# CAMD AD Hippocampal Volume Team

*Derek Hill of IXICO plc on behalf of the team*

IXICO

## Annual Meeting, October 15 2015

Slides from:
Adam Schwarz
Chahin Pachai
Robin Wolz

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10 YEARS

# AD HV Imaging Project Team

- ***AbbVie***—David Ryman
- ***Alzheimer's Association***—Maria Carrillo, Jim Hendrix
- ***BioClinica***—Joyce Suhy, Joel Schaerer, Luc Bracoud
- ***Biohaven Medical Services***—Robert Berman
- ***Boehringer Ingelheim***—Mark Gordon
- ***Critical Path Institute***—Diane Stephenson, Klaus Romano, Volker Kern, Steve Arnerić
- ***Eli Lilly***—Peng Yu, Brian Willis
- ***Fatebenefratelli***—Giovani Frisoni, Alberto Redolfi, Marina Boccardi
- ***FDA***—Jim Kaiser
- ***Icon***—David Raunig
- ***Ixico***—Derek Hill, Robin Wolz, Katherine Gray
- ***Janssen***—Mahesh Samtani, Jerry Novak
- ***Novartis***—Richard Meibach, Paul Maguire
- ***Pentara***—Suzanne Hendrix
- ***Pfizer***—Kaori Ito, Rachel Schindler, Sean Xie
- ***Roche***—*Tracie Carey*
- **Takeda**—Pat Cole
- ***USDavis***—Laurel Beckett
- ***University of Trento, Italy***—Jorge Jovicich
- Chahin Pachai

# Overview

- Context: Recent clinical trial results have important implications subject selection in future trials
- The need for enrichment/stratification strategies is increasingly apparent
- Update on the maturity and value of hippocampal volume (HCV) as an enrichment biomarker
- Looking to the future: combining biomarkers and incorporating disease models

# Recent Scientific Data

- Increasing evidence that amyloid-targeted treatment is effective in some people:
  - Early in disease,
  - Amyloid positive,
  - Rapidly progressing,
  - Sufficient dose.

**Challenge is finding these people:**

- In clinical trials
- Even more so in the clinic

# Emerging case for careful patient selection

## Bapineuzumab & Solanazumab Mild to Moderate Phase III Results

The NEW ENGLAND JOURNAL of MEDICINE

**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., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D. for the Bapineuzumab 301 and 302 Clinical Trial Investigators

N Engl J Med 2014; 370:322-333 | January 23, 2014 | DOI: 10.1056/NEJMoa1304839

alzheimer's association® | Alzheimer's & Dementia® THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Alzheimer's & Dementia: The Journal of the Alzheimer's Association
Volume 9, Issue 4, Supplement , Pages P888-P889, July 2013

**Incidence and clinical progression of placebo-treated amyloid-negative subjects with mild-to-moderate Alzheimer's disease (AD): Results from the phase III PET substudies of bapineuzumab and solanezumab**

Stephen Salloway, Reisa Sperling, Keith Gregg, Peng Yu, Abhinav Joshi, Ming Lu, Mark Mintun, Michael Pontecorvo, Kevin Booth, Bradley Wyman, Jia Sun, Karen Sundell, Mark Schmidt, Richard Margolin, Daniel Skovronsky, Enchi Liu, Eric Siemers, Robert H. Brashear

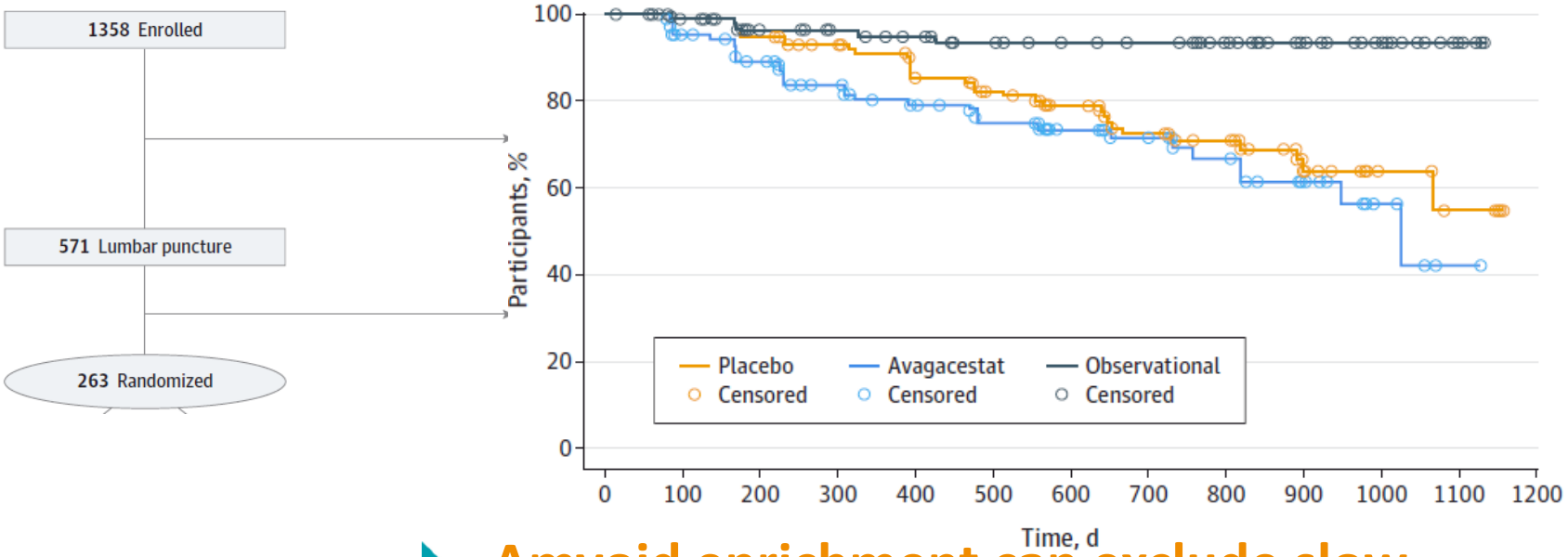
- 6.5% of APOEε4 carriers and 36.1% of noncarriers amyloid –ve on PET
- Aβ- subjects did not demonstrate the same rate of cognitive decline typically observed in AD dementia
- **Should amyloid targeted therapies only be given to amyloid +ve subjects?**

# Emerging case for careful patient selection:
## Amyloid enrichment in Avagacestat trial

Original Investigation | CLINICAL TRIAL

## Targeting Prodromal Alzheimer Disease With Avagacestat
## A Randomized Clinical Trial

Vladimir Coric, MD; Stephen Salloway, MD; Christopher H. van Dyck, MD; Bruno Dubois, MD; Niels Andreasen, MD, PhD; Mark Brody, MD; Craig Curtis, MD; Hilkka Soininen, MD; Stephen Thein, PhD; Thomas Shiovitz, MD; Gary Pilcher, PhD; Steven Ferris, PhD; Susan Colby, BA; Wendy Kerselaers, BA; Randy Dockens, PhD; Holly Soares, PhD; Stephen Kaplita, MSc; Feng Luo, PhD; Chahin Pachai, PhD; Luc Bracoud, MSc; Mark Mintun, MD; Joshua D. Grill, PhD; Ken Marek, MD; John Seibyl, MD; Jesse M. Cedarbaum, MD; Charles Albright, PhD; Howard H. Feldman, MD; Robert M. Berman, MD




- **Amyoid enrichment can exclude slow progressors, but screen failure rate very high**

# Emerging case for careful patient selection

## Gantanerumab MCI *post hoc* analysis (SCarlet RoAD)

- Prodromal AD study with amyloid biomarker terminated early due to futility analysis
- Post hoc analysis stratifying patient groups into slow and fast progressors using CDR-SOB, FAQ and HCV as covariates.

