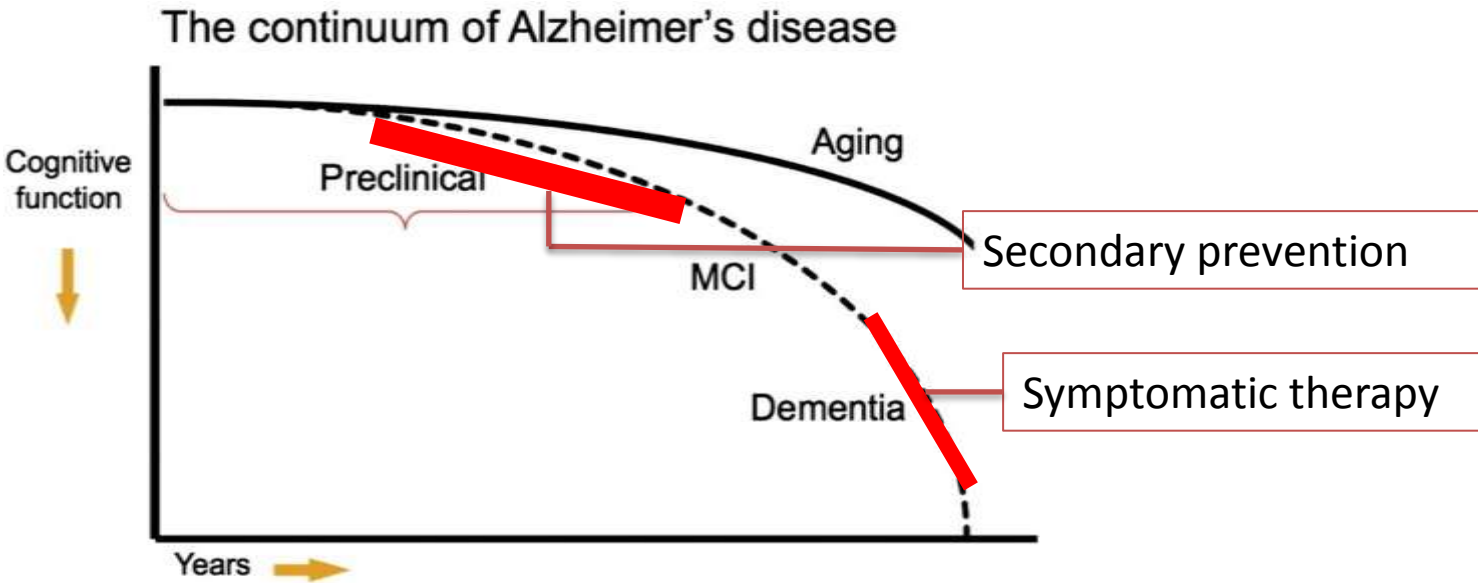
Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Dubois, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., Paul S. Aisen, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D. for the Alzheimer's Disease Cooperative Study Committee and the Solanezumab Study Group

