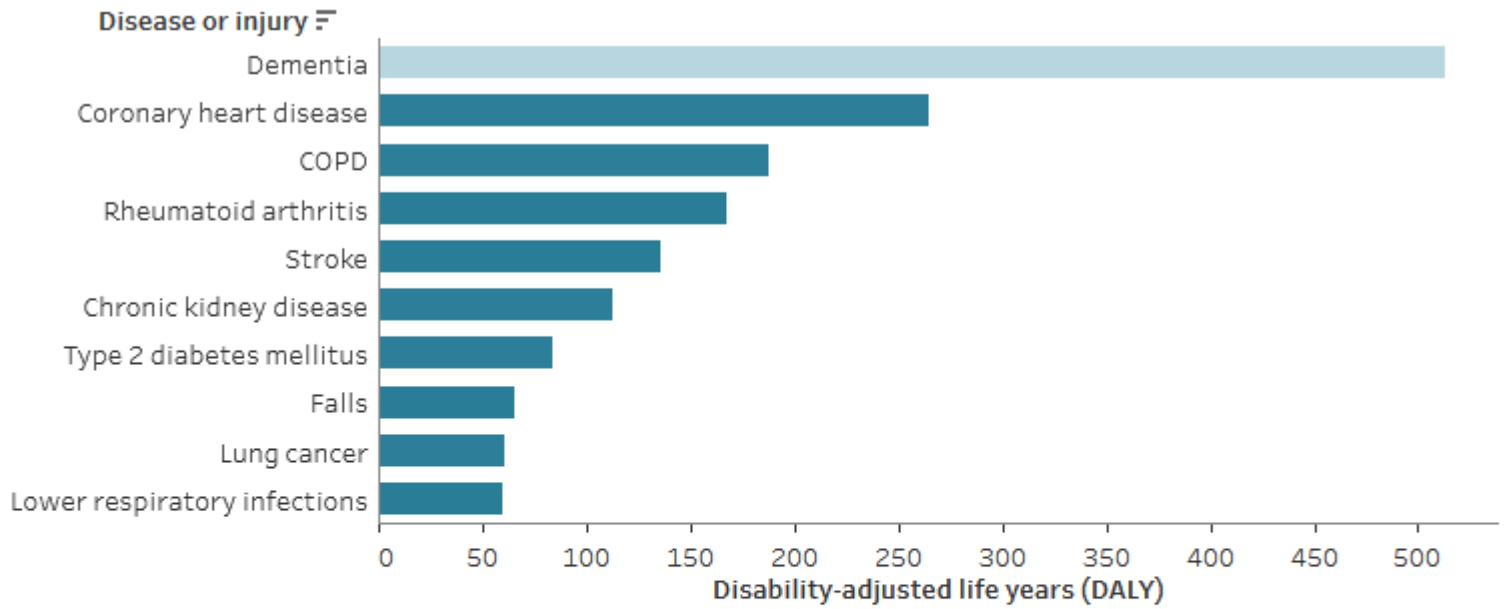
Dementia in Australia

Findings from the Australian Institute of Health and Welfare report on Dementia in Australia (2024) :

- In 2023, it is estimated that 411,100 Australians are living with dementia
- Dementia was the 2nd leading cause of death in Australia in 2022
- Around 2 in 3 Australians with dementia were living in the community in 2022
- $3.7 billion of Australia's health and aged care expenditure was spent directly on dementia in 2020–21

Leading 10 causes of disease burden (DALY) among First Nations people, by sex and age, in 2018



Notes

1. DALY represents the total burden and is the sum of all disability-adjusted life years.
2. COPD refers to chronic obstructive pulmonary disease.
3. Lower respiratory infections include influenza and pneumonia.
4. Conditions which were not grouped into residual categories in the Australian Burden of Disease Study 2018 (such as 'Other musculoskeletal conditions') are not included in the rankings.

Source: AIHW Australian Burden of Disease Study 2018.

https://www.aihw.gov.au

Development of the Aβ Theory of the Etiology of Alzheimer's Disease

- **Step 1. Identification of Aβ-amyloid and its biochemical and molecular genetic characterization which elucidated its neuronal origin and its definition as a diagnostic and therapeutic target.**
- **Step 2. Genetic linkages of Aβ/APP and adaptive/innate immune involvement confirm the role of Aβ/APP in the etiology of AD.**
- **Step 3. The normal function of APP provides an explanation for where AD starts.**
- **Step 4. Improved techniques for Aβ detection by molecular imaging and biofluid assay allows depiction of when AD starts during its natural history of preclinical, prodromal and clinical stages.**
- **Step 5. Imbalances between production and clearance provide explanations for why AD occurs.**
- **Step 6. Immunotherapy to promote Aβ clearance provides a strategy for how to treat and prevent AD.**
- **Step 7. A unified and coherent theory of Aβ the etiology of AD is formulated.**

Two main types of Alzheimer's disease (but phenotypic varients exist)

Autosomal Dominant AD (ADAD) and Down's Syndrome (DS); (Early Onset):

Over-production of Aβ

Mean age symptomatic onset: 46y (ADAD); 52y (DS)

Pathogenic mutations in APP/PSEN1,2 (ADAD); triplications APP (DS)

18% increased production of $[A\beta_{42}]_{CSF}$

Aβ-PET accumulation rates same as sporadic AD

Sporadic (Late Onset):

Failure of Aβ clearance

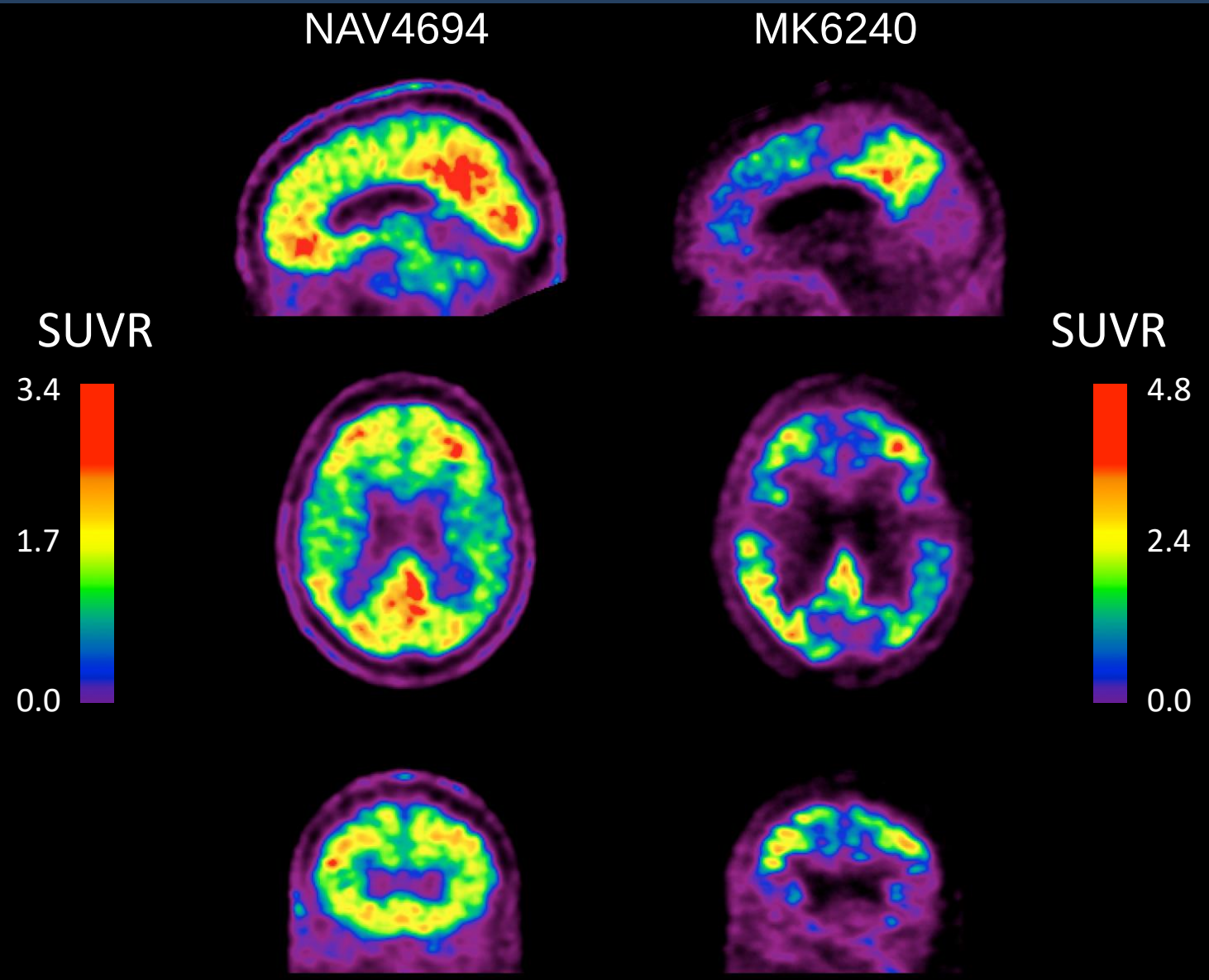
Mean age dementia onset: 78y ($\varepsilon_4^{+/+}$ 68y, $\varepsilon_4^{+/-}$ 76y, $\varepsilon_4^{-/-}$ 86y)

$[A\beta]_{CSF}$: turnover 19h (13h control): 49% slower than control

$T_{1/2}$ 9.4 h (3.8 h young control)

Aβ-PET: accumulation CL 4 %/y; (28 ng/hr, 5% of production rate)

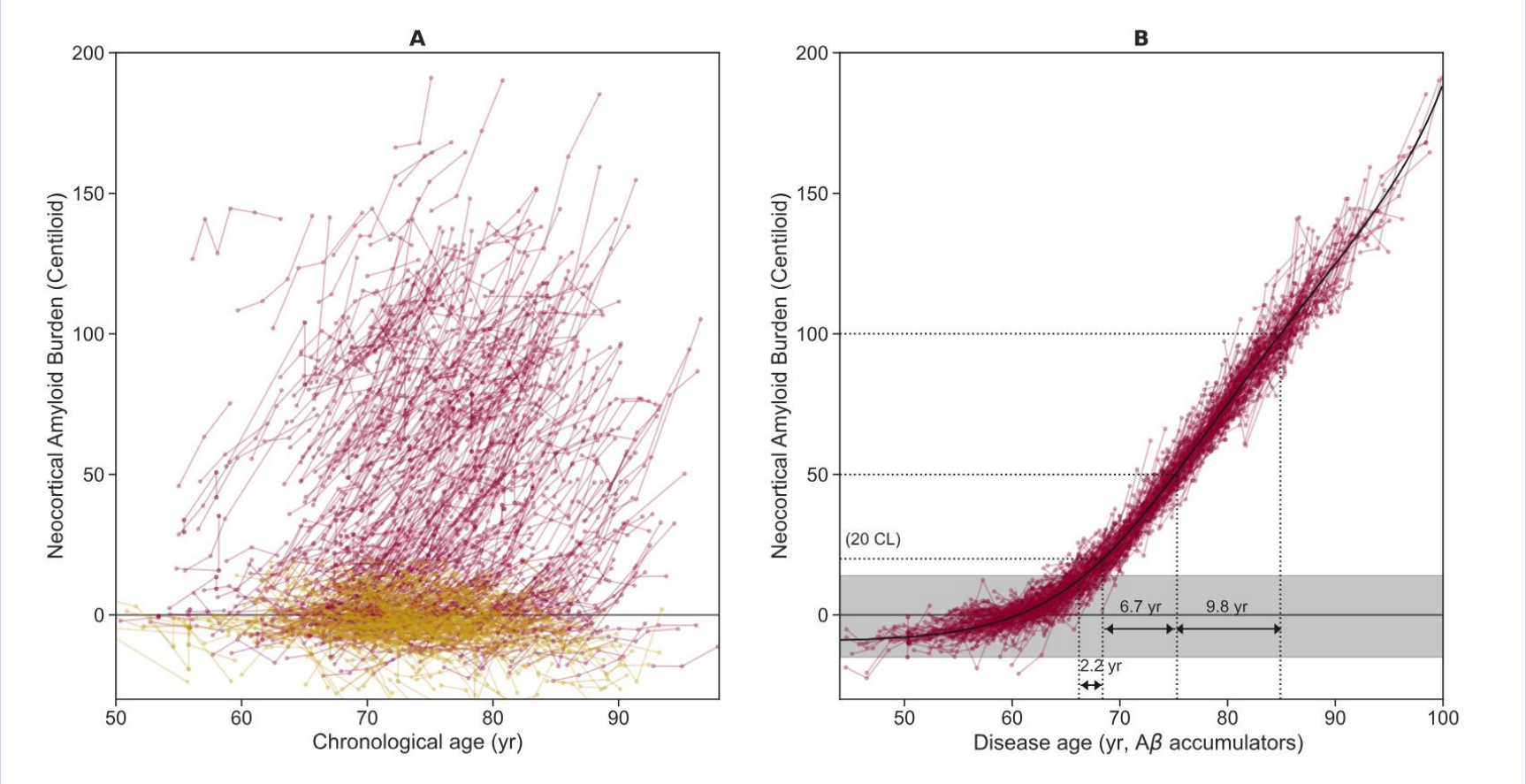
Second generation Aβ and Tau Imaging in AD (^{18}F) (Villemagne and Rowe)



When does Alzheimer's disease start?
Aβ-PET [n=1088, ADOPIC (ADNI, AIBL, OASIS)]

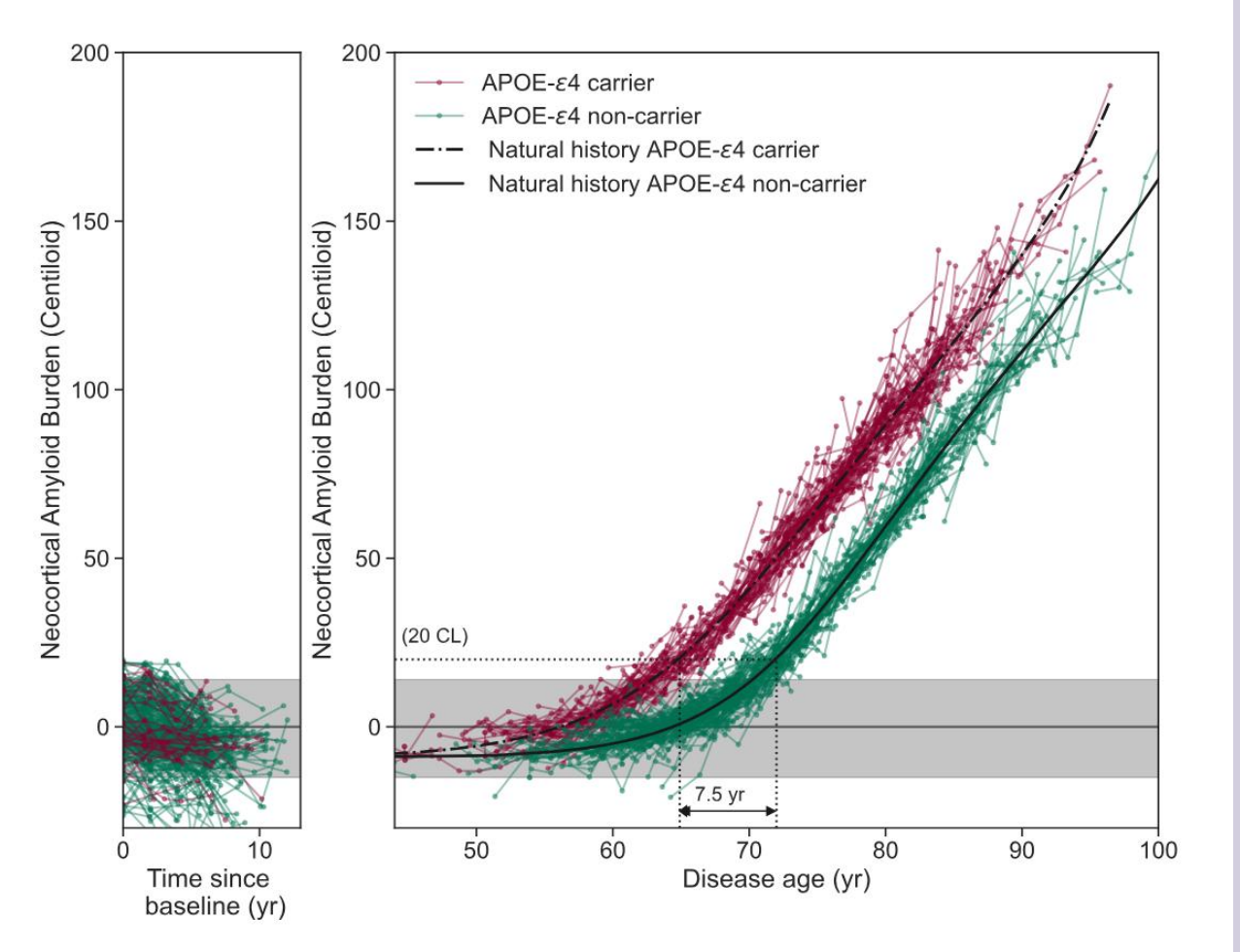
≥ 3-TP actual data

"Disease age"