> Covariates identified for assignment to the slow- or fast-progressing MCI groups at study entry were CDR-SOB, FAQ, and the hippocampal volume normalized for age and head size.

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e78; doi:10.1038/psp.2013.54

www.nature.com/psp

ORIGINAL ARTICLE

**Modeling Alzheimer's Disease Progression Using Disease Onset Time and Disease Trajectory Concepts Applied to CDR-SOB Scores From ADNI**

I Delor[1], J-E Charoin[2], R Gieschke[2], S Retout[2] and P Jacqmin[1]; for the Alzheimer's Disease Neuroimaging Initiative

- In fast progressors, Roche detected a "concentration-dependent treatment effect on ADASCog and MMSE".

**Is an amyloid biomarker alone insufficient?**

### Aducanumab, Solanezumab, Gantenerumab Data Lift Crenezumab, As Well

Series - Alzheimer's Association International Conference 2015: Part 4 of 6: Ac

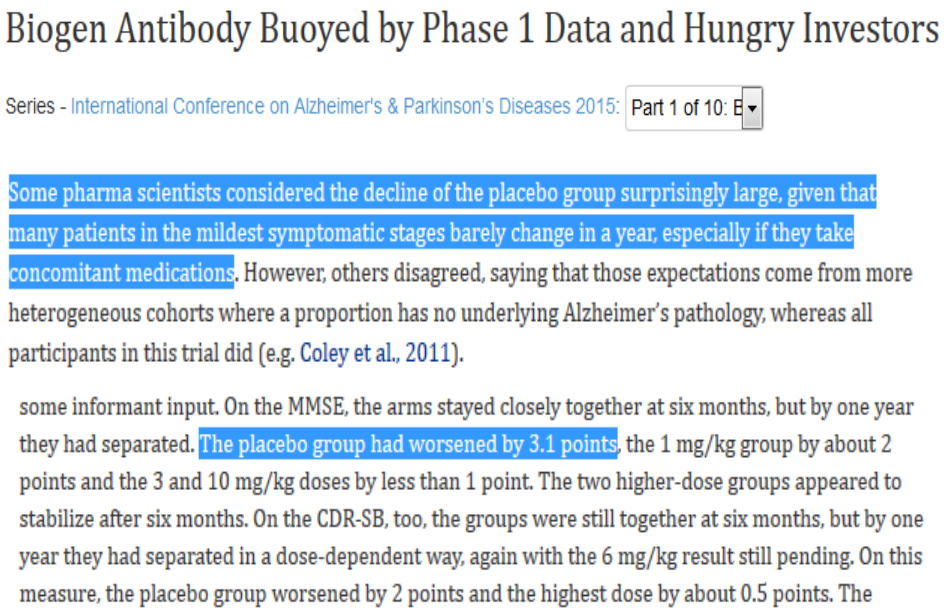
that made no difference in the overall outcome. Different progression rates from person to person, and the field's inability to predict with any precision how quickly a given person will progress, are longstanding problems in Alzheimer's disease trials. In this instance, the fast progressors—i.e., those whose hippocampal volume and CDR-SB performance declined the most over the duration of the trial—appeared to benefit, especially those whose serum levels of gantenerumab were high. "In fast progressors, we detected a concentration-dependent treatment effect on ADASCog and MMSE," Lasser said. "This is a *post hoc* analysis, however."

http://www.alzforum.org/news/conference-coverage/aducanumab-solanezumab-gantenerumab-data-lift-crenezumab-well

# Emerging case for careful patient selection

## Aducanumab Results and Solanezumab Delayed Start Analysis

- Aducanumab phase Ib data
  - Evidence of efficacy with dose effect
    - Suggestion the placebo group more rapidly progressing than in other studies.
- Solanezumab delayed start trial design analysis
  - Potential case for disease modification from EXPEDTION EXT
  - modest therapeutic benefit.
- Will amyloid +ve enrichment in EXPECTION 3 increase clinical effect?
  - **Or are there lessons from SCarlet RoAD?**



Biogen Antibody Buoyed by Phase 1 Data and Hungry Investors

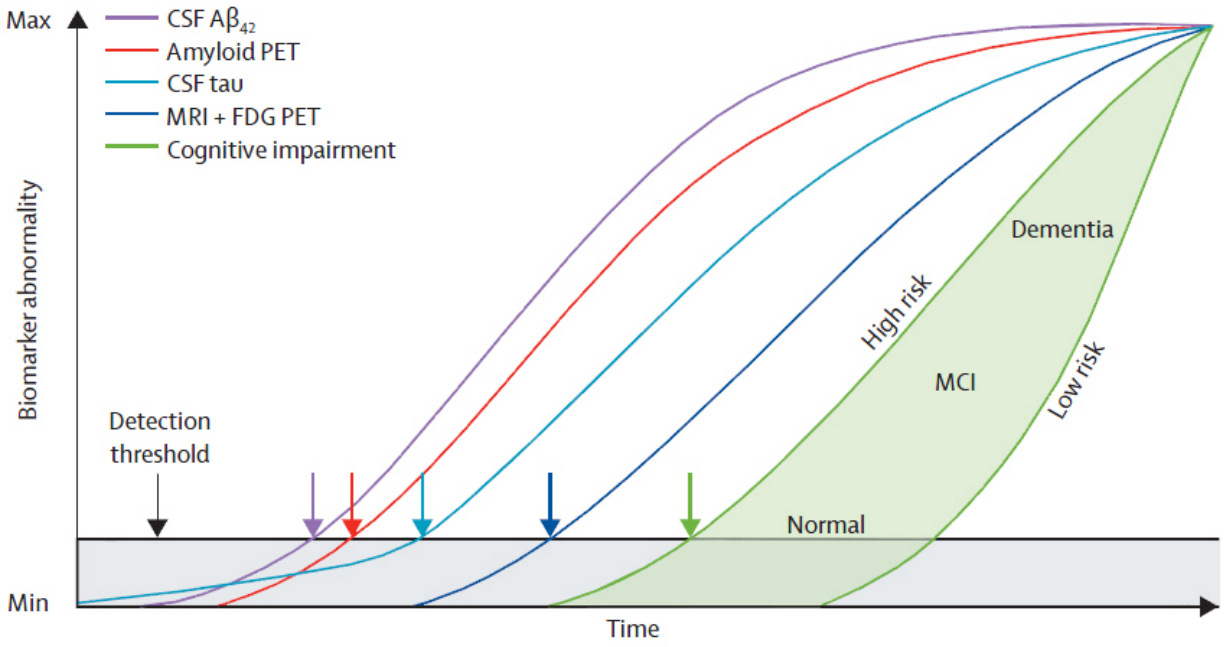
Series - International Conference on Alzheimer's & Parkinson's Diseases 2015: Part 1 of 10: E