CONCLUSIONS

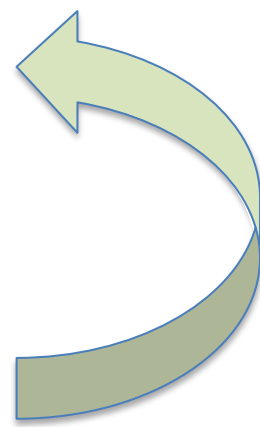
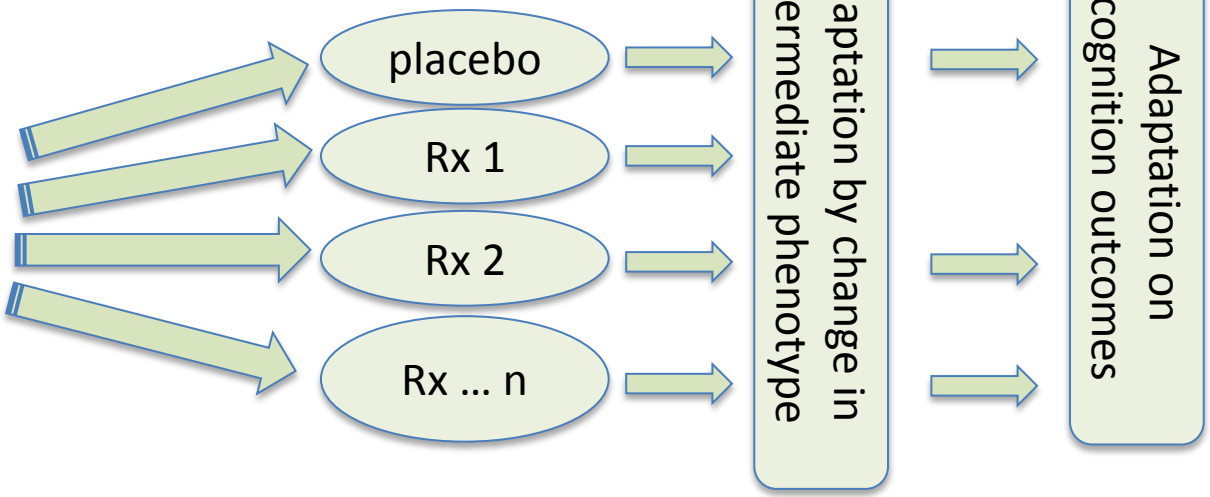
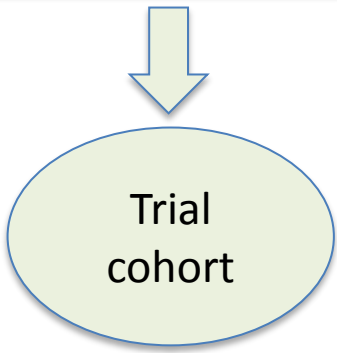
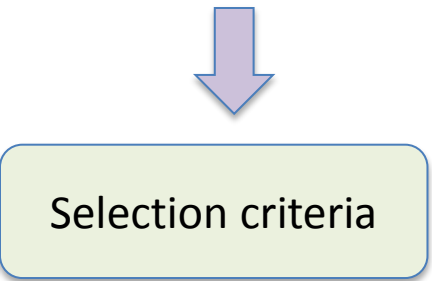
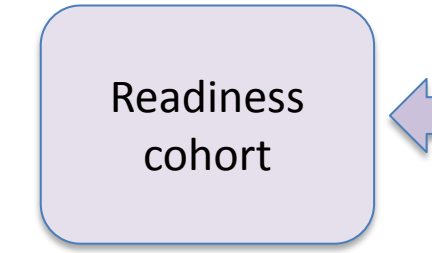
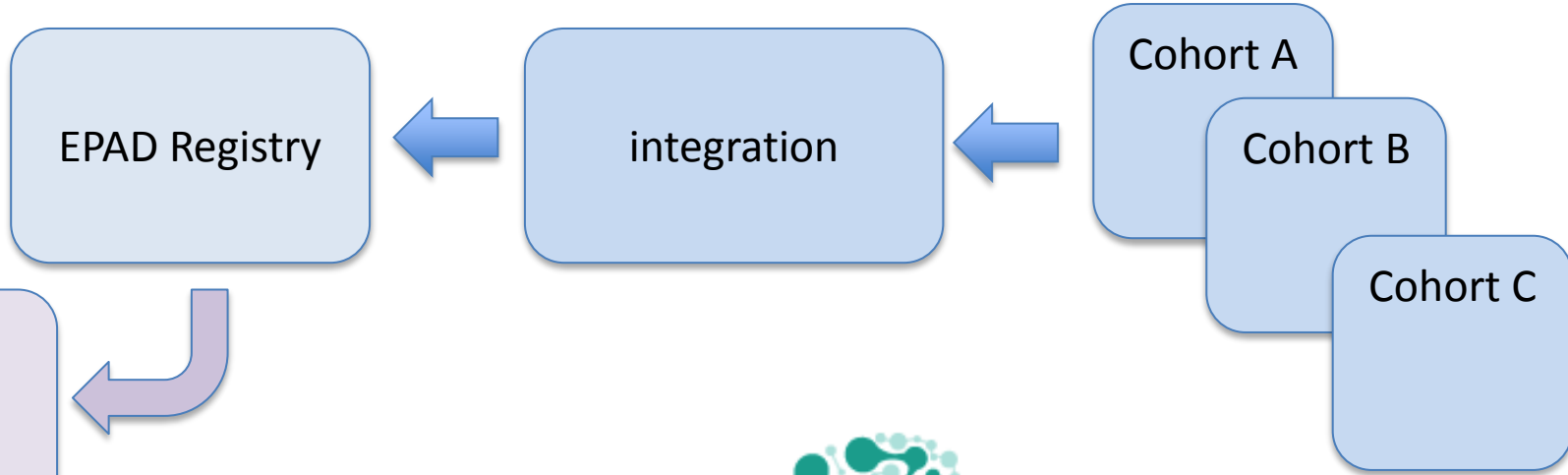
Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)