Non-accumulators Intercept point (0CL) 61 y;
Accumulators Inflection point (13 CL) 66 y; Threshold (20 CL) 68 y

When does Alzheimer's disease start?
Aβ-PET stratified by APOE ε4 status

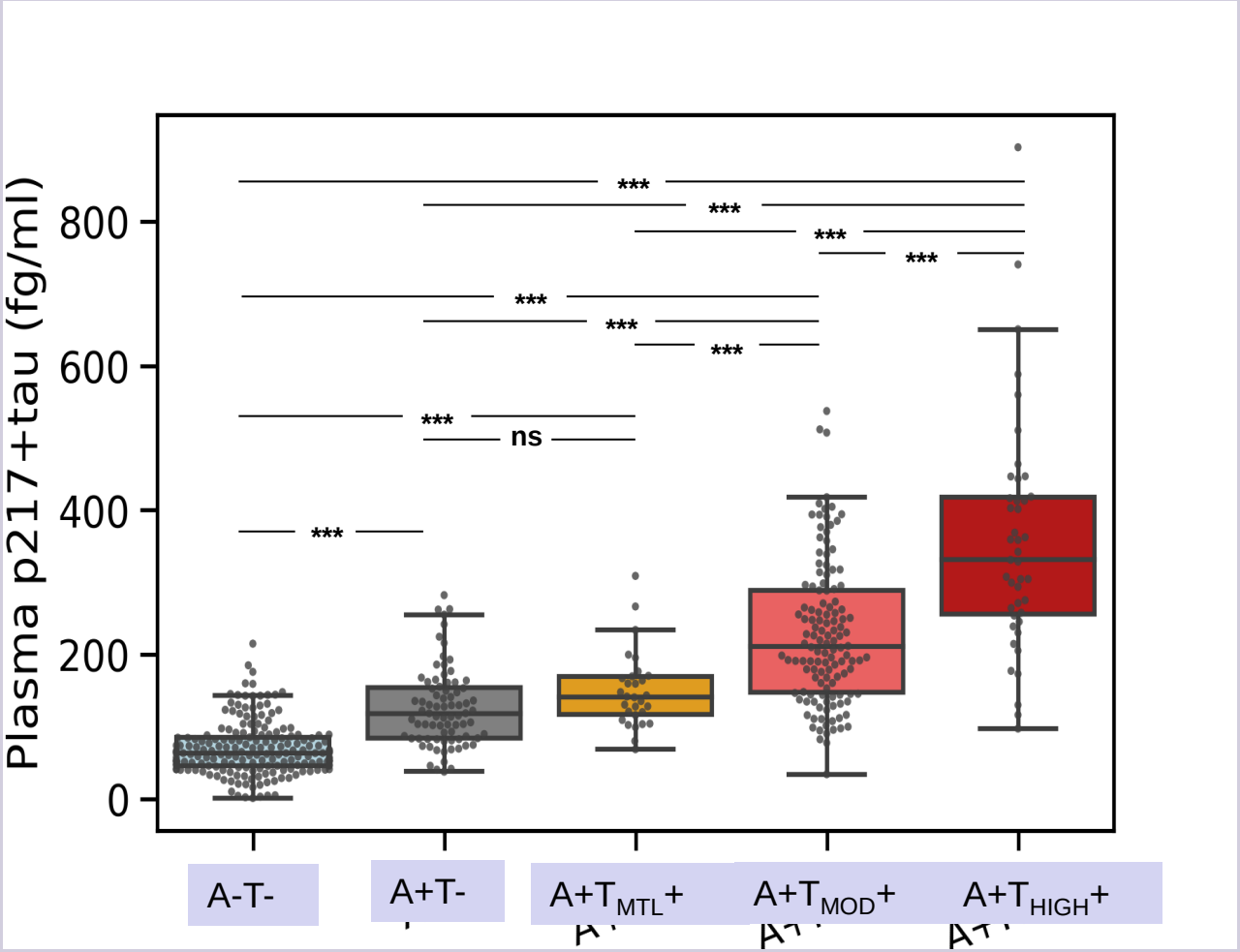


Intersection points:	$E4^+$ 55 y,	$E4^-$ 63 y;
Inflection points:	62 y,	70 y;
Thresholds:	65 y,	73 y.

ADOPIC of ages at onset (years): Aβ-PET

	Disease Age at Intersection point	Disease Age at Inflection Point	Disease Age at 20CL (threshold)	Range of estimated onsets
Whole cohort	60.6±0.9	66,2±1.1	68·4±0·9	61 to 68
APOE e4 carriers	54.8±1.7	62.1±0.8	64·9±1·9	55 to 65
APOE e4 non-carriers	63.0±3.4	70.1±1.6	72·4±1·9	63 to 72

Plasma p-tau217+ stratified by Tau-PET status



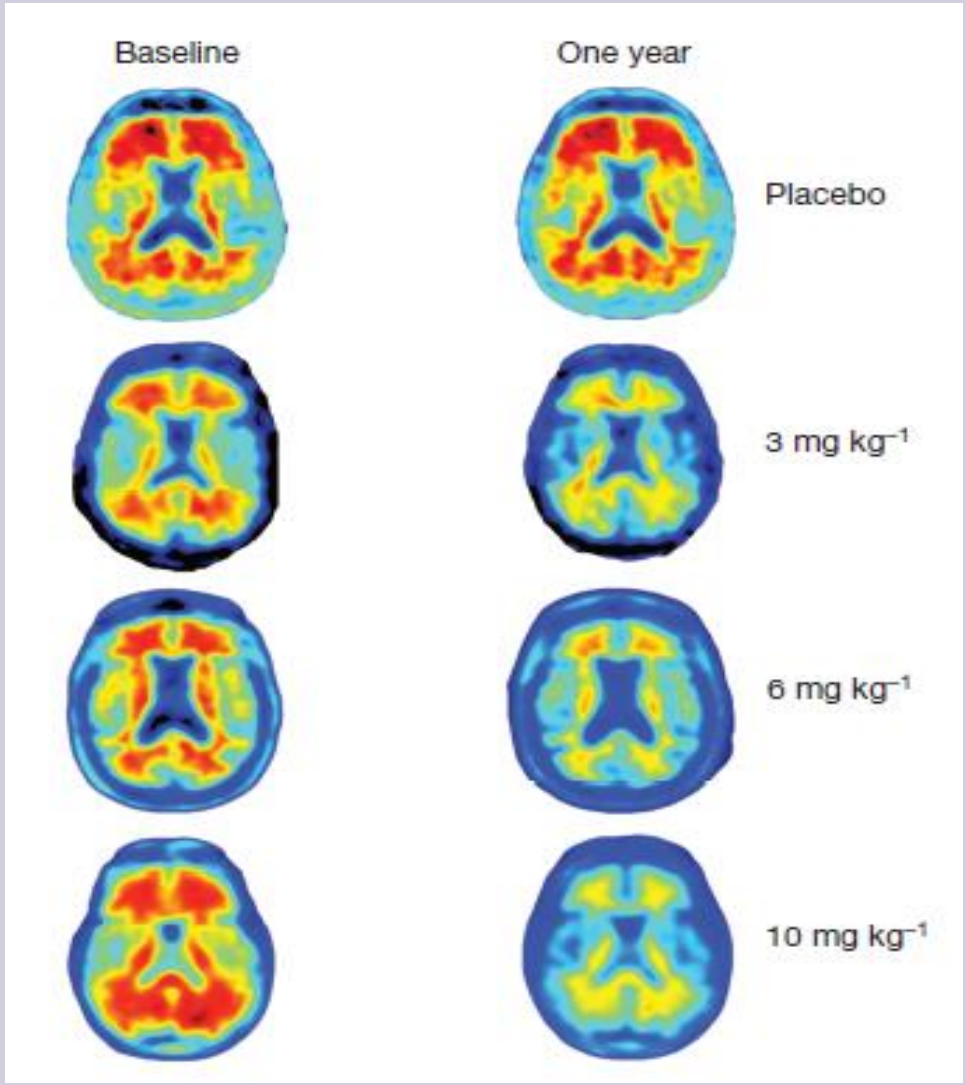
N=472

Feizpour, Rowe et al., 2023

Aβ passive immunization: how to inhibit primary and secondary nucleation and promote clearance

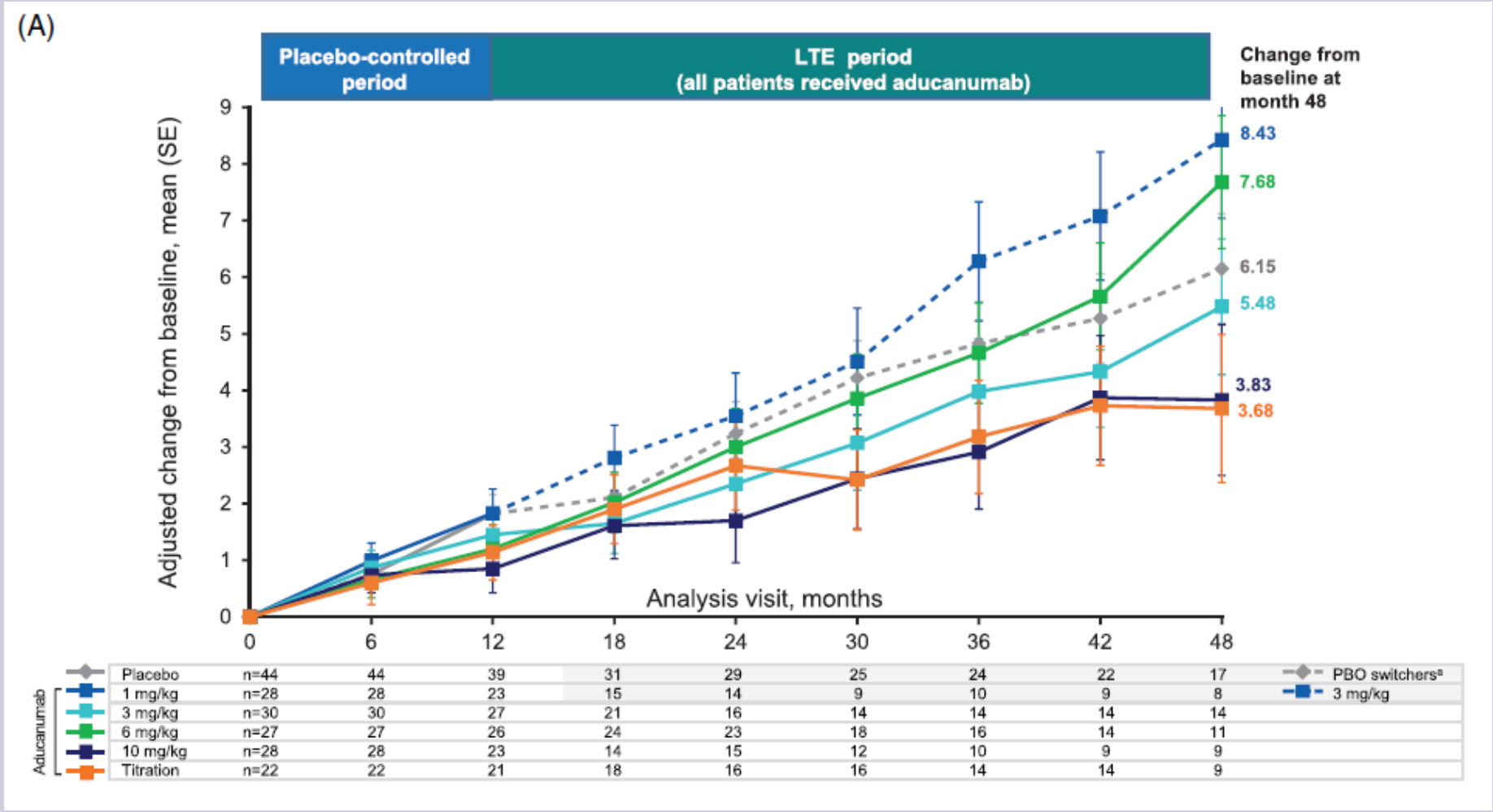
- Aducanumab (Aduhelm, Biogen) >70%
- Gantenerumab (Roche) >70%
- Trontinemab Brain-shuttle (Roche) Gante follow-on
- Lecanemab (Leqembi, Eisai/Biogen) >80%
- Donanemab (Lilly) >85%
- Remternetug (Lilly) >100% in 12 weeks
- Bapineuzumab (J&J/Pfizer/Janssen) 12-25%
- Solanezumab (Lilly) 12%
- Crenezumab (Roche/Genentech/AC Immune)

Aβ amyloid reduction with aducanumab: example florbetapir PET images at baseline and week 54



Sevigny et al, Nature, September 2016

Effect of aducanumab on clinical endpoints through 48 months



(Chen et al.)