Some pharma scientists considered the decline of the placebo group surprisingly large, given that many patients in the mildest symptomatic stages barely change in a year, especially if they take concomitant medications. However, others disagreed, saying that those expectations come from more heterogeneous cohorts where a proportion has no underlying Alzheimer's pathology, whereas all participants in this trial did (e.g. Coley et al., 2011).

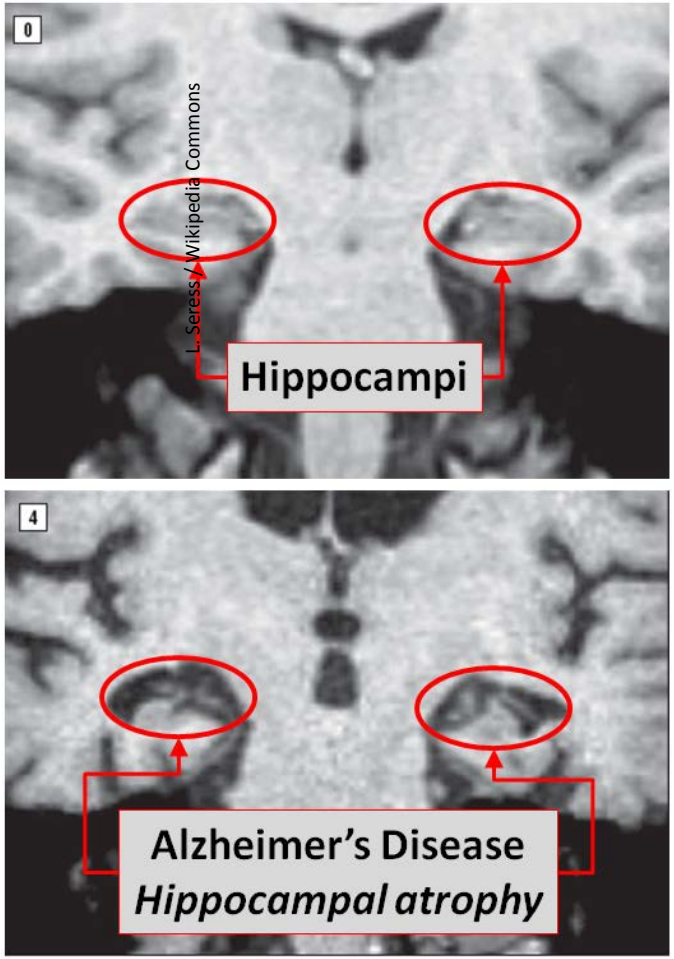
some informant input. On the MMSE, the arms stayed closely together at six months, but by one year they had separated. The placebo group had worsened by 3.1 points, the 1 mg/kg group by about 2 points and the 3 and 10 mg/kg doses by less than 1 point. The two higher-dose groups appeared to stabilize after six months. On the CDR-SB, too, the groups were still together at six months, but by one year they had separated in a dose-dependent way, again with the 6 mg/kg result still pending. On this measure, the placebo group worsened by 2 points and the highest dose by about 0.5 points. The

# Where does hippocampal volume (HCV) fit in?

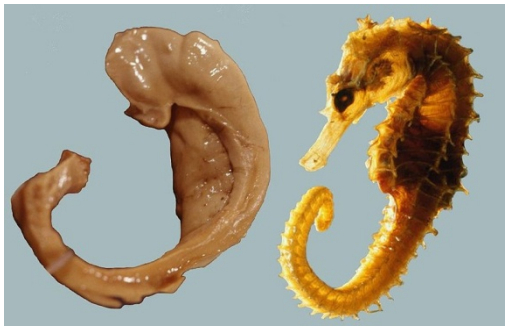
- Low hippocampal volume is a biomarker of a neurodegenerative phenotype
- Face validity and > 20 years of clinical data
- It is later in the disease development than amyloid accumulation therefore provides “proximity marker” to clinical disease
- Potential value either alone or with other biomarkers

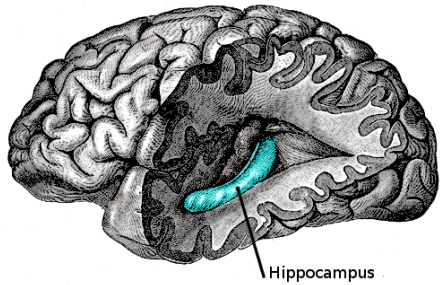


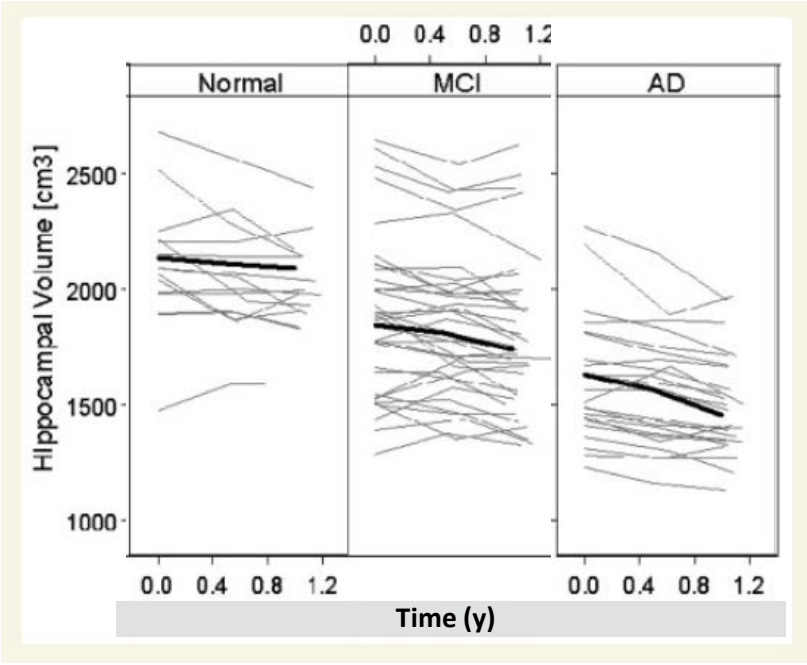
# Hippocampal atrophy in Alzheimer's Disease