# Markers to enable secondary prevention



Adapted from Sperling et al (2011) Alzheimer's and dementia 7 280-92





# Collaboration for Translational Research in Dementia

**Alzheimer's  
Research UK Oxford  
Drug  
Development  
Institute**

**Wellcome  
Neuroinflammation  
consortium**

**Wellcome Target  
Enabling Packages**



**Dementias Platform  
UK**

Dementia Discovery  
cohorts  
(n=2m)

Dementia UK  
BioBank cohort  
(n=10k)

Deep and Frequent  
Phenotyping cohort



**IMI-EPAD**

European  
Prevention of  
Alzheimer's  
disease

Readiness  
register, cohort  
and  
Early Phase  
Trials

Pre-competitive  
drug development

Pre-competitive  
cohort repurposing for  
experimental medicine

Pre-competitive  
Data reuse for  
biomarkers

Pre-competitive  
Proof of Concept  
clinical trials



# UK Biobank Enhancements for Dementia Research

- Web-based questionnaires for additional exposures and outcomes (cognition, mental health, occupation..)
- Wrist-worn accelerometers mailed to 100,000 participants to measure physical activity
- Multimodal imaging in 100,000 - brain, cardiac and body fat MRI; bone & joint DEXA; 3D carotid ultrasound
- Repeat Neuroimaging in 20,000
- Genotyping of all participants (820,000 SNPs)
- Repeat cognition, sampling
- Connectivity to EMRs for mental health





# Use of EMRs for research



- SLaM CRIS
  - South London and Maudsley NHS BRC implementation
- D-CRIS
  - Cambridge & Peterborough, Oxford Health, West London, Camden and Islington
  - 1 million plus patients
- UK-CRIS
  - 10 site extension
  - Connectivity to UK BioBank
- Mike Denis and Simon Lovestone





# Deep and Frequent Phenotyping

## Deep phenotyping

- PET *A $\beta$  and tau tracers*
- CSF *repeated measures*
- MRI *serial imaging with noise reduction strategy*
- Electrophysiology *EEG and MEG*
- Peripheral markers *noise reduction, change measurement*
- Cognitive markers *computerised batteries, web testing integration*
- Novel markers *retinal imaging, quantitative gait measures*