First disease modifying drug for Alzheimer's disease (June 7, 2021)

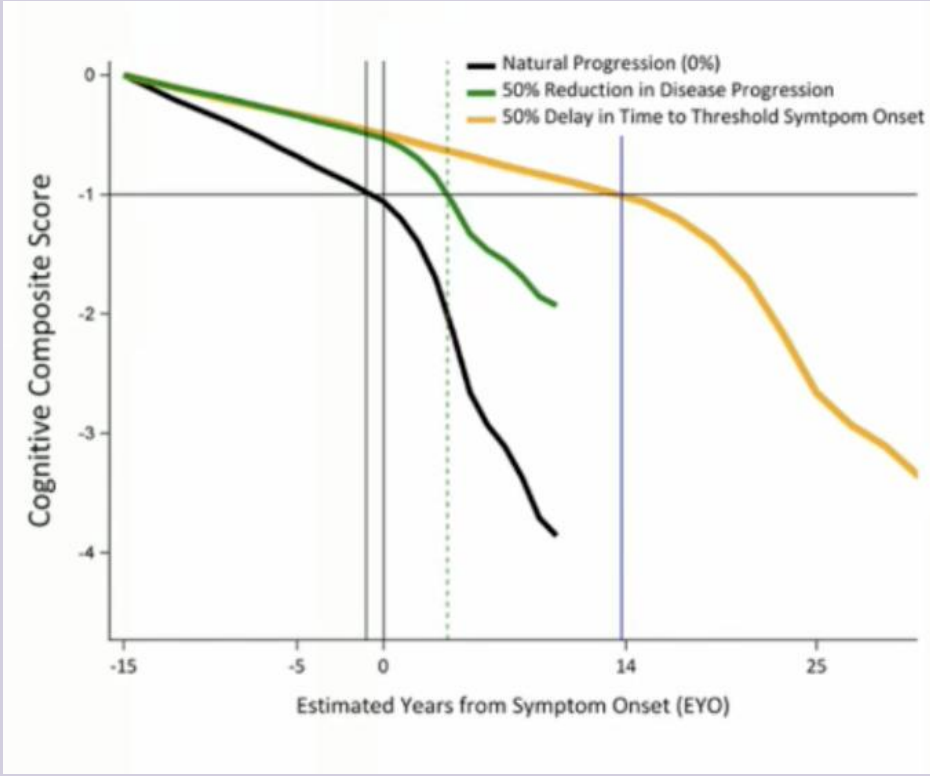
Biogen 2021

Gantenerumab (Roche):

- 60 CL reduction in PET-Aβ signals at 104 weeks, falling below lower threshold to 18CL
- Directional trend for slower clinical decline with higher reduction in PET signal
- Binds “aggregated” Aβ and to growth ends of fibrils
- Strong signals from DIAN-TU trial at highest doses:

  Aβ-PET/CSF, tau/p-tau and NfL CSF
- High levels of ARIA-E/H at highest doses
- Brain-shuttle follow up (Trontinemab)
- 50% reduction in hazard ratio for conversion from preclinical to prodromal/clinical ADAD after 8 years on treatment; those with symptoms delayed by 6 years from EYO

Model of cognitive decline and treatment effects to delay onset of symptoms from Alzheimer's disease by 5 to 15 years

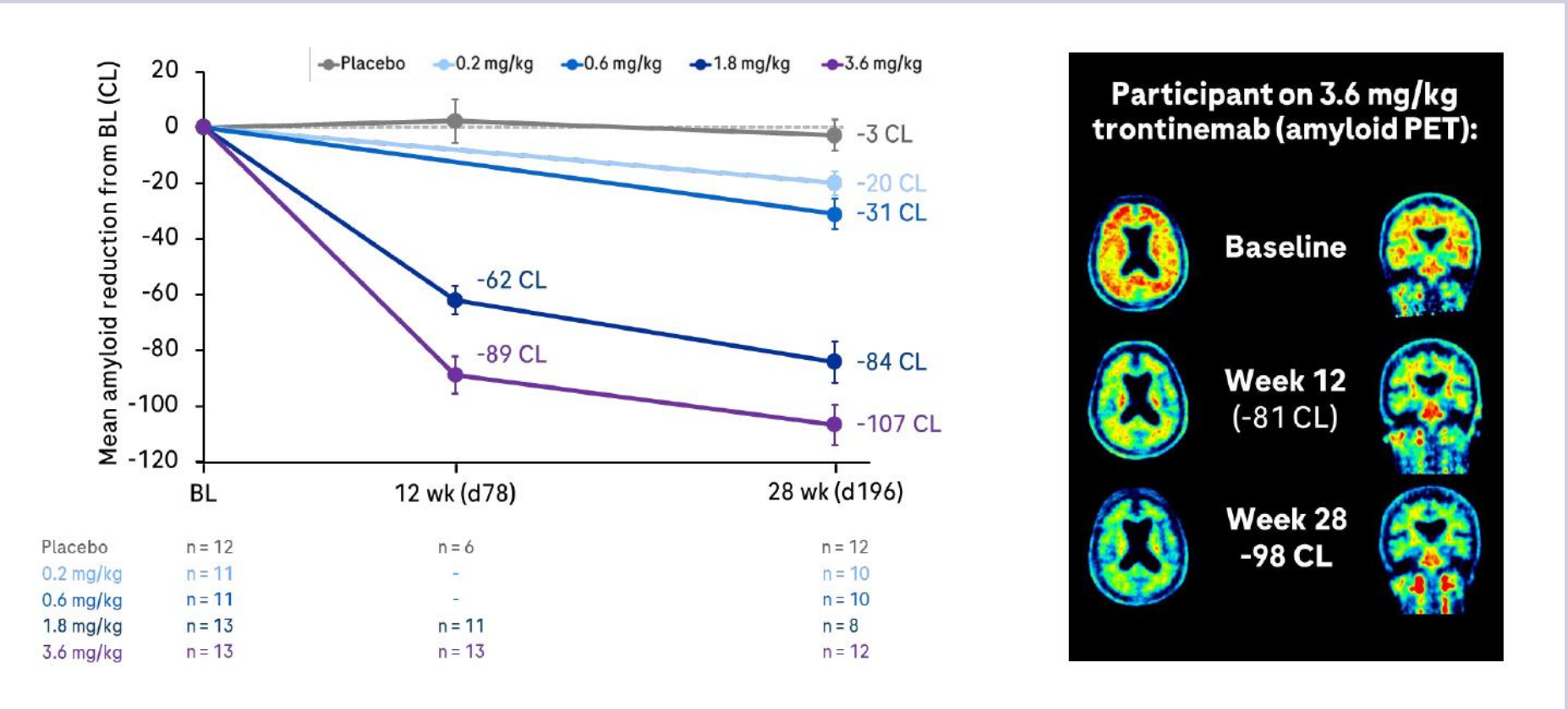


Delay in cognitive decline (Symptomatic Onset) in years from Natural Progression		
% Change in Decline	Proportional Reduction	Delay in Time
50%	5 years	15 years

KNIGHT FAMILY DIAN TU

AAIC July 2024

Trontinemab: Rapid and robust amyloid plaque depletion after 28 weeks of treatment

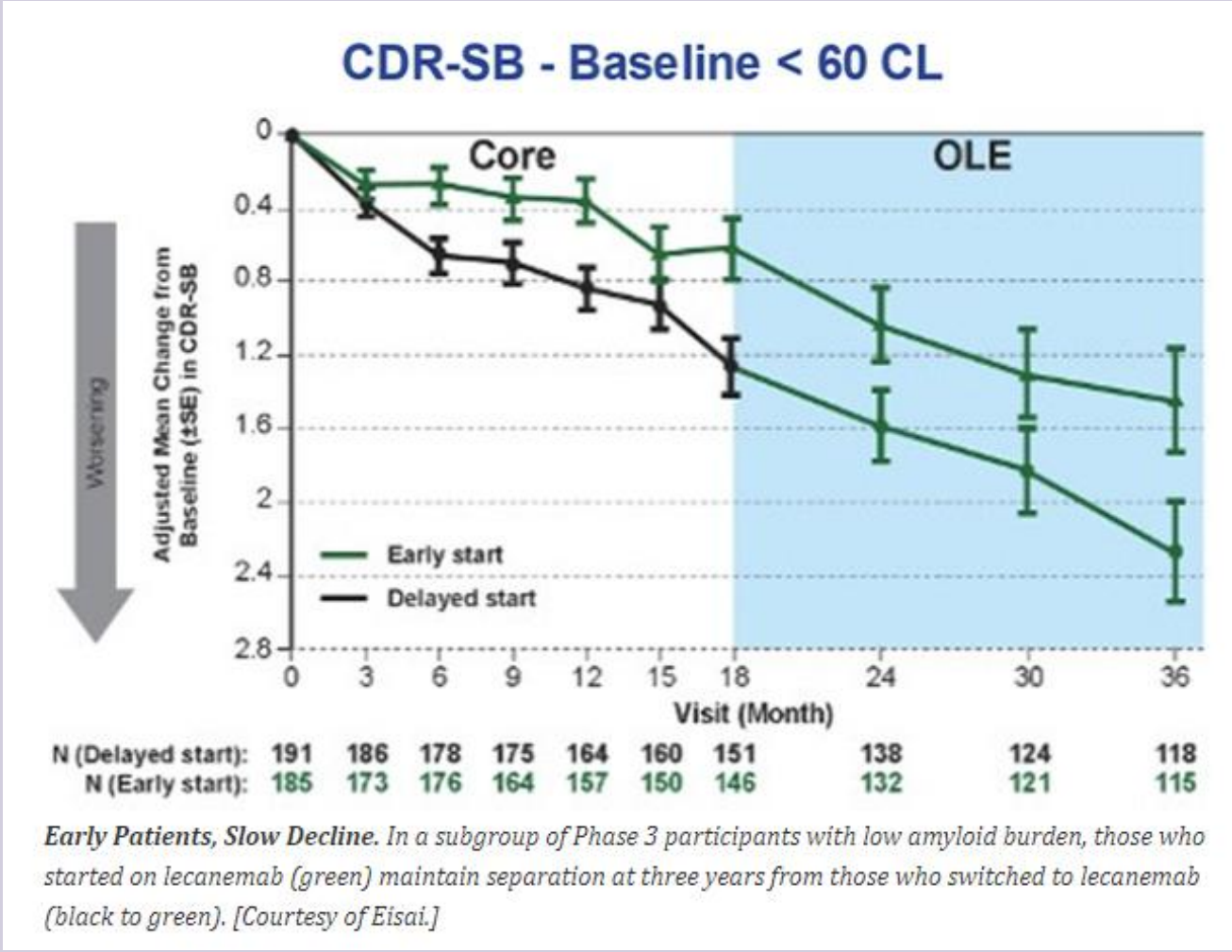


(Kulic, 2024)

Lecanemab (Leqembi; Eisai/BioArctic/Biogen)

- Phase 3 CLARITY study (n=1,795) (December, 2022)
- Reduces Aβ-PET 80%; 80% negative after 12 months
- Extent of Aβ-PET reduction correlates with degree of slowing in cognitive decline, 27% overall and 40% in $E4^-$ subjects (6 months delay); Quality of life 50% slowing
- CSF and plasma biomarkers improved
- ARIA-E 22%, symptomatic 3% (E4- 7%, E4+ 12%, E4++ 35%);
- ARIA-H: macrohemorrhage (2.6% on, and 0.4% off anticoagulants)
- FDA full approval July, 2023; CMS will pay
- AUR: no anticoags, clotting disorders, strokes, seizures
- Low tau-PET subgroup show improving CDR-SB

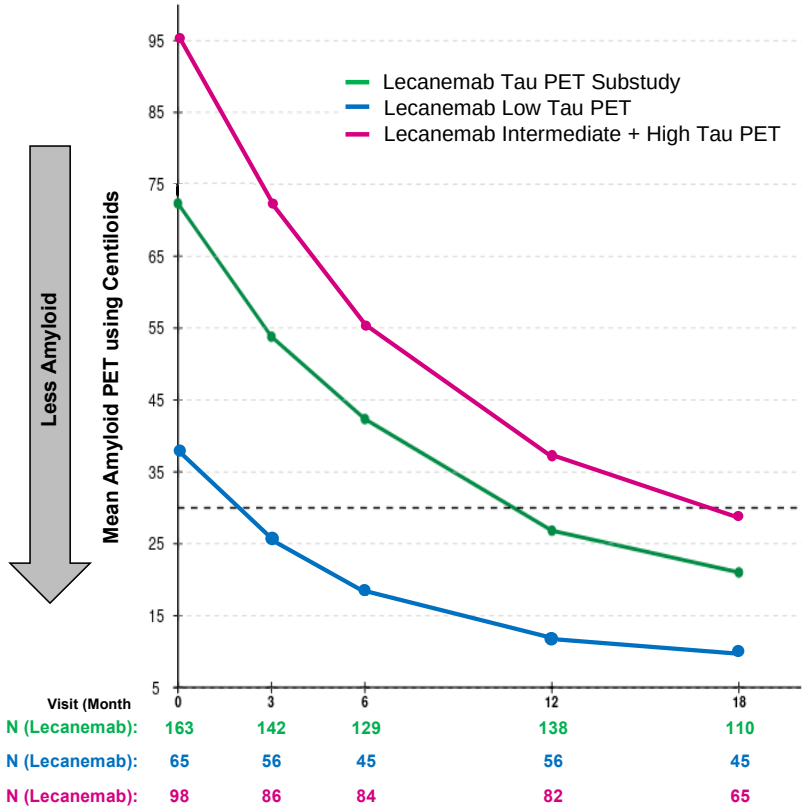
Lecanemab: 14 months gained in early/low amyloid burden



Early Patients, Slow Decline. *In a subgroup of Phase 3 participants with low amyloid burden, those who started on lecanemab (green) maintain separation at three years from those who switched to lecanemab (black to green). [Courtesy of Eisai.]*

Lecanemab Effect on Amyloid in Tau PET Substudy

Consistent Amyloid Reductions for Subgroups Across Clinical Assessments

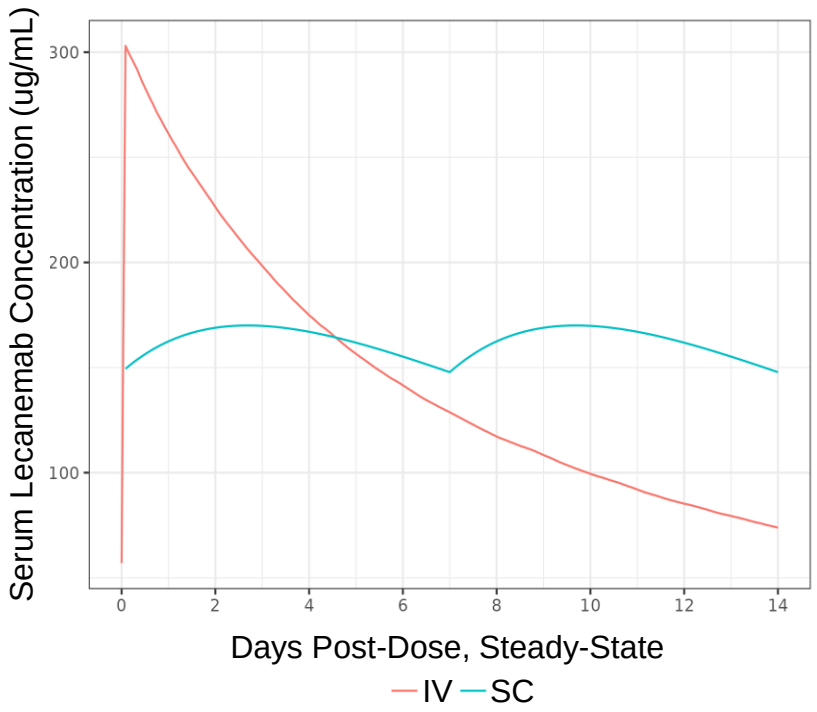


Amyloid PET clearance (% <30 CL) in lecanemab	6m n (%)	12m n (%)	18m n (%)
Tau PET Substudy	48 (37.2)	83 (60.1)	79 (71.8)
Intermediate + High Tau PET	17 (20.2)	35 (42.7)	**37 (56.9)**
Low Tau PET	31 (68.9)	48 (85.7)	**42 (93.3)**

Observed data.
CL, clearance; m, month; PET, positron emission tomography.