L. Seress / Wikipedia Commons



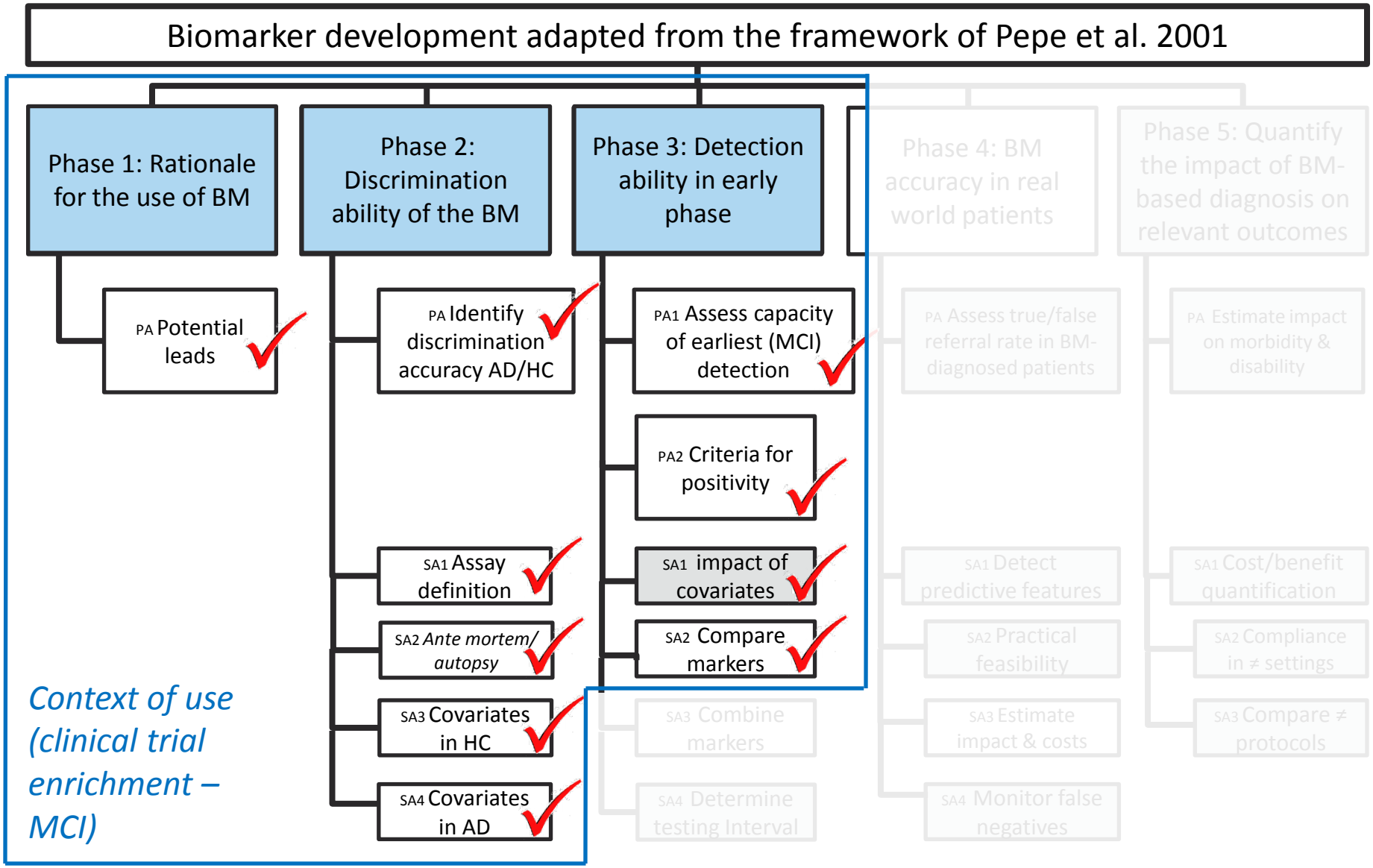



deCarli *et al.* (2007) *Arch Neurol* **64** 108

Schuff *et al.* (2009) *Brain* **132** 1067

AD = Alzheimer's Disease. MCI = Mild Cognitive Impairment.




*Slide courtesy of Marina Boccardi & Giovanni Frisoni*

# Biomarkers of neurodegeneration are embedded in the 2011 NIA-AA research criteria for MCI due to AD

## The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]

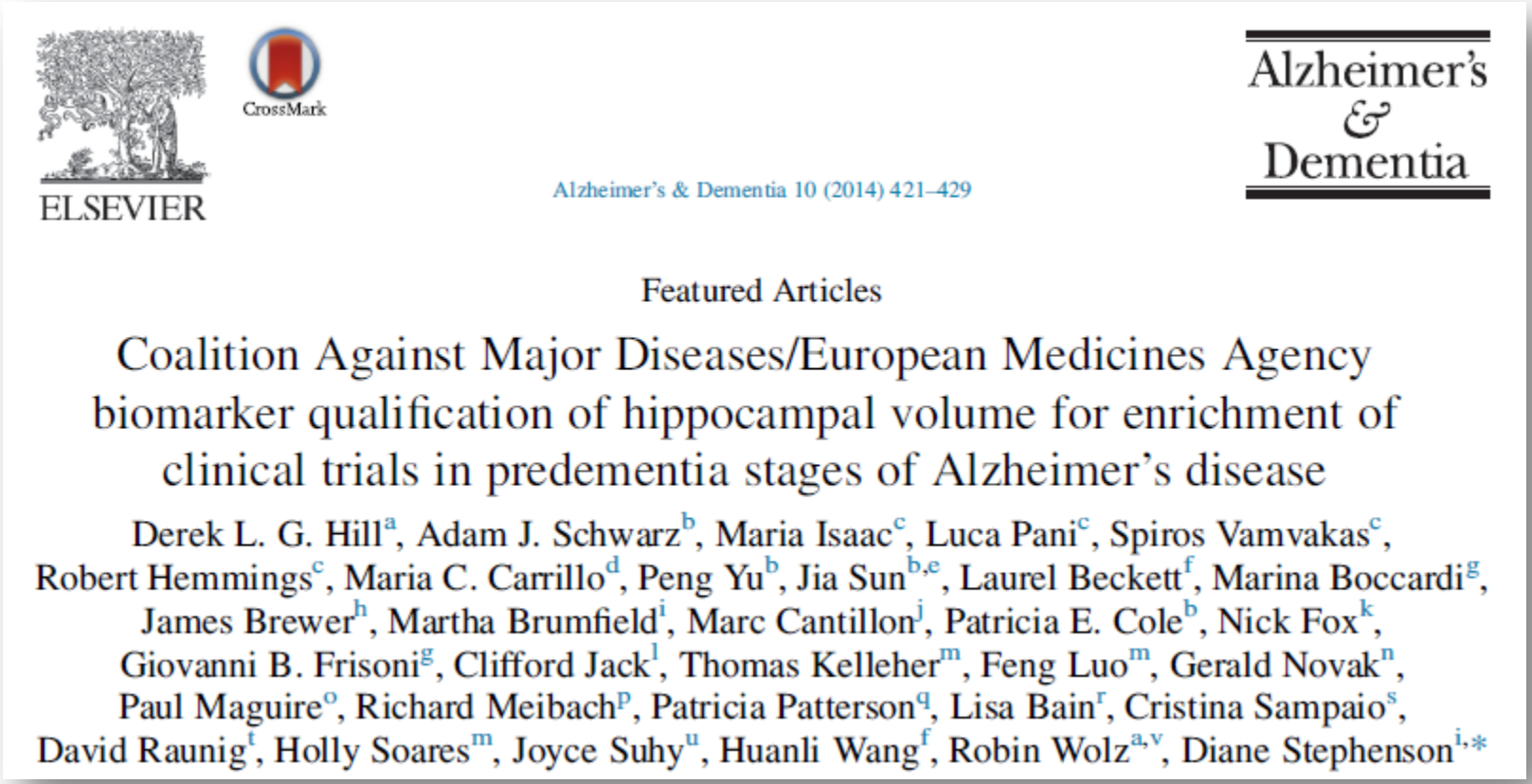
Table 3
MCI criteria incorporating biomarkers