## Frequent phenotyping

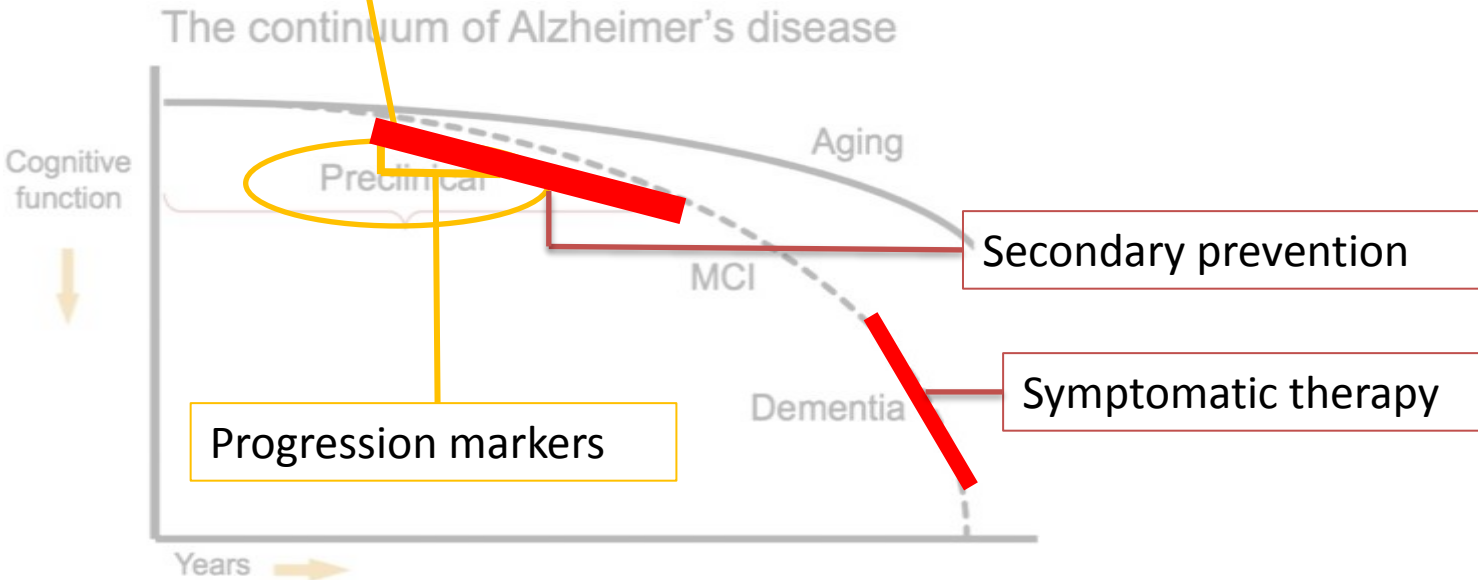
- Test the limits of acceptability *monthly, bi-monthly*





# Markers to enable secondary prevention

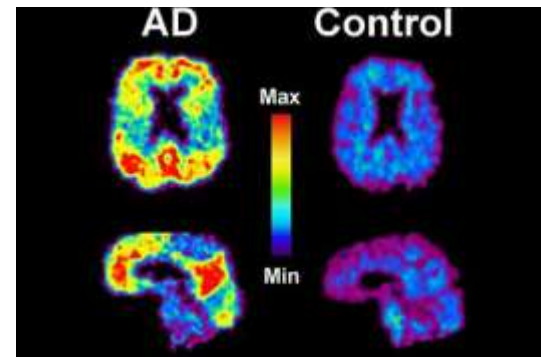
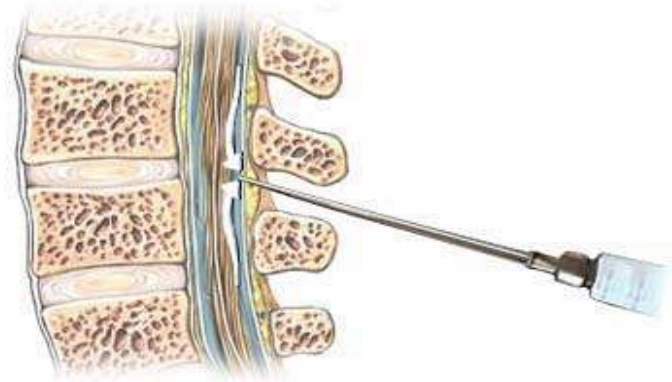
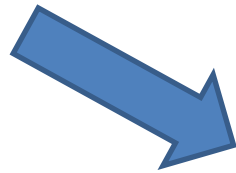
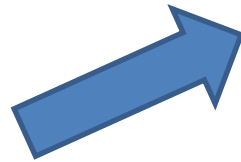
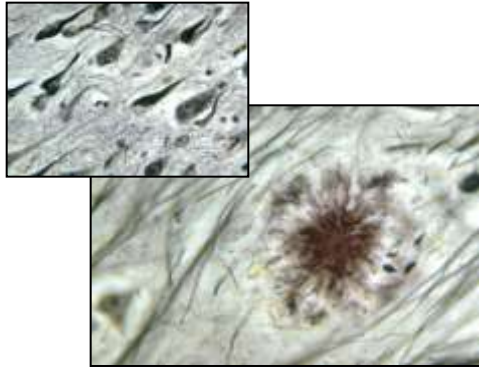
Selection and stratification markers