Subcutaneous formulation of Lecanemab: Effect of PK Profile on Incidence of ARIA-E

- AUC strongly predicted amyloid lowering
- Exposure-safety analyses based on IV in our Phase 2 and 3 trials (red line) found that lecanemab exposure (as $C_{max,ss}$, AUC_{ss}, $C_{min,ss}$) was correlated with ARIA-E
- **Of these predictors, $C_{max,ss}$ was strongest predictor of ARIA-E incidence following IV administration**
- SC lecanemab results in minimal fluctuations between $C_{max,ss}$ and $C_{min,ss,}$ which is further influenced by more frequent dosing (weekly) compared to IV (biweekly)
- **Thus, following SC administration, AUC_{ss}, a more representative exposure parameter of a flat PK profile, may be a better predictor of incidence of ARIA-E**



Based on PK modeling

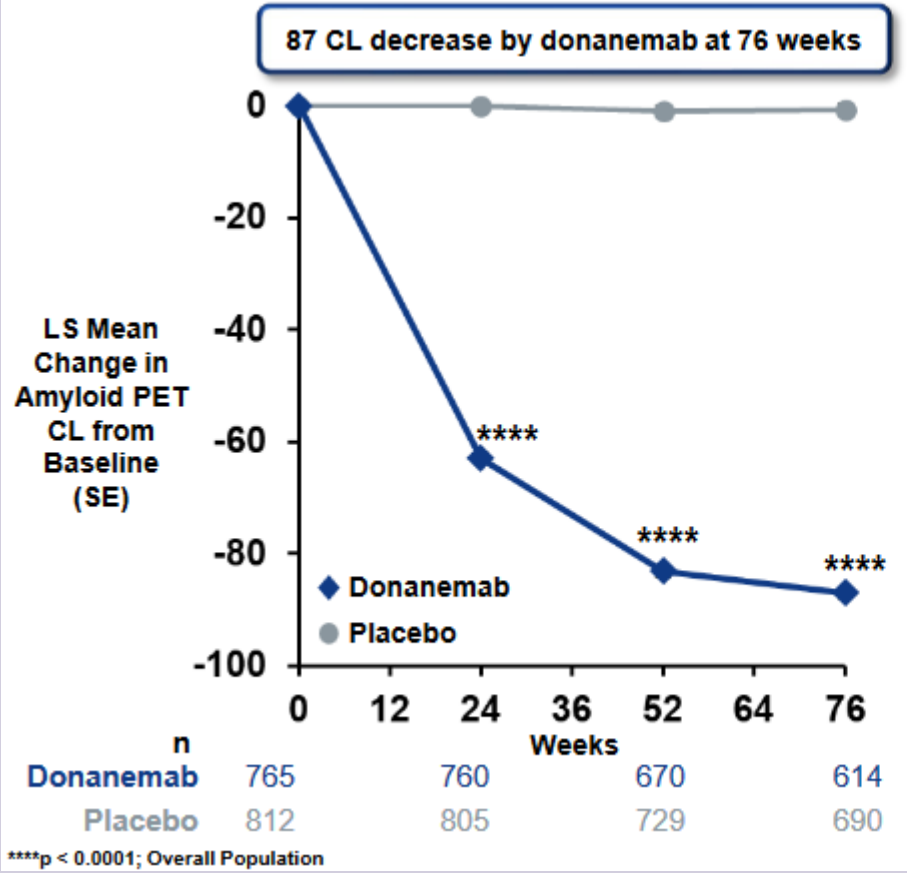
ARIA-E, amyloid related imaging abnormalities - edema; AUC_{ss}, area under the curve at steady state; Cmax,ss, maximum concentration at steady state; Cmin,ss, minimum concentration at steady state; IV, intravenous; PET, positron emission tomography; SC, subcutaneous.

Eisai website

Donanemab (Trailblazer Alz2, Lilly)

- 700 to 1400mg/month, IV, 72 weeks
- @12mth, 50% “neg” PET (10-25 CL), dosing ceased
- Mean baseline 100CL reduced 88%
- Significant relationship of Aβ lowering and slowing of clinical decline: 36% CDR-SB in low/med tau+ group; 50-60% slowing in milder cases
- 47% no progression of CDR-SB at 1 year, compared to 29% placebo; subjects 2 years less advanced 88% slowing, 2 years more advanced 6% slowing
- 40% lowering of plasma p-tau217, 20% GFAP
- p-tau181 reflects clearance at 24 weeks
- ARIA-E: 24% (6% symptoms; 1.5% serious); ARIA-H only if ARIA-E
- Trailblazer Alz5 (April ’27)

Amyloid reduction and effect in disease-relevant biomarkers supported donanemab use in all baseline tau participant groups

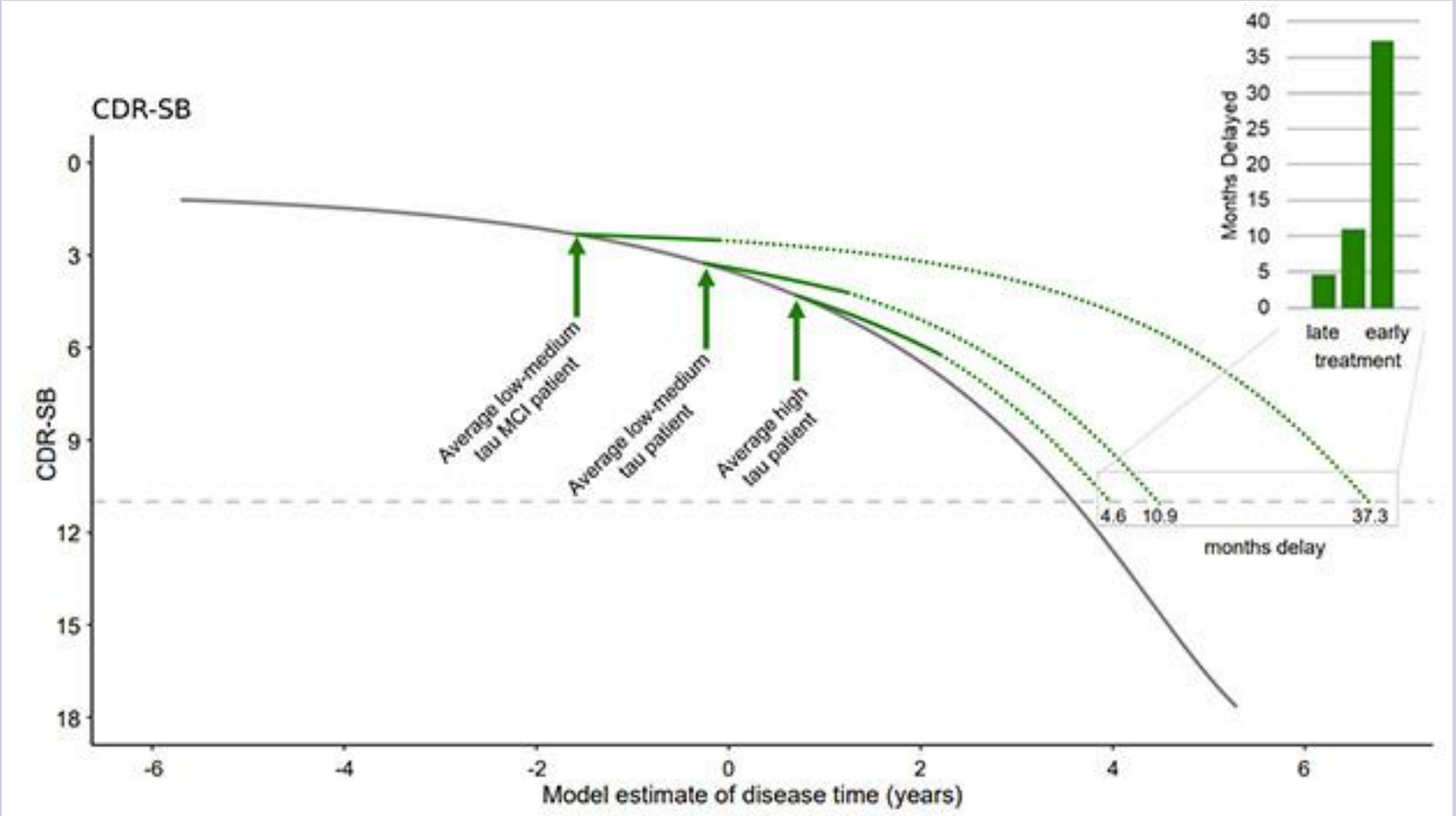


Percent* change from baseline at 76 weeks	No / Very-Low Tau† N (195-203)	Low – Medium Tau N (395-433)	High Tau N (173-181)
Amyloid reduction	86%	85%	80%
P-tau217 reduction	56%	39%	33%
GFAP reduction	22%	21%	18%

*Percentages are based on estimated mean changes from MMRM analyses
† Data from TRAILBLAZER-ALZ 2 addendum, which collected biomarker and safety data in amyloid positive participants and included participants with no/very low tau.

Abbreviations: CL = Centiloids; GFAP = glial fibrillary acidic protein; LS = least square; MMRM = mixed model repeated measures; N, n = number of participants; PET = positron emission tomography; P-tau217 = phosphorylated tau217; SE = standard error

A model based on Phase 3 donanemab data predicts that treatment effects will be greater in people who start at an earlier disease stage



Mcab passive immunotherapy learnings so far

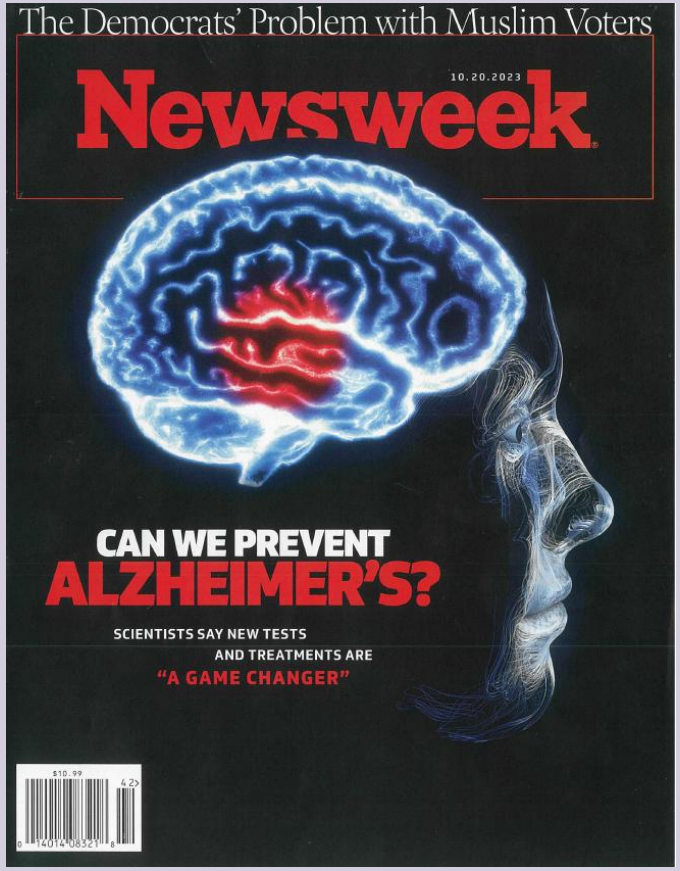
- Go early, drive Aβ-PET to baseline
- Higher exposure, faster clearance, better outcomes
- Lower baseline Aβ and tau (before neocortical spread) have better outcomes, even reversing cognitive impairments
- Proof of concept that Aβ-lowering prevents/delays onset

Strategies for prevention (primary and secondary): Asymptomatic: (preclinical cognitive learning deficit; biofluid biomarker positive; genetic risk [*APOE*, PRS])

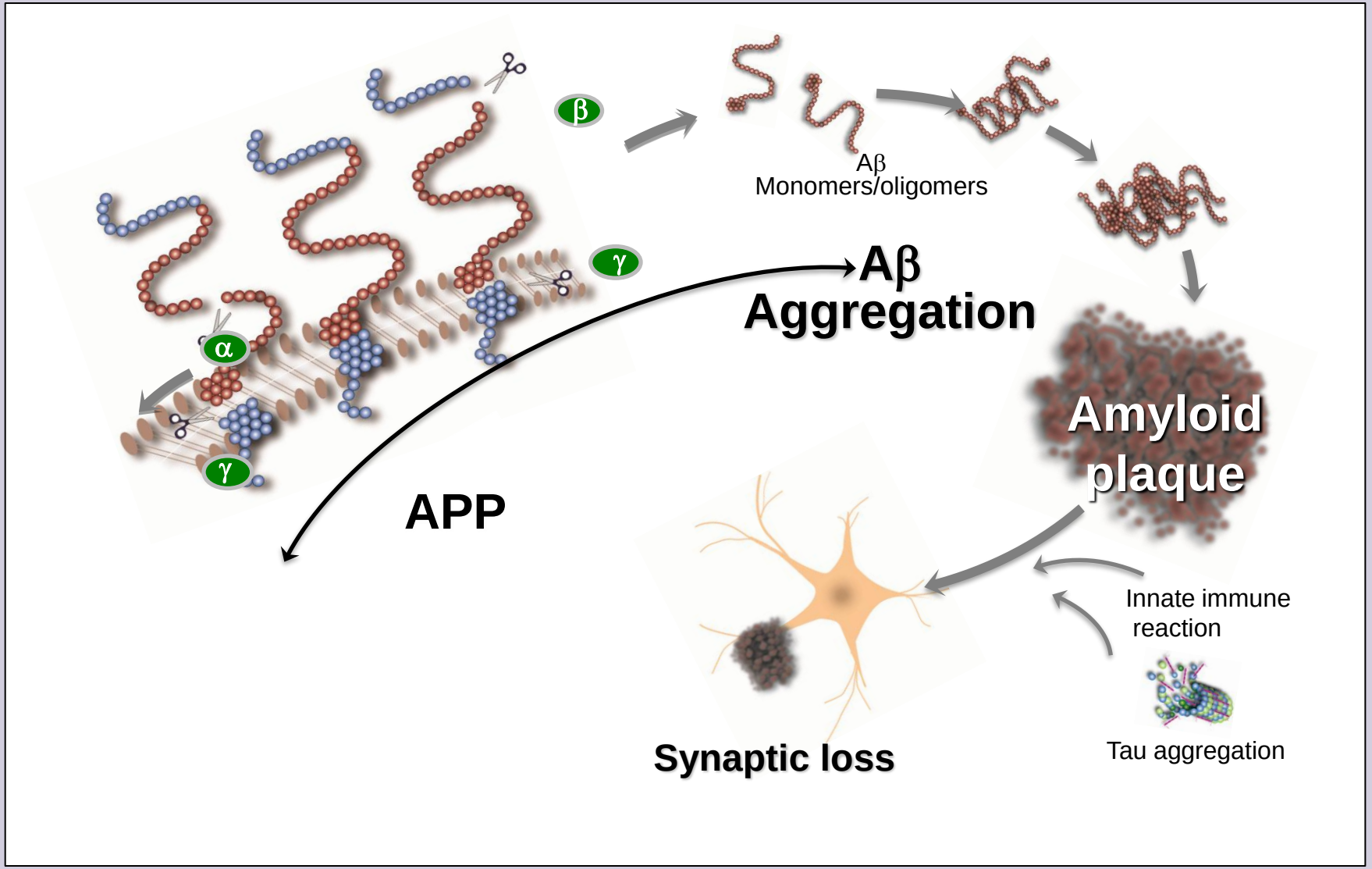
Secondary prevention, determined by cognitive (learning) and biofluid/PET markers: similar strategies as for symptomatic AD.