| Diagnostic category | Biomarker probability of AD etiology | Aβ (PET or CSF) | Neuronal injury (tau, FDG, sMRI) |
|---|---|---|---|
| MCI–core clinical criteria | Uninformative | Conflicting/indeterminant/untested | Conflicting/indeterminant/untested |
| MCI due to AD—intermediate likelihood | Intermediate | Positive | Untested |
| | | Untested | Positive |
| MCI due to AD—high likelihood | Highest | Positive | Positive |
| MCI—unlikely due to AD | Lowest | Negative | Negative |

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Albert M et al. (2011) Alzheimers & Dementia

# A systematic survey of the published literature indicated strong evidence for low hippocampal volume as an enrichment biomarker in MCI



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Alzheimer's & Dementia 10 (2014) 421–429

Alzheimer's & Dementia

Featured Articles

## Coalition Against Major Diseases/European Medicines Agency biomarker qualification of hippocampal volume for enrichment of clinical trials in predementia stages of Alzheimer's disease

Derek L. G. Hill[a], Adam J. Schwarz[b], Maria Isaac[c], Luca Pani[c], Spiros Vamvakas[c], Robert Hemmings[c], Maria C. Carrillo[d], Peng Yu[b], Jia Sun[b,e], Laurel Beckett[f], Marina Boccardi[g], James Brewer[h], Martha Brumfield[i], Marc Cantillon[j], Patricia E. Cole[b], Nick Fox[k], Giovanni B. Frisoni[g], Clifford Jack[l], Thomas Kelleher[m], Feng Luo[m], Gerald Novak[n], Paul Maguire[o], Richard Meibach[p], Patricia Patterson[q], Lisa Bain[r], Cristina Sampaio[s], David Raunig[t], Holly Soares[m], Joyce Suhy[u], Huanli Wang[f], Robin Wolz[a,v], Diane Stephenson[i,*]

# *De novo* calculations confirmed literature findings and robustness to HCV measurement algorithm

Table 1
Results of Coalition Against Major Diseases' *de novo* analysis. The AUC for four different hippocampal volume quantification algorithms applied to ADNI-1 data indicate the prediction by MRI hippocampal volume of clinical conversion to Alzheimer's dementia within two years.

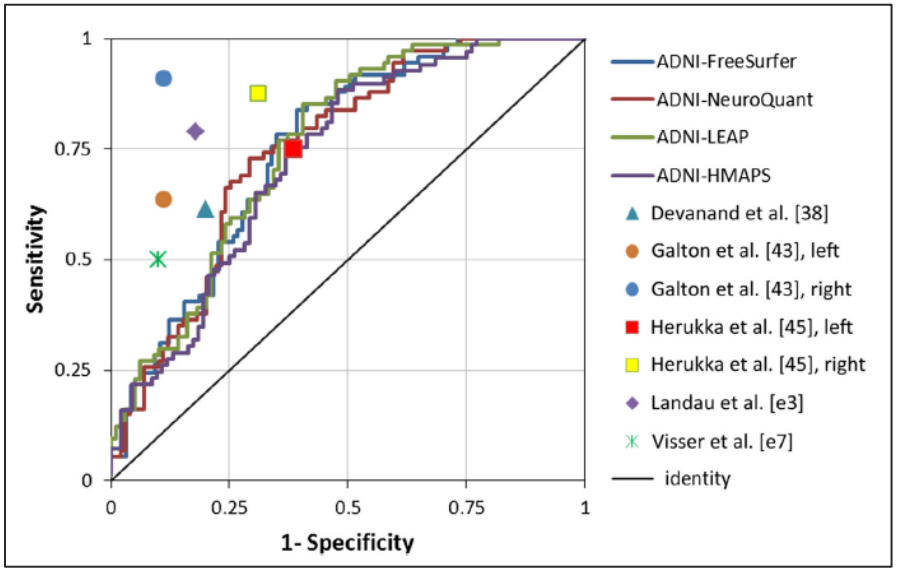
| Algorithm | Training, n | Testing, n | AUC based on clinical conversion |
|---|---|---|---|
| LEAP | 149 | 173 | 0.7565 |
| NeuroQuant | 149 | 173 | 0.7516 |
| FreeSurfer | 148 | 171 | 0.7536 |
| HMAPS | 128 | 161 | 0.7290 |

Abbreviations: AUC, area under the receiver–operating characteristic curves; LEAP, Learning Embeddings for Atlas Propagation; HMAPS, Hippocampus Multi-Atlas Propagation and Segmentation.

Table 2
AUC values reported in the Coalition Against Major Diseases literature review