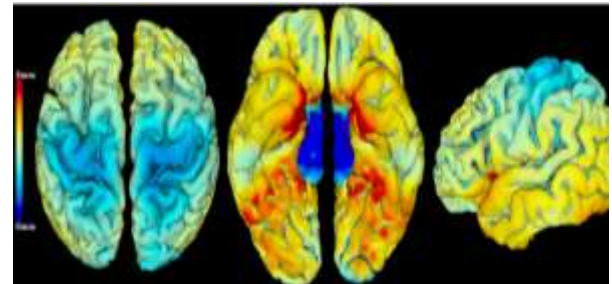
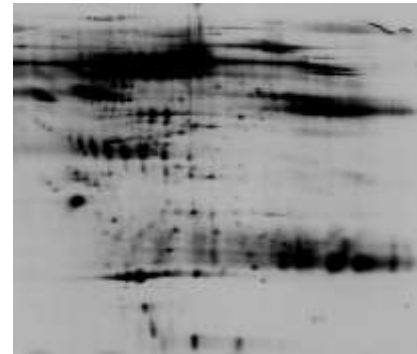
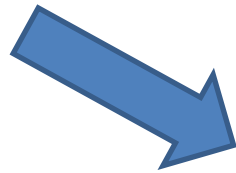
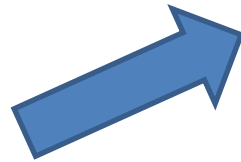
# Biomarkers for dementia

- CSF A $\beta$  and tau; PET amyloid ligands





# Biomarkers for dementia – alternative approaches





# Blood based biomarkers - prediction of conversion from MCI

- Machine learning training and test
- Ten proteins predict conversion with 87% accuracy