Primary prevention, low dose inhibition of production/aggregation if genetic risk factors present.

Pharma spent US$600b 1999-2023 (Newsweek, October 20, 2023)



Step 7. A unified and coherent theory of Aβ the etiology of AD is formulated.



From little things, big things grow (Kelly and Carmody 1991)

ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

AIBL Study team:

Alex Barac	Eugene Hone	Steph Rainey-Smith	Rob Williams
Pierrick Bourgeat	Fiona Lamb	Jo Robertson	Michael Woodward
Sveltana Bozinovski	Simon Laws	Mark Rodrigues	Paul Yates
Belinda Brown	Hugo Leroux	Christopher Rowe	George Zisis
Lesley Cheng	Qiao-Xin Li	Rebecca Rumble	
Steven Collins	Florence Lim	Greg Savage	
Tim Cox	Lucy Lim	KaiKai Shen	
James Doecke	Lucy Mackintosh	Brendan Silbert	
Vincent Dore	Ralph Martins	Harmid Sohrabi	
Denise El-Sheikh	Paul Maruff	Kevin Taddei	
Binosha Fernando	Colin Masters	Tania Taddei	
Christopher Fowler	Simon McBride	Christine Thai	
Jurgen Fripp	Tash Mitchell	Brett Trounson	
Sam Gardener	Steve Pedrini	Regan Tyrell	
Simon Gibson	Kelly Pertile	Larry Ward	
Rodney Guzman	Tenielle Porter	Mike Weinborn	

AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au

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The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

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CRC for Mental Health
AUSTRALIA ECU EDITH COWAN UNIVERSITY
Austin Health
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YULGILBAR The Yulgilbar Foundation

Collaborators

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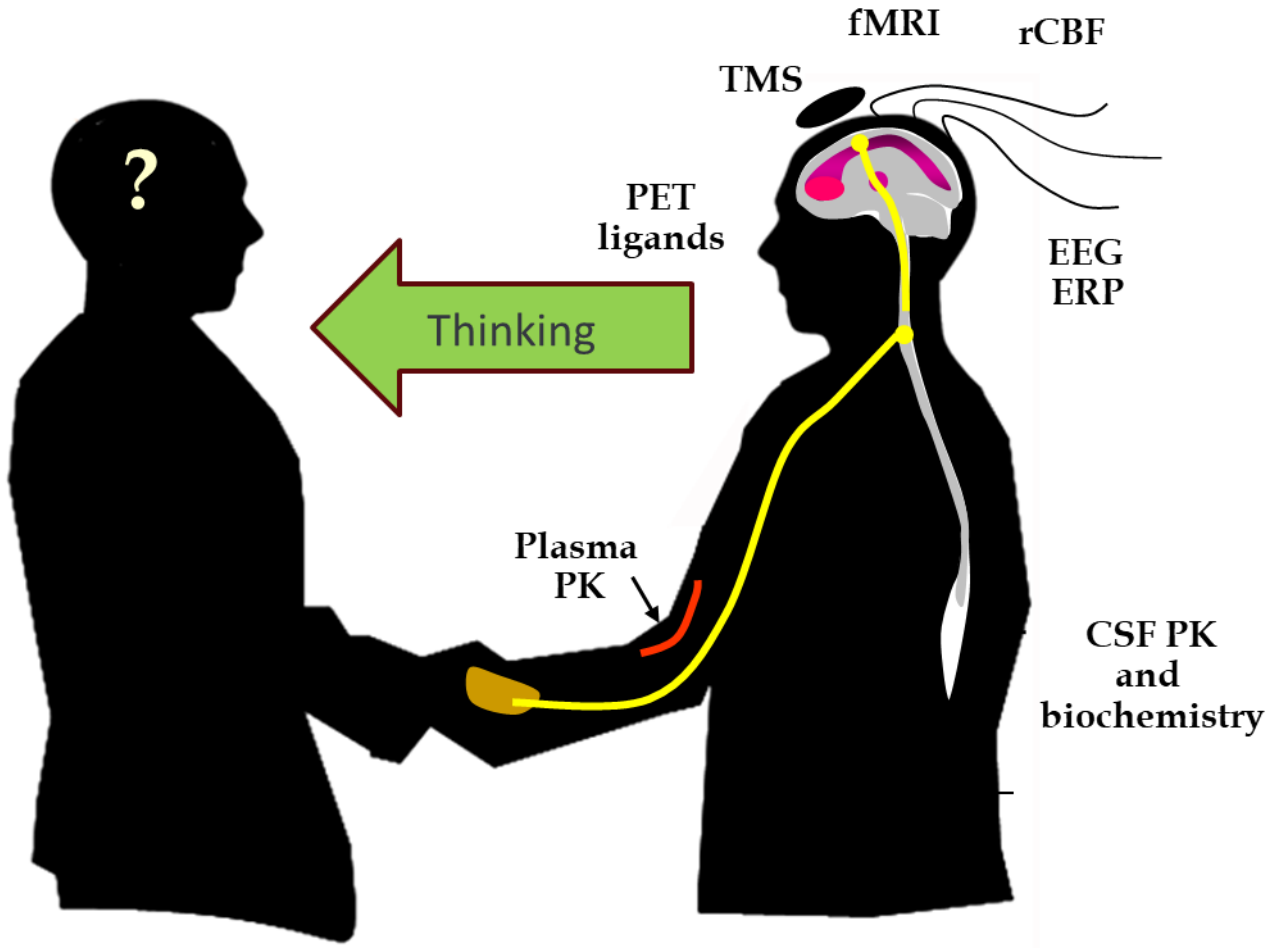
THE UNIVERSITY OF WESTERN AUSTRALIA
DCRC Dementia Collaborative Research Centres
janssen
Pfizer
Alzheimer's Australia Living with dementia
Navidea BIOPHARMACEUTICALS

How cognitive and clinical data from AIBL has influenced clinical trial design

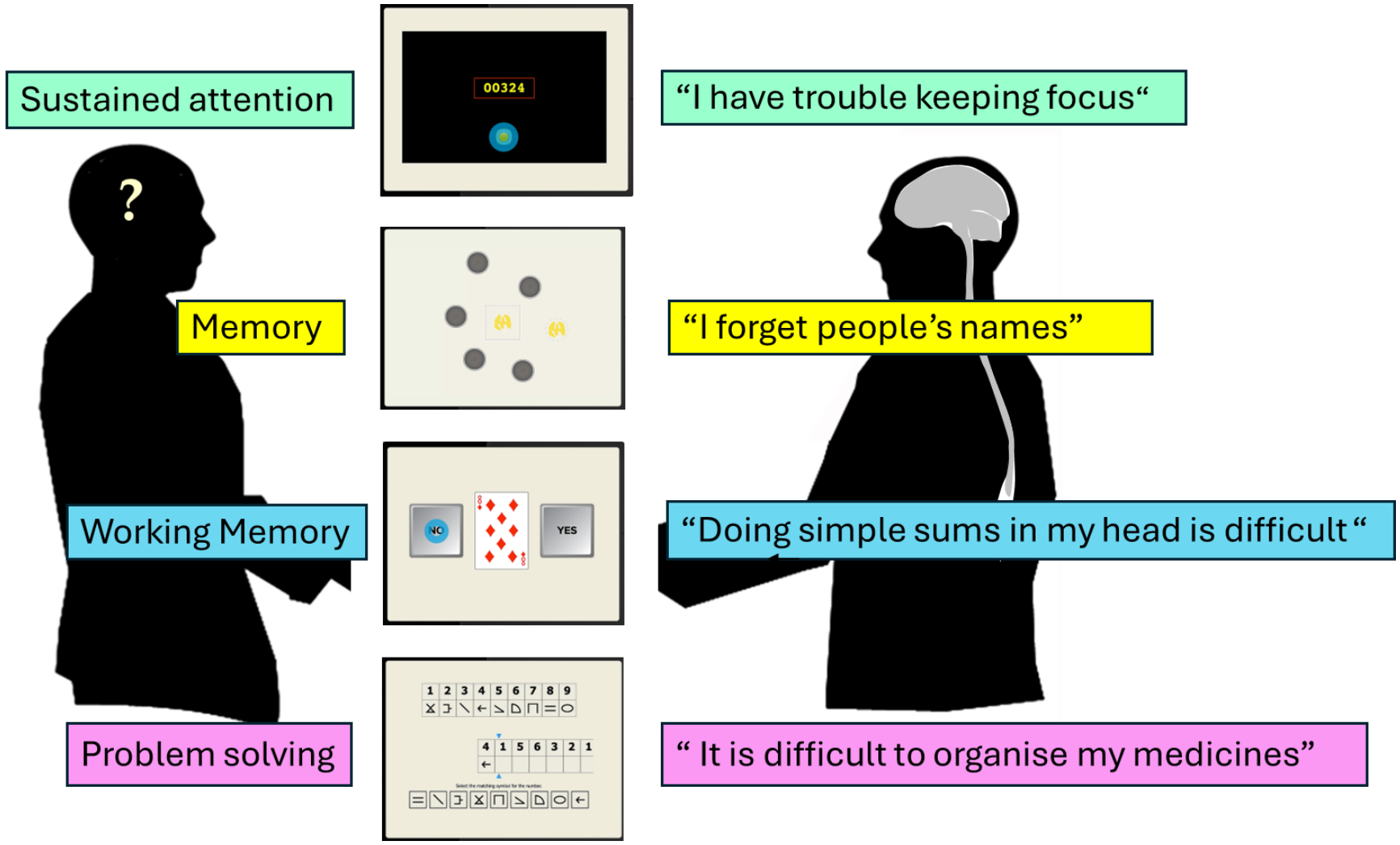
Paul Maruff

On behalf of the AIBL clinical group, and the AIBL study

Clinical and cognitive (thinking) symptoms are expressions of Alzheimer's disease



To assess thinking we ask, and we measure



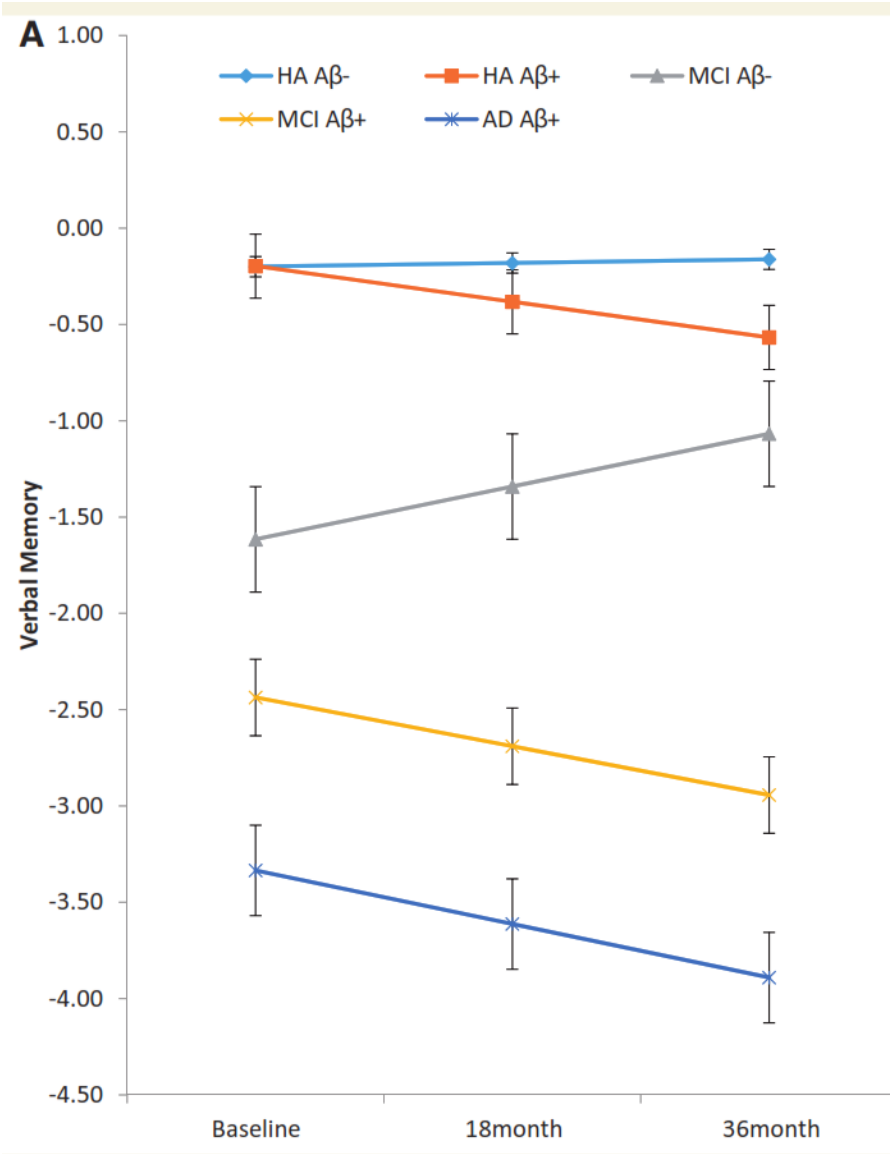
THEN: First detailed model of association between brain amyloid level and cognitive decline was from AIBL

doi:10.1093/brain/awt286 Brain 2013: Page 1 of 11 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease

Yen Ying Lim,[1] Paul Maruff,[1,2] Robert H. Pietrzak,[3] David Ames,[4,5] Kathryn A. Ellis,[1,4,5] Karra Harrington,[1] Nicola T. Lautenschlager,[4,6] Cassandra Szoeke,[5,7] Ralph N. Martins,[8] Colin L. Masters,[1] Victor L. Villemagne[1,9,10] and Christopher C. Rowe[9,10], for the AIBL Research Group



NOW: There are two drugs that interfere with amyloid approved for the treatment of Alzheimer's disease