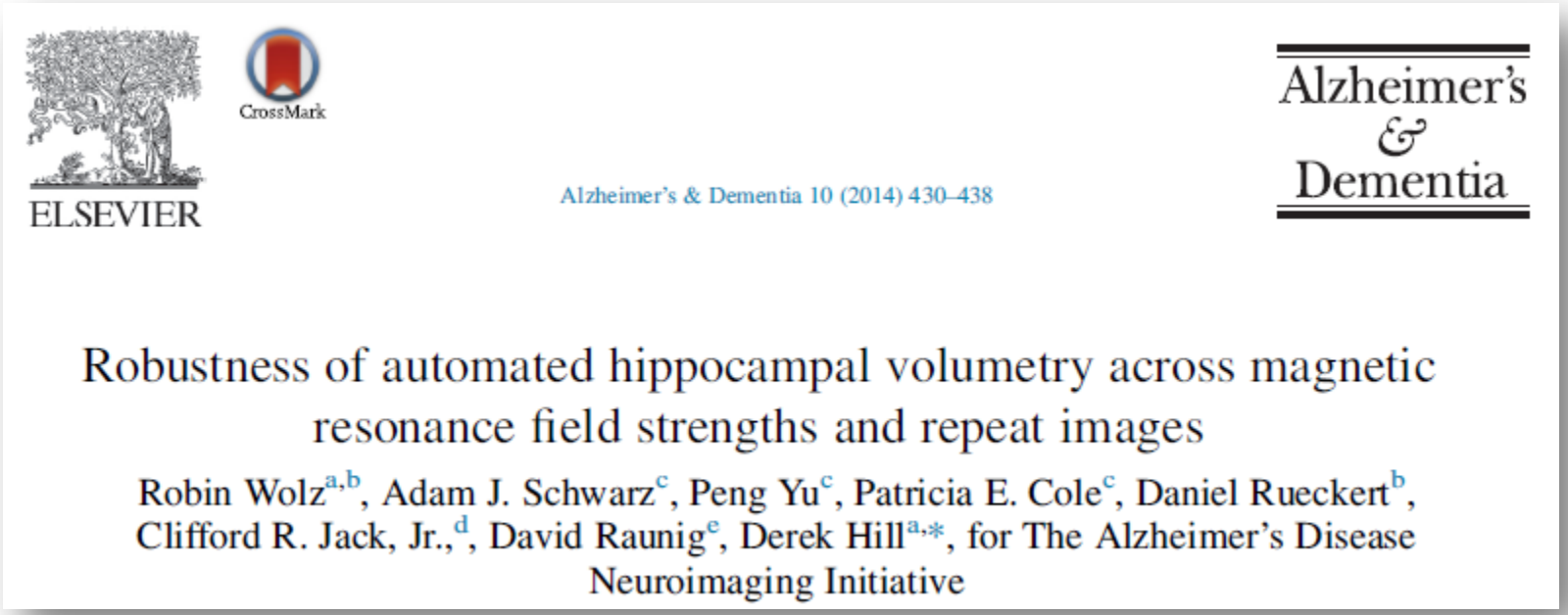
| Study | n | AUC based on clinical conversion |
|---|---|---|
| Bakkour et al. [e9] | 49 | 0.65 |
| Devanand et al. [38] | 139 | 0.77 |
| Fleisher et al. [e10] | 129 | 0.60 |
| Galluzzi et al. [42] | 90 | 0.73 |

Abbreviation: AUC, area under the receiver–operating characteristic curves.




Hill DLG *et al*. (2014) *Alzheimers & Dementia* **10** 421

# Analytic validation: test-retest reliability



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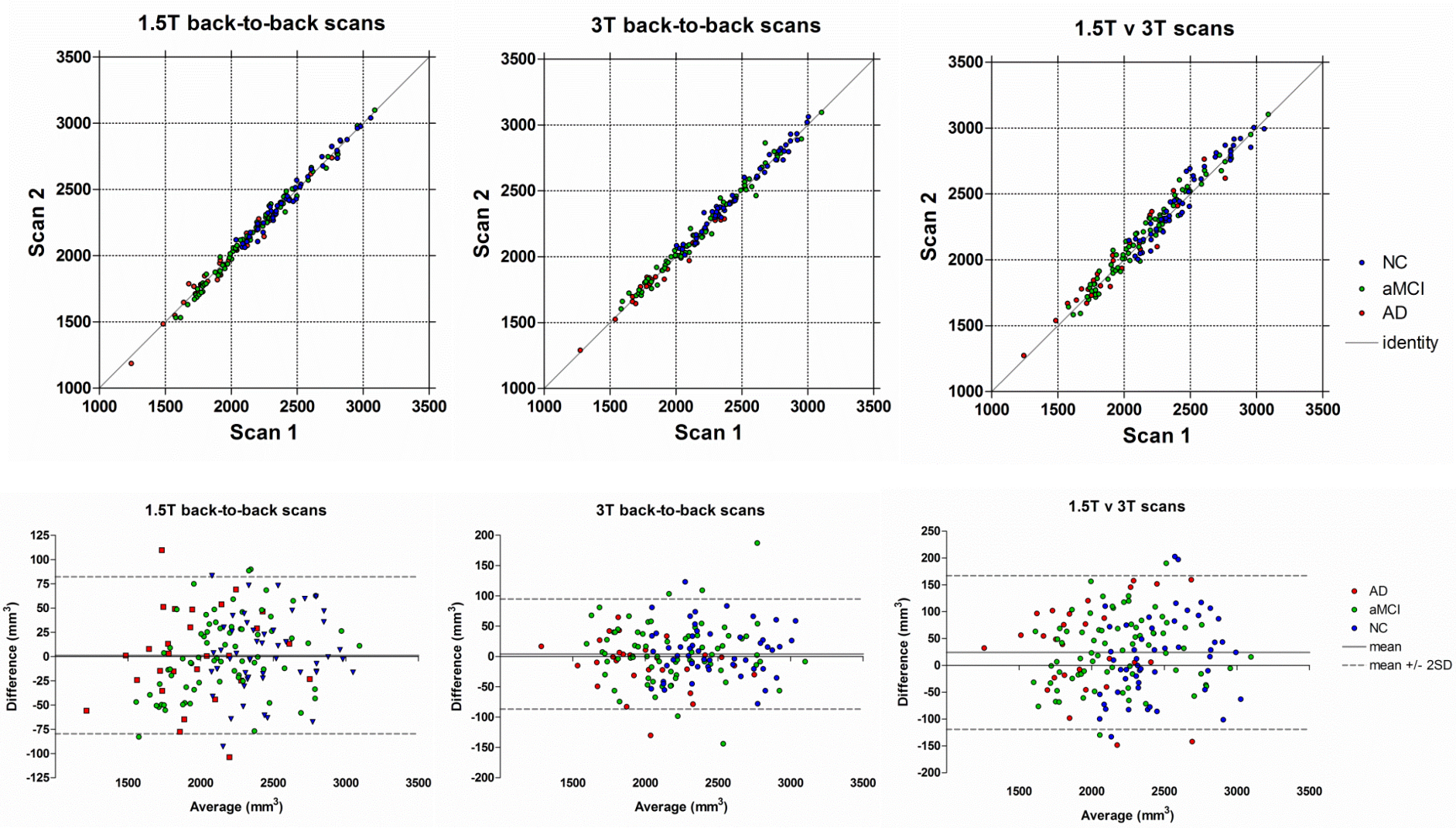
Alzheimer's & Dementia 10 (2014) 430–438

Alzheimer's & Dementia

## Robustness of automated hippocampal volumetry across magnetic resonance field strengths and repeat images

Robin Wolz[a,b], Adam J. Schwarz[c], Peng Yu[c], Patricia E. Cole[c], Daniel Rueckert[b], Clifford R. Jack, Jr.,[d], David Raunig[e], Derek Hill[a,*], for The Alzheimer's Disease Neuroimaging Initiative