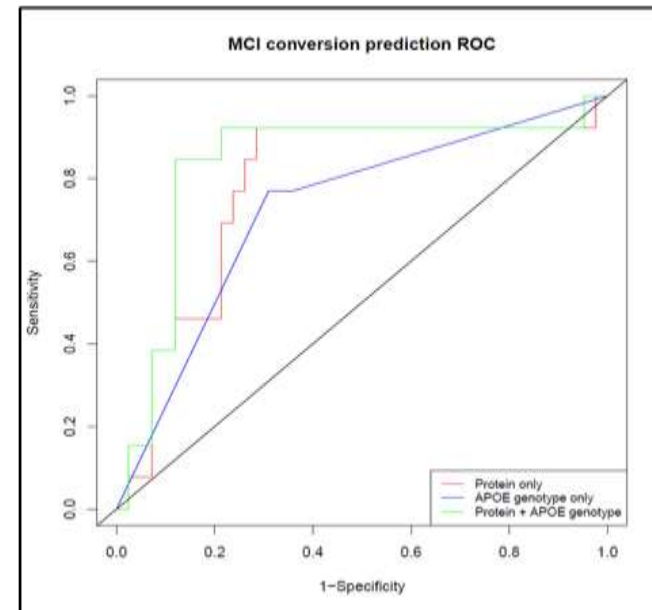
Alzheimer's & Dementia ■ (2014) 1-9

Alzheimer's  
&  
Dementia

Research Article

## Plasma proteins predict conversion to dementia from prodromal disease<sup>☆</sup>

Abdul Hye<sup>a,1</sup>, Joanna Riddoch-Contreras<sup>a,1</sup>, Alison L. Baird<sup>b</sup>, Nicholas J. Ashton<sup>b</sup>,  
Chantal Bazenet<sup>c</sup>, Rufina Leung<sup>a</sup>, Eric Westman<sup>a,†</sup>, Andrew Simmons<sup>a</sup>, Richard Dobson<sup>a</sup>,  
Martina Sattler<sup>c</sup>, Michelle Lupton<sup>a,‡</sup>, Katie Lunnon<sup>d</sup>, Aoife Keohane<sup>a</sup>, Malcolm Ward<sup>c</sup>,  
Ian Pike<sup>a</sup>, Hans Dieter Zucht<sup>e</sup>, Danielle Pepin<sup>f</sup>, Wei Zheng<sup>f</sup>, Alan Tunnicliffe<sup>f</sup>, Jill Richardson<sup>a</sup>,  
Serge Gauthier<sup>a,§</sup>, Hilka Soiminen<sup>g</sup>, Iwona Kloszewska<sup>h</sup>, Patrizia Mecocci<sup>i</sup>, Magda Tsolaki<sup>m</sup>,  
Bruno Vellas<sup>a</sup>, Simon Lovestone<sup>a,\*,§,¶</sup>

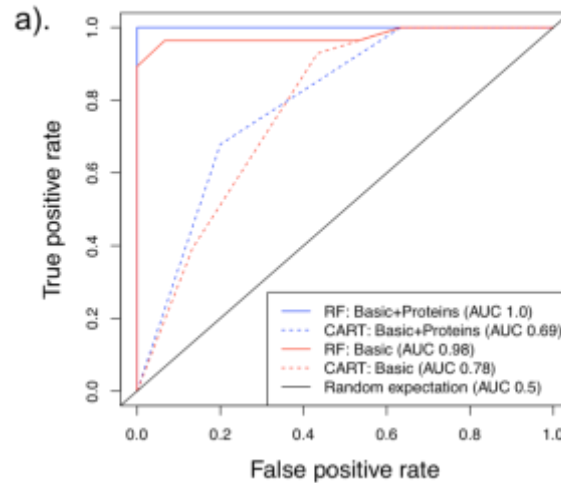




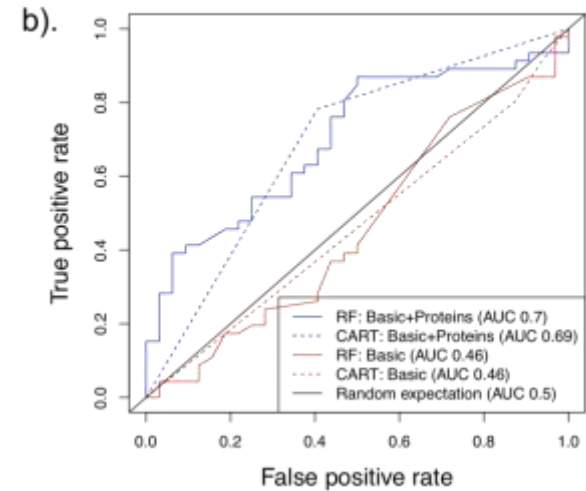
# Blood based biomarkers

## - prediction of PET measures of pathology

Train in AIBL



Test in UCSF



Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2015) 1-13

Alzheimer's  
&  
Dementia

Research Article

Blood protein predictors of brain amyloid for enrichment  
in clinical trials?

Nicholas J. Ashton<sup>a,b,c,d,1</sup>, Steven J. Kiddie<sup>a,c,d,1</sup>, John Graff<sup>d</sup>, Malcolm Ward<sup>e</sup>, Alison Baird<sup>d,f</sup>,  
Abdul Hye<sup>a,b</sup>, Sarah Westwood<sup>a,b</sup>, Karyuan Vivian Wong<sup>g</sup>, Richard J. Dobson<sup>a,b</sup>,  
Gil D. Rabinovic<sup>h</sup>, Bruce L. Miller<sup>h</sup>, Howard J. Rosen<sup>h</sup>, Andrew Torres<sup>d</sup>, Zhanqian Zhang<sup>d</sup>,  
Lennart Thurfjell<sup>h</sup>, Antonia Covin<sup>i</sup>, Cristina Tan Hehlig<sup>d</sup>, David Baker<sup>i</sup>, Chantal Bazenet<sup>a,b</sup>,  
Simon Lovestone<sup>a,d</sup>, and on behalf of the AIBL Research Group<sup>2</sup>

CF- classification and regression trees  
RF- Random Forrest