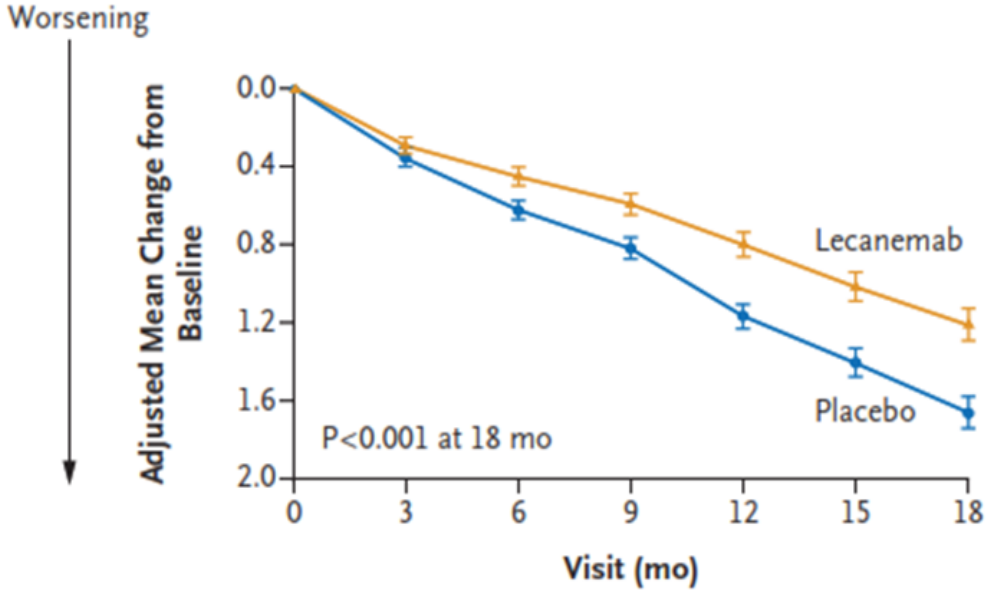
Approved Jan 2023

ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

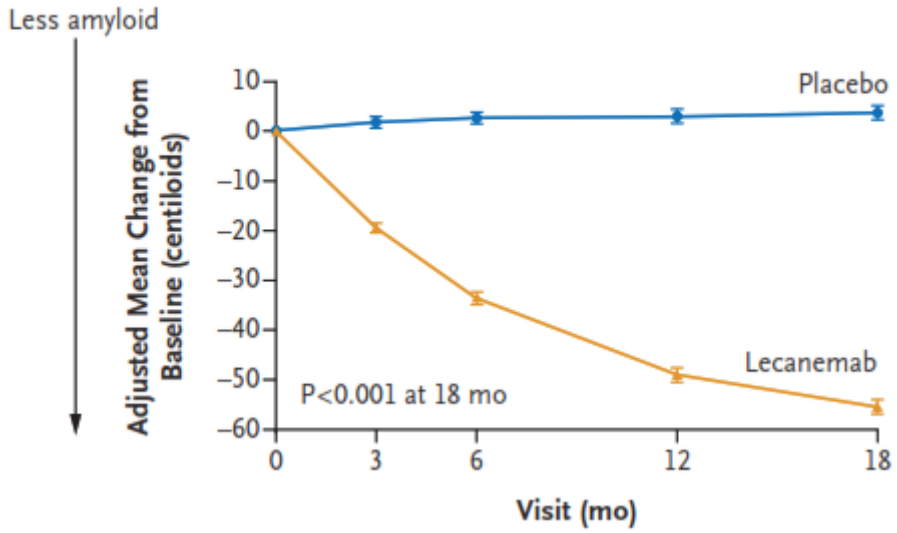
CDR-sum of boxes



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

B Amyloid Burden on PET



There are now drugs that interfere with amyloid approved for the treatment of Alzheimer's disease

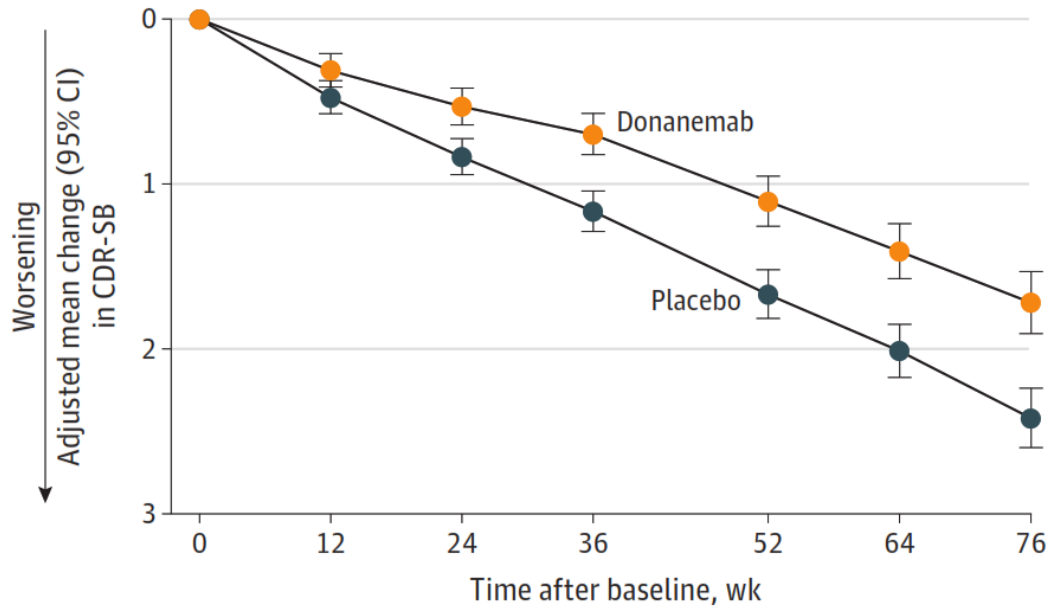
JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

Approved July 2024

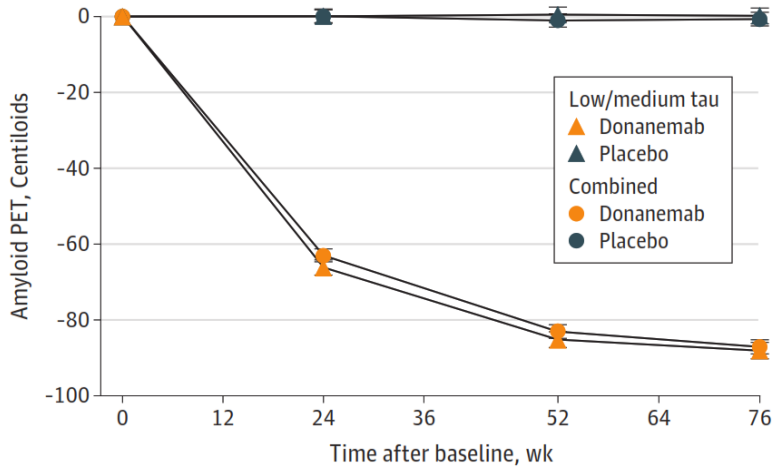
D CDR-SB in combined population



No. of participants

Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

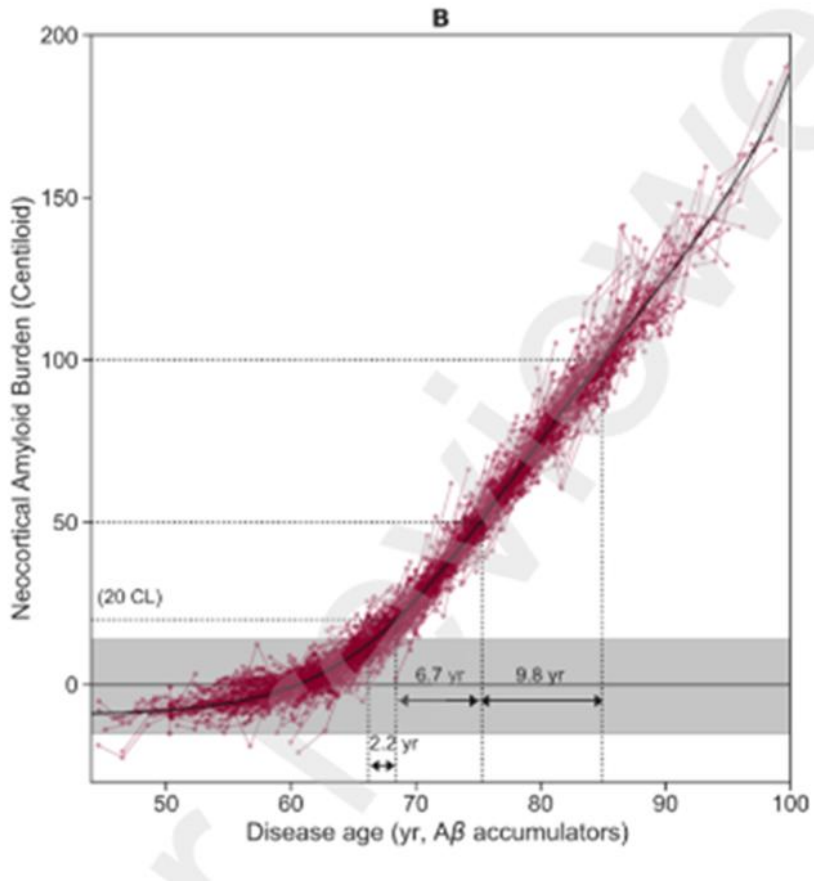
A Adjusted mean change (95% CI) in amyloid PET

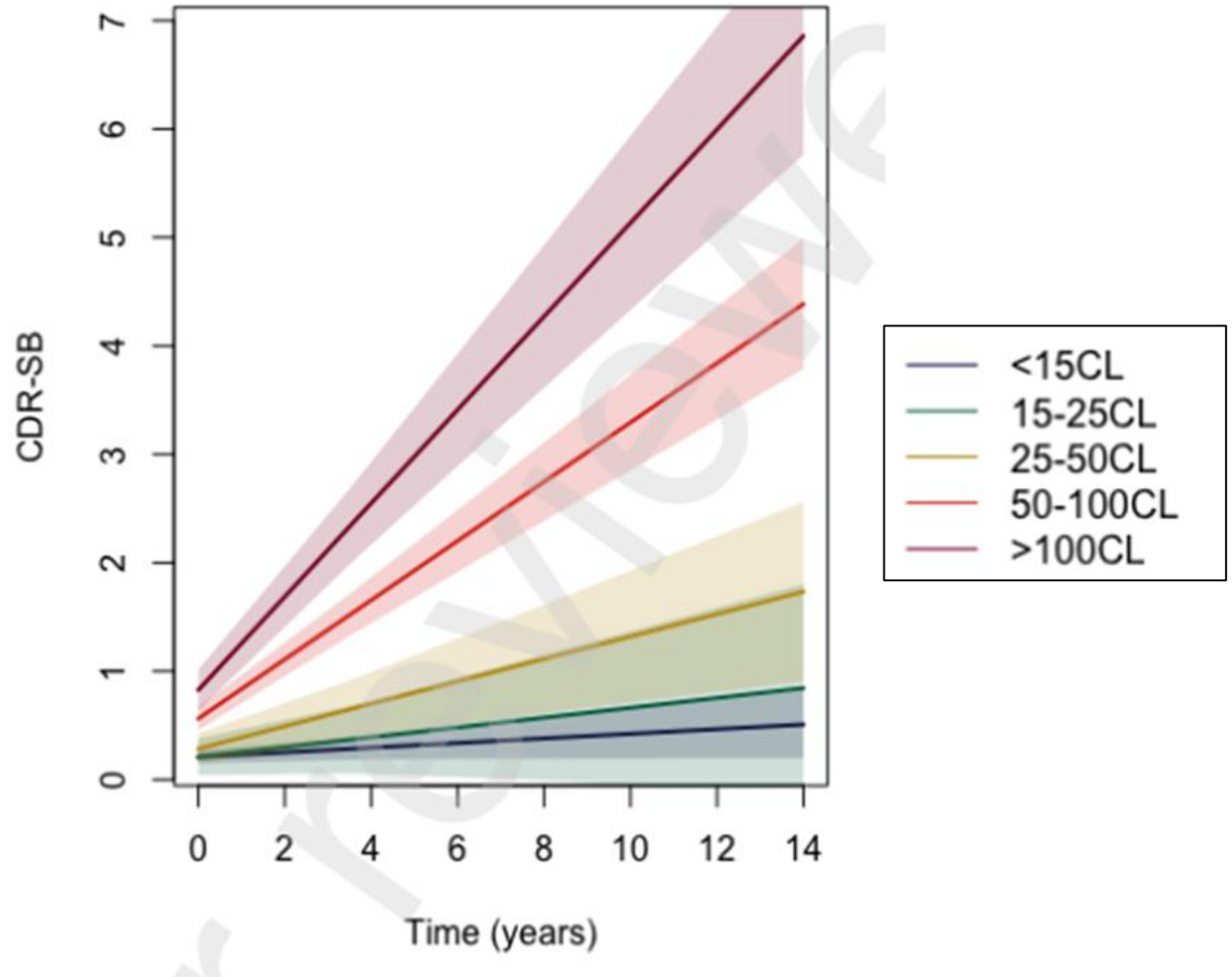


The clinical outcome used to decide that new drugs were efficacious was the clinical dementia rating scale (CDR)

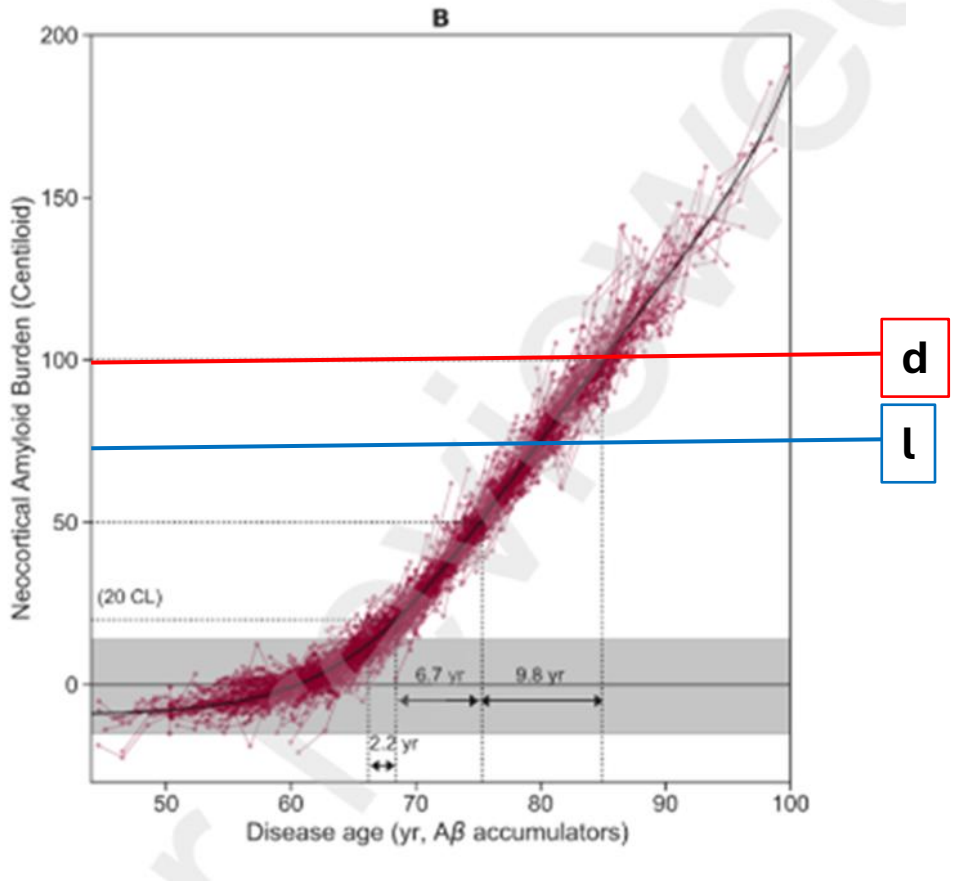
	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home