# Hippocampal volume measurements are highly reliable (test-retest)




Wolz R *et al*. (2014) *Alzheimers & Dementia* **10** 430

# Operational considerations and practical implications for trials

Neurobiology of Aging 35 (2014) 808–818

Contents lists available at ScienceDirect

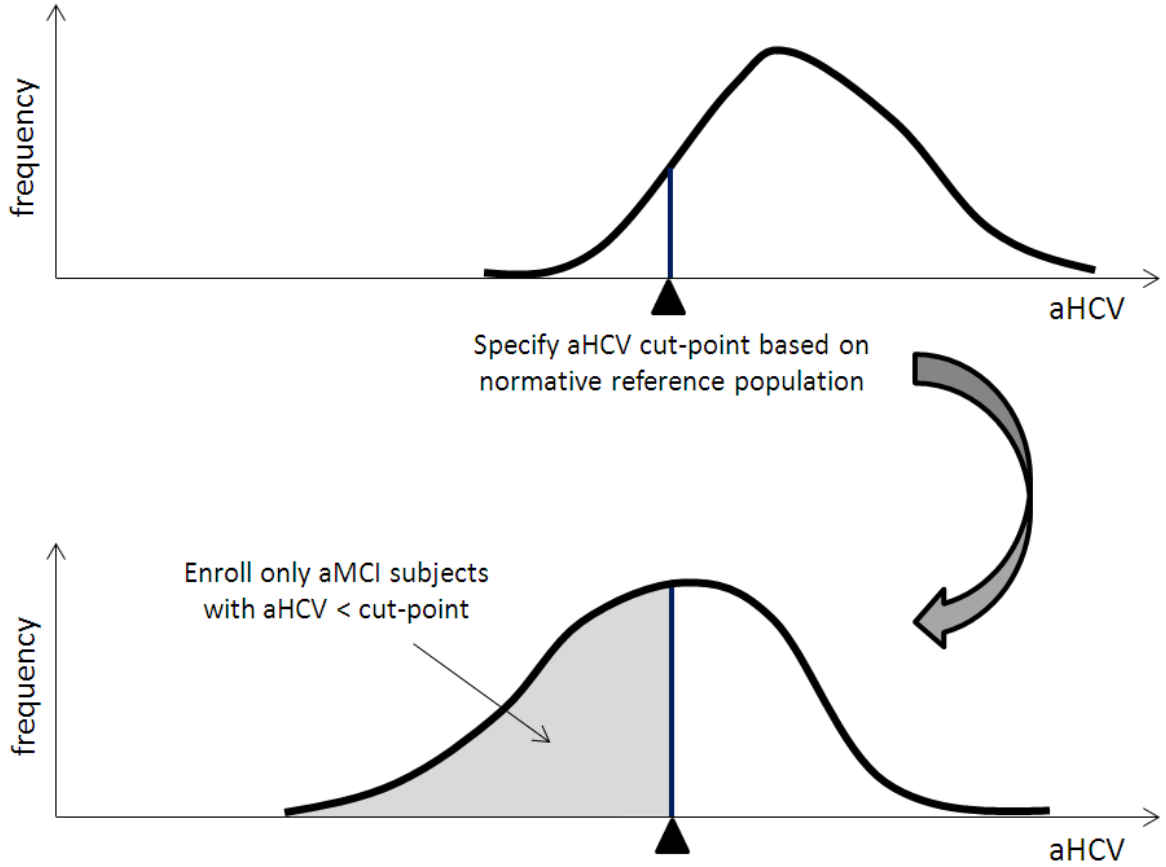
Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging


## Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size

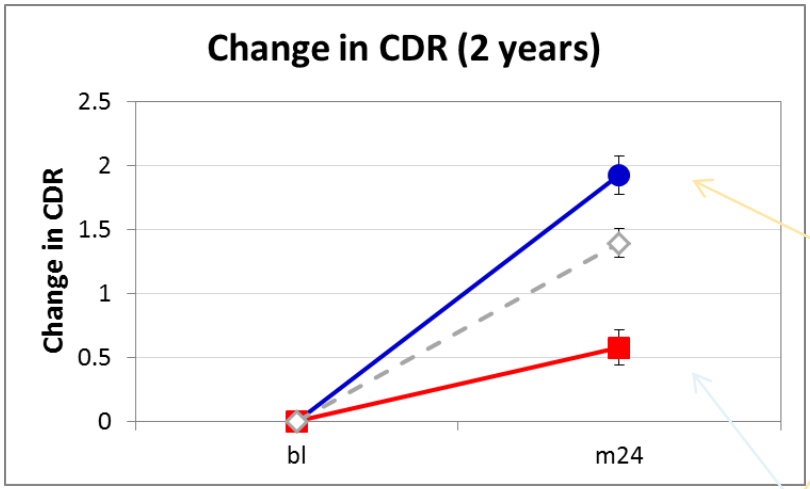
Peng Yu [a], Jia Sun [a,b], Robin Wolz [c,d], Diane Stephenson [e], James Brewer [f], Nick C. Fox [g], Patricia E. Cole [h], Clifford R. Jack Jr [i], Derek L.G. Hill [c,g], Adam J. Schwarz [h,*], for the Coalition Against Major Diseases and the Alzheimer's Disease Neuroimaging Initiative

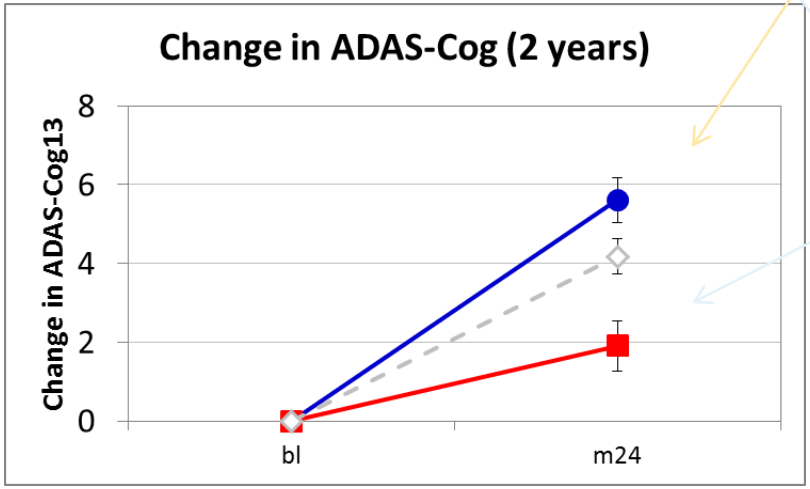
# Cut-point defined with respect to normative reference range



# MCI subjects with smaller hippocampi progress more rapidly

- Enriched population (HV < 25% of normal)
- All MCI subjects
- Subjects excluded (HV >= 25% of normal)