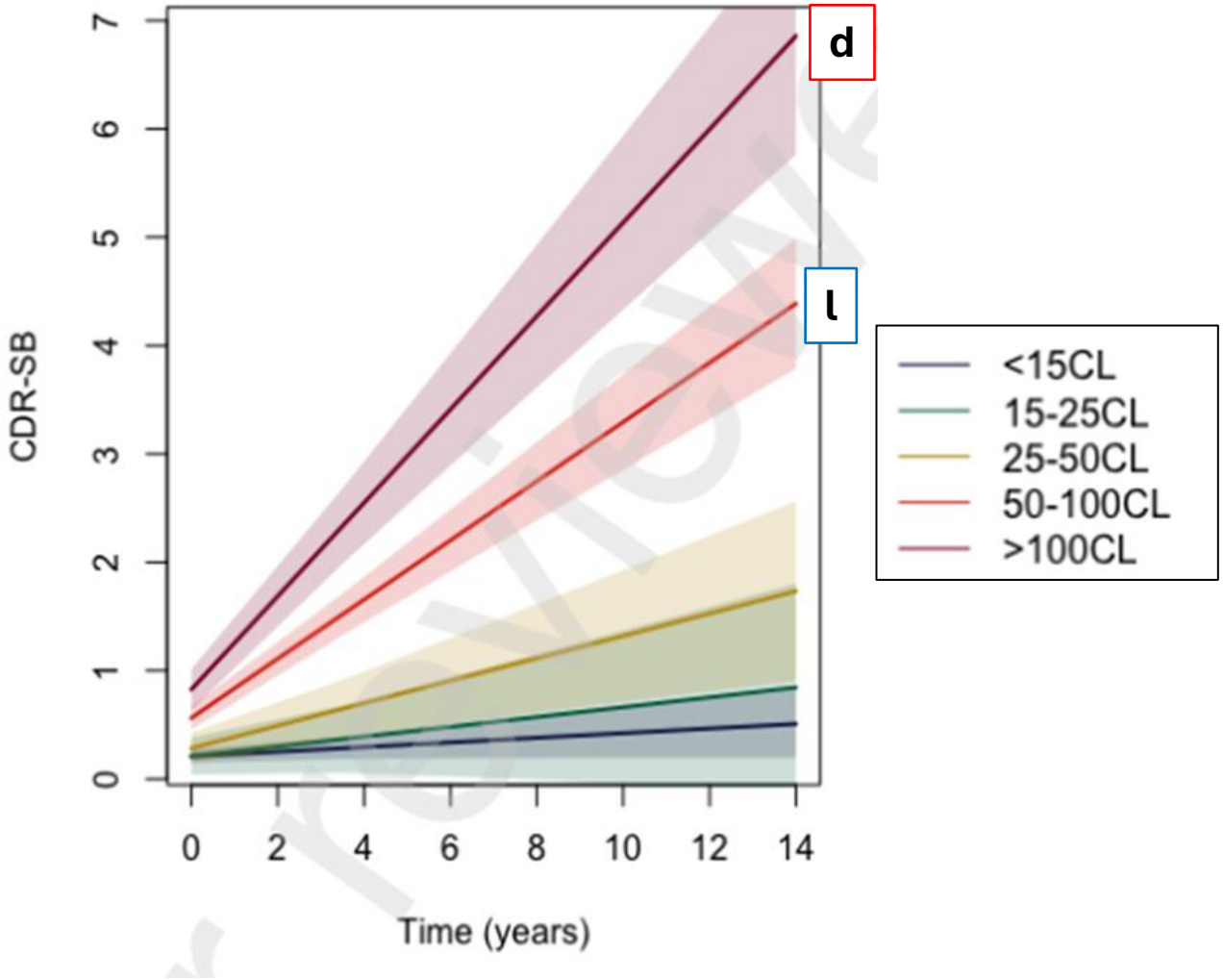
Modelling relationship between clinical and biological aspects of Alzheimer's disease in AIBL



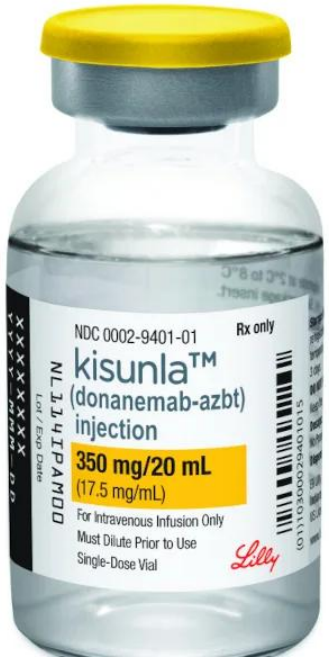


Modelling relationship between clinical and biological aspects of Alzheimer's disease in AIBL

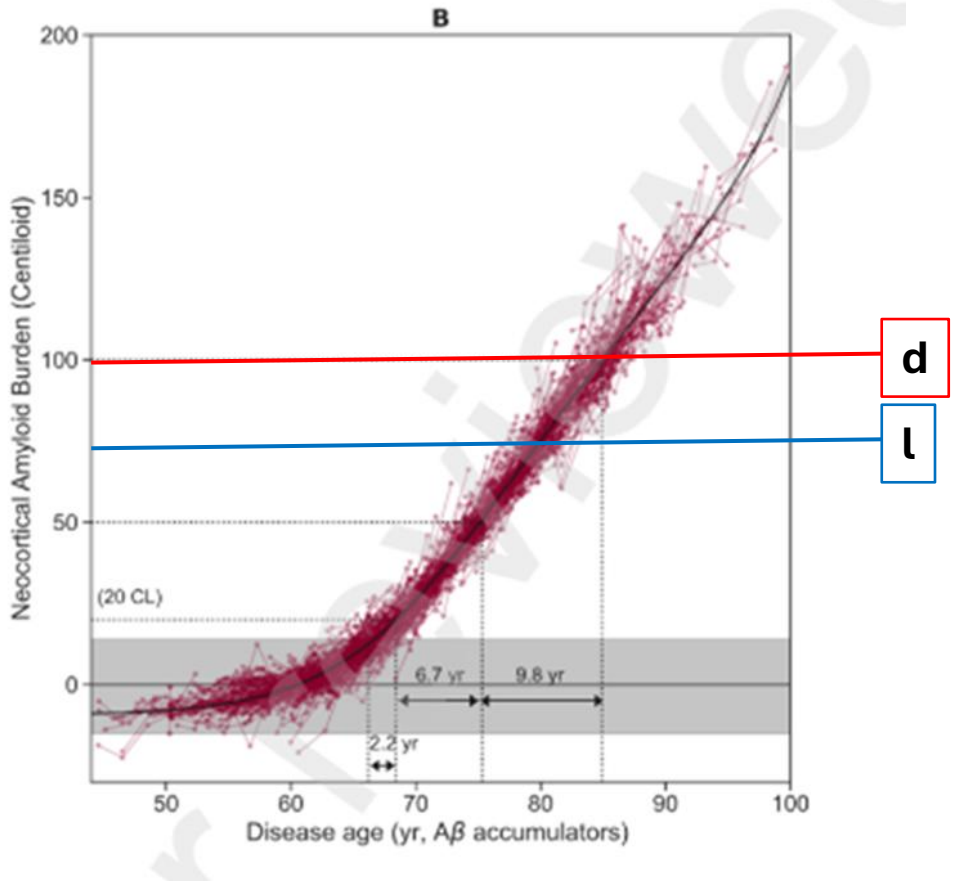


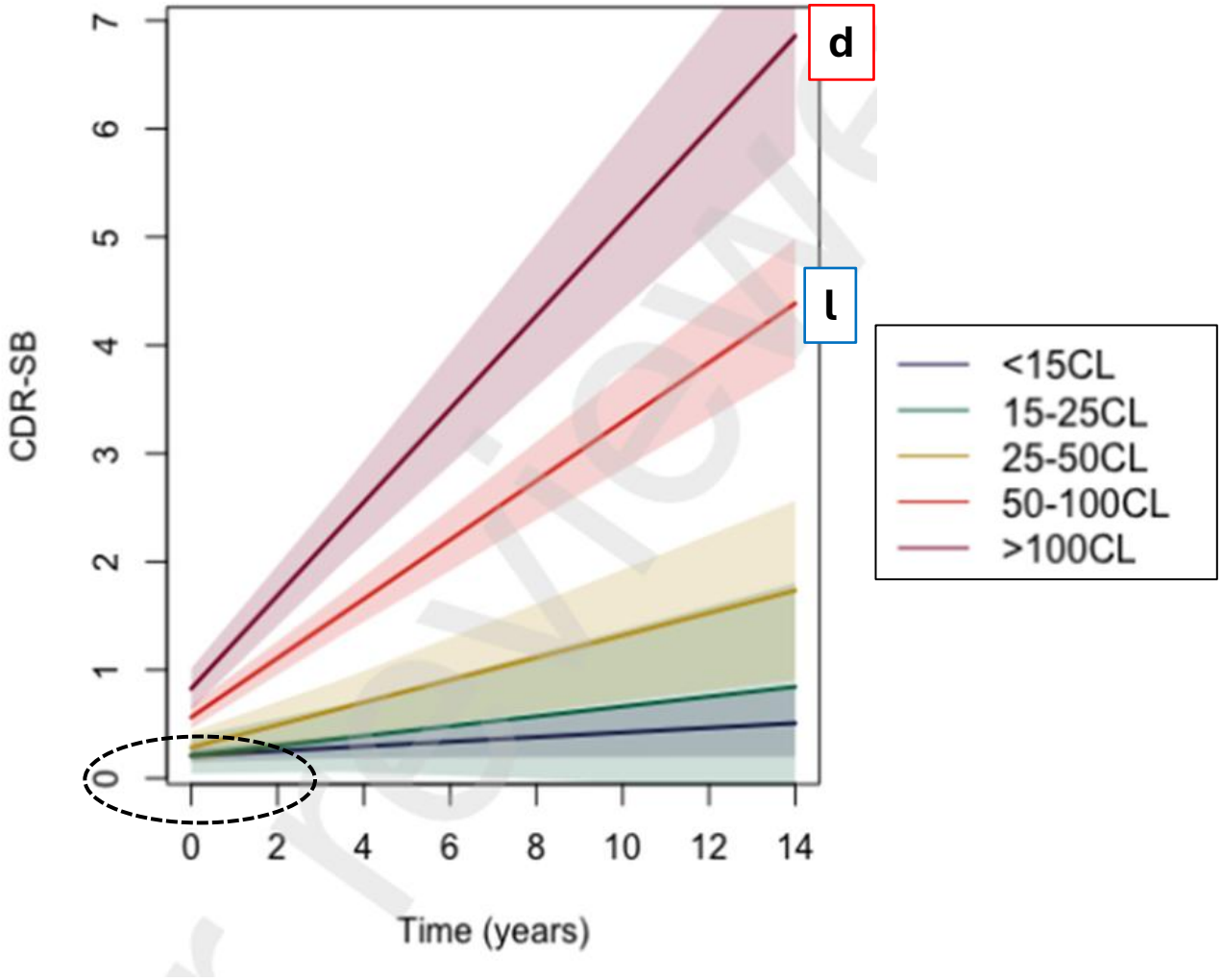


Two drugs approved by FDA, more to come.

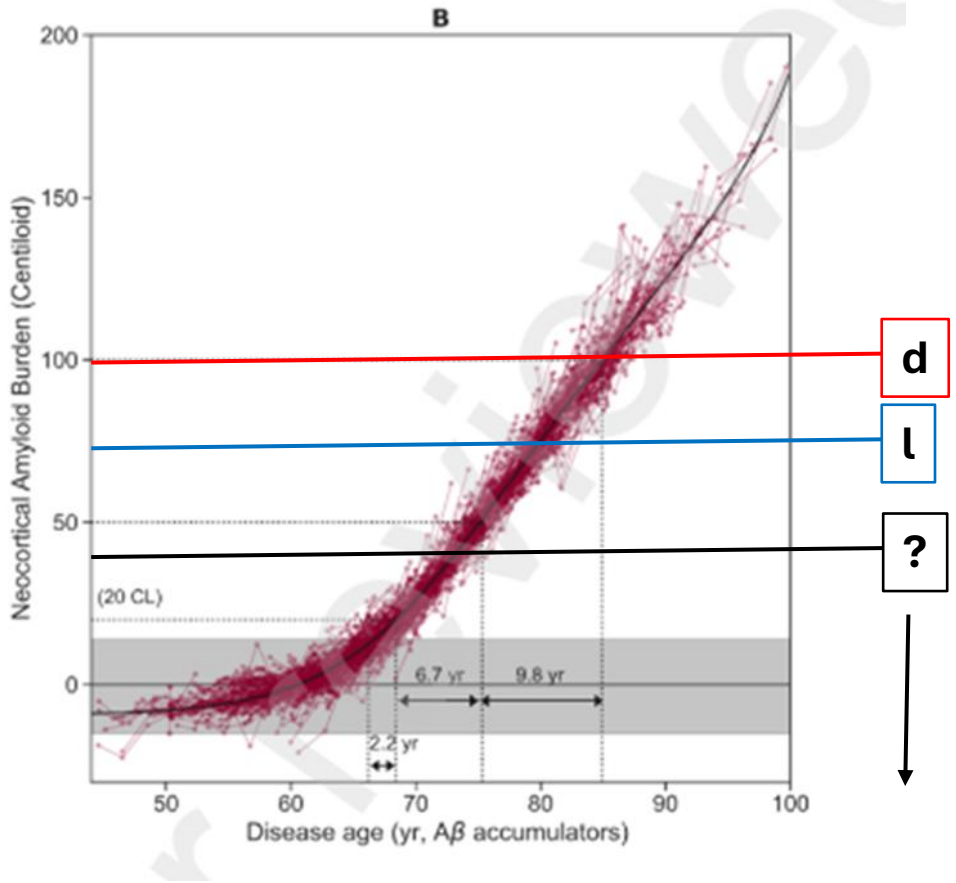


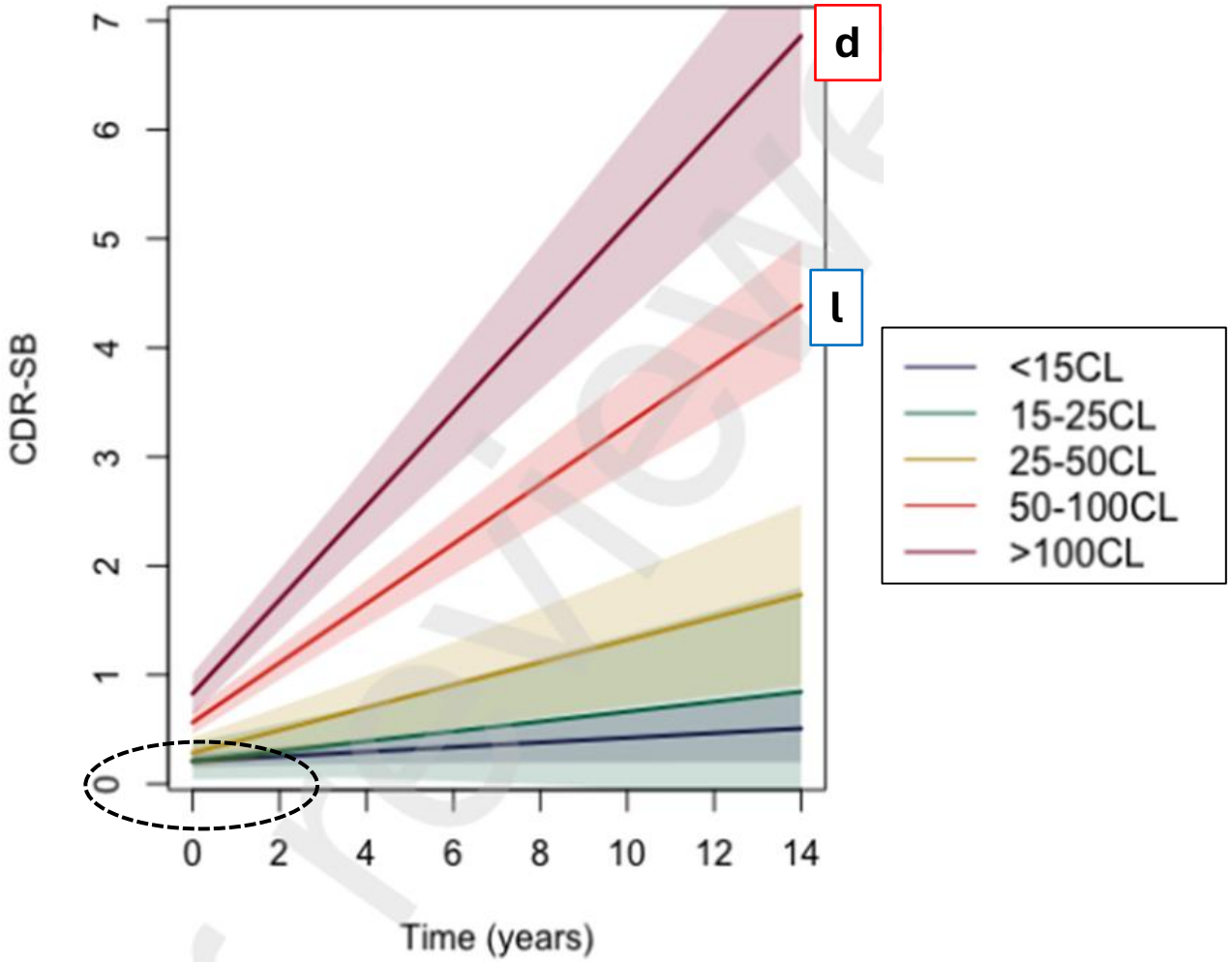
Modelling relationship between clinical and biological aspects of Alzheimer's disease in AIBL