Subjects with smaller HV at baseline progress more rapidly

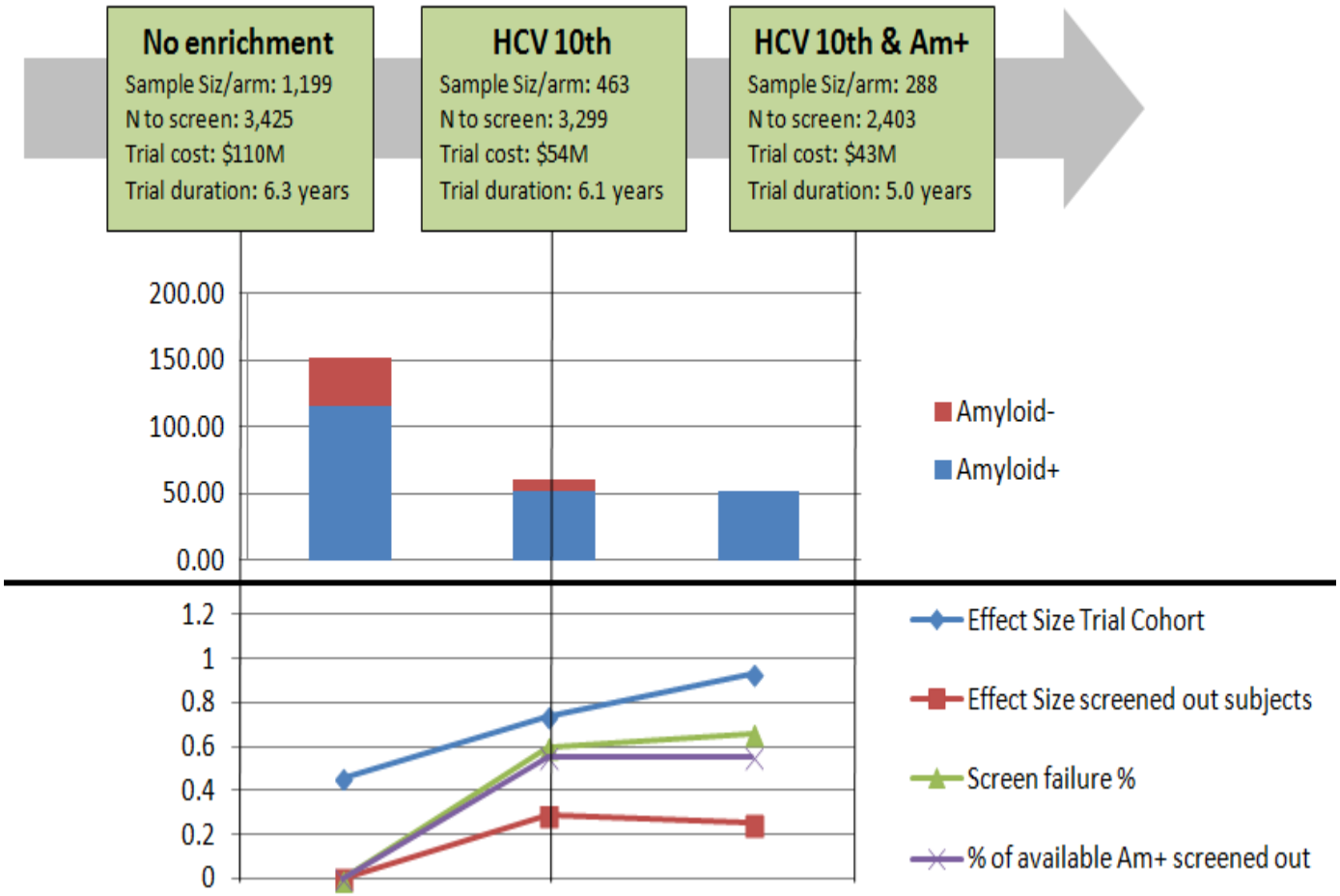
Slower progressing subjects are excluded

# Prospective application of HCV biomarker to clinical trial cohort

- Re-use of (negative) clinical trial data remains a significant challenge for biomarker qualification
- Access to raw data (MRI scans etc) is especially difficult to secure
- CAMD is delighted to have access to the Novartis IndeXX study data
- IndeXX had a very slow rate of conversion from MCI to AD in the placebo group, making it an especially interesting, if challenging, dataset for enrichment biomarkers
- CAMD is proposing an analysis plan to the FDA for this dataset.

# Combining Amyloid +ve & Hippocampal Volume
## ADNI MCI cohort

Stepwise enrichment with HCV and Am+




*Austin et al*. Combination of biomarkers for amyloid positivity and structural neurodegeneration for enrichment of amnestic MCI clinical trials
CTAD 2014

# Combining HCV and Amyloid biomarkers
## Clinical trial data (Avagacestat)

| | HCV+ Whole cohort | HCV- Whole cohort | HCV+ PET cohort | HCV- PET cohort | HCV+/PET+ | Non-(HCV+/PET+) |
|---|---|---|---|---|---|---|
| Number of subjects (%) | 152 (80%) | 37 (20%) | 29 (67%) | 14 (33%) | 25 (58%) | 18 (41%) |
| Annualized Brain volume loss (mL/y) - SE | 11.6 (0.4) | 7.1 (0.6) | 11.2 (0.9) | 5.8 (1.0) | 11.6 (0.9) | 5.8 (0.9) |
| Annualized Ventricular volume increase (mL/y) - SE | 2.89 (0.09) | 1.62 (0.10) | 2.81 (0.22) | 1.32 (0.22) | 2.88 (0.21) | 1.37 (0.22) |
| Annualized Hippocampal volume loss ($mm^3$/y) - SE | 241 (7) | 133 (12) | 235 (18) | 96 (24) | 246 (18) | 95 (22) |

| | ADNI NC | ADNI MCI Non-Converters | ADNI MCI Converters | ADNI AD |
|---|---|---|---|---|
| Number of subjects | 160 | 237 | 109 | 123 |
| Annualized Brain volume loss (mL/y) - SE | 5.9 (0.5) | 7.0 (0.7) | 10.0 (0.9) | 13.7 (0.9) |
| Annualized Ventricular volume increase (mL/y) - SE | 1.42 (0.11) | 1.88 (0.17) | 3.08 (0.25) | 4.22 (0.28) |
| Annualized Hippocampal volume loss ($mm^3$/y) - SE | 105 (5) | 174 (7) | 266 (9) | 344 (9) |

BMS and Bioclinica

# Conclusions and next steps

- Recent scientific data supports need for improved clinical trial enrichment methodology
- While amyloid biomarkers (CSF, Amyloid PET) have clear benefit,  the HCV biomarker provides complementary information about progression
- Literature review and prospective application to ADNI 1 and 2 cohorts demonstrates enrichment performance of HCV
- Plan to apply HCV to assess enrichment performance on IndeXX study being submitted to FDA
- Increasing data illustrating potential for HCV to be used in combination with other biomarkers (eg: Amyloid) and clinical data (eg: cognitive/function tests) to provide better enrichment performance
- Computer modelling appear to lead to better enrichment performance compared to sequential application of biomarkers
- CAMD is exploring opportunities for qualfication or combination biomarkers for AD