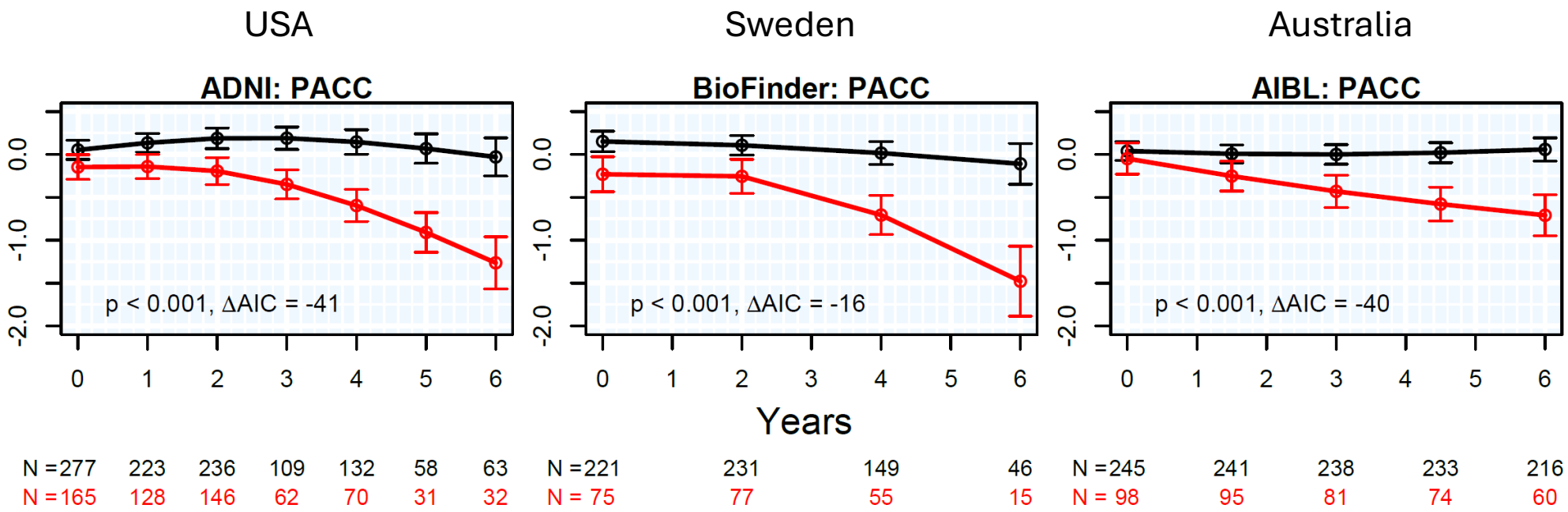


Modelling relationship between clinical and biological aspects of Alzheimer's disease in AIBL





Alzheimer's disease without symptoms – preclinical AD



Insel et al Neurology 2019

PACC: Examples of the assessments you have done over the years that contribute to this outcome

LIST A	1	2	3	4	5
DRUM					
CURTAIN					
BELL					
COFFEE					
SCHOOL					
PARENT					
MOON					
GARDEN					
HAT					
FARMER					
NOSE					
TURKEY					
COLOR					
HOUSE					
RIVER					
SCORE					

Memory for Lists

Maria's / child / Ricky / played / soccer / every / Monday /

at 3:30. / He / liked / going / to the field / behind / their / house /

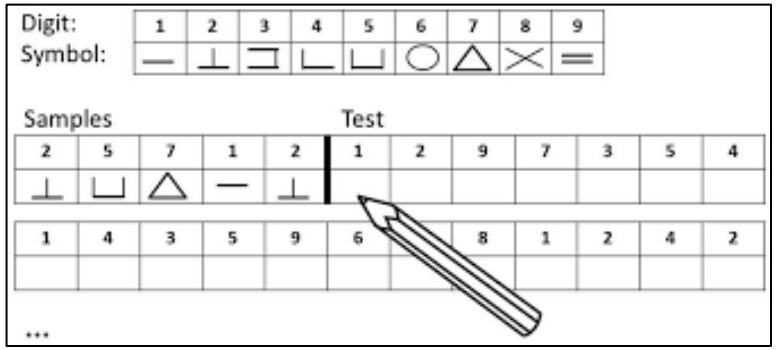
and joining / the game. / One / day, / he / kicked / the ball / so / hard /

that it / went / over / the neighbor's / fence / where three / large /

dogs / lived. / The dogs' / owner / heard / loud / barking, / came /

out, / and helped / them / retrieve / the ball.

Memory for stories



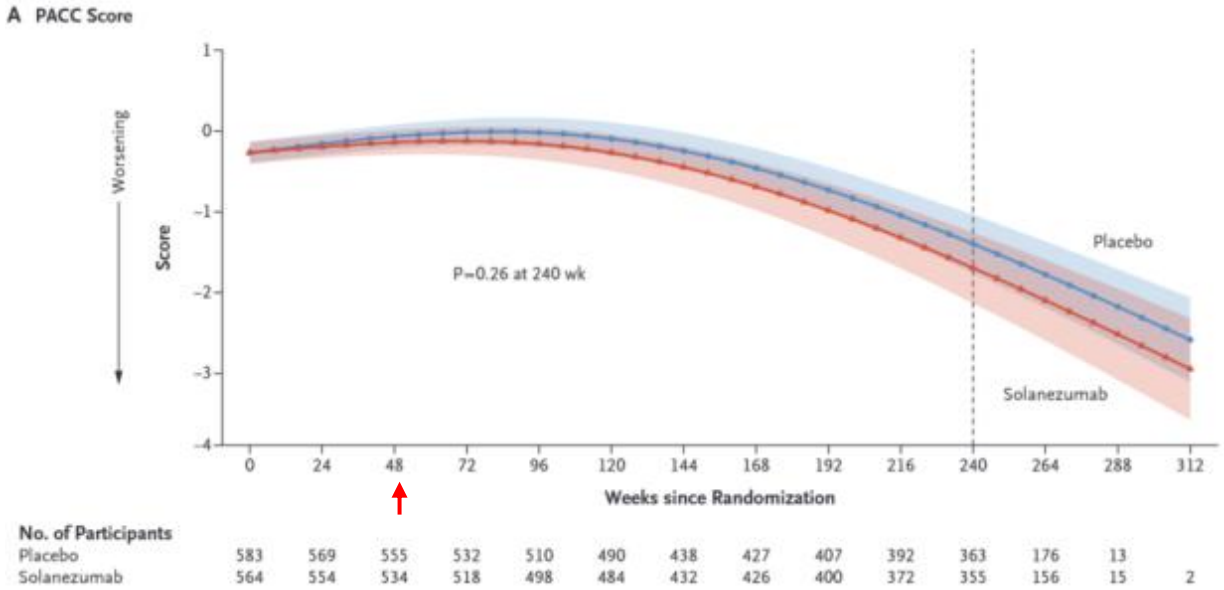
Pattern matching

"As many animals as you can think of"

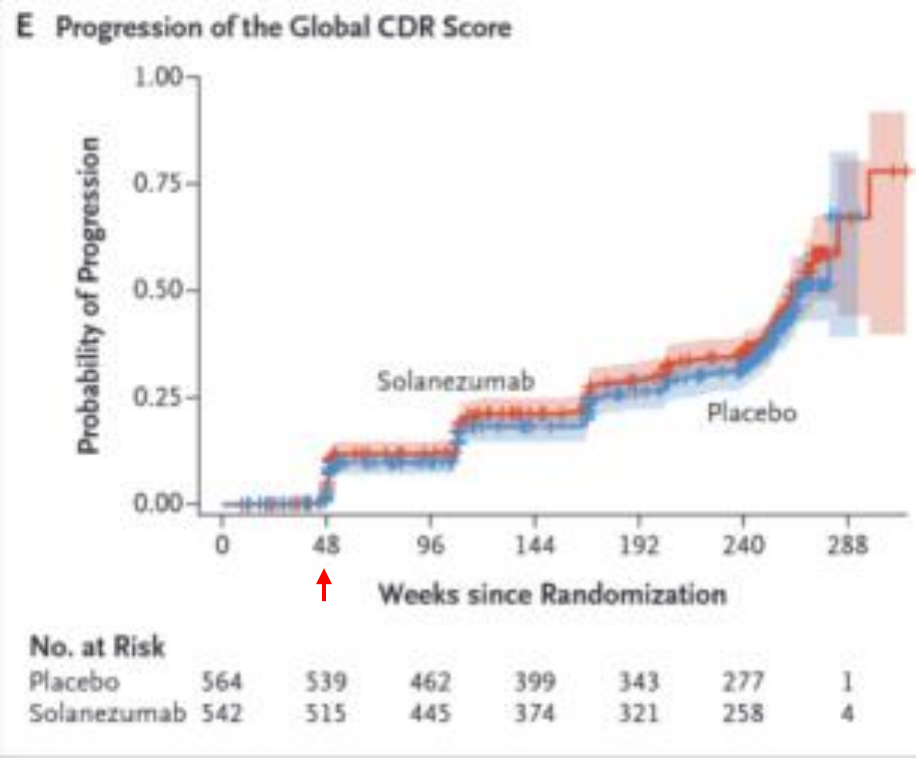
Novelty generation

The first study investigating whether amyloid accumulation could be stopped before symptoms. (FAILED)

The A4 Study
NOW IS THE TIME | LEARN



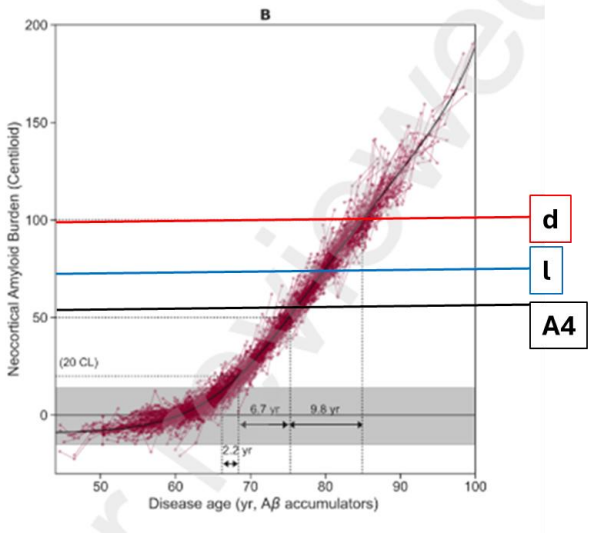
No decline in PACC score at one year



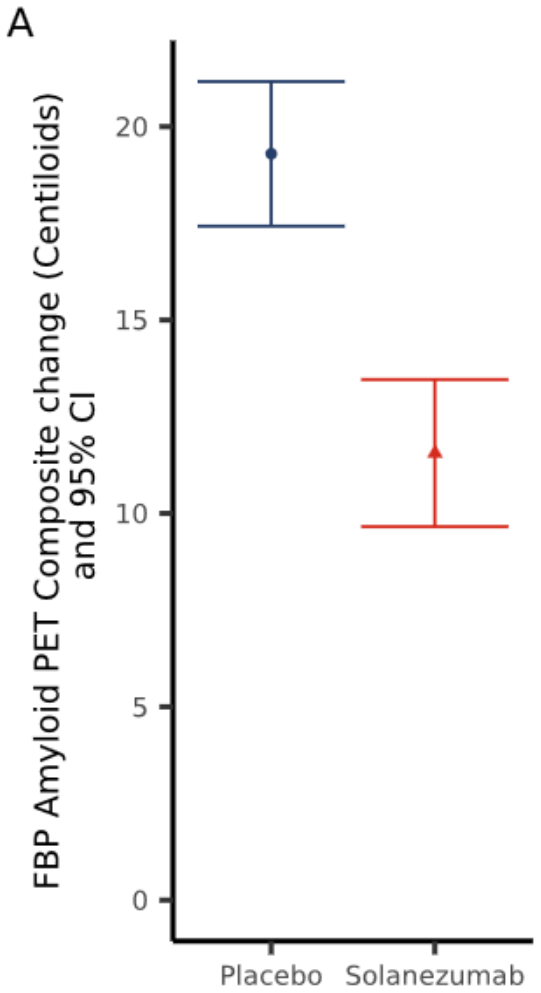
~10% progression to MCI at one year

Sperling et al NEJM 2023

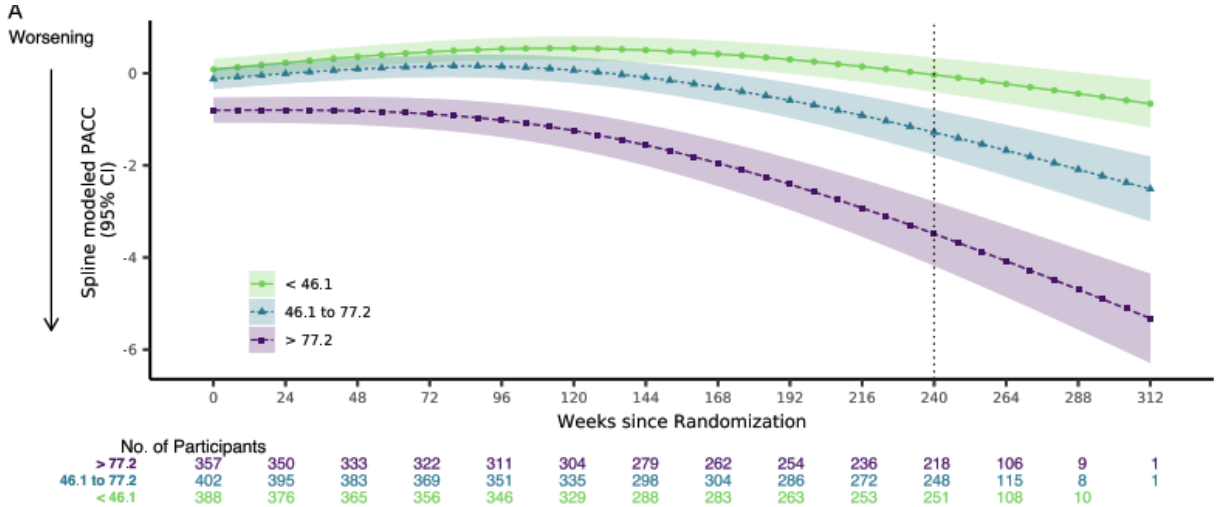
This is most likely that the drug was not effective, rather than the hypothesis was incorrect



Despite being asymptomatic amyloid levels were very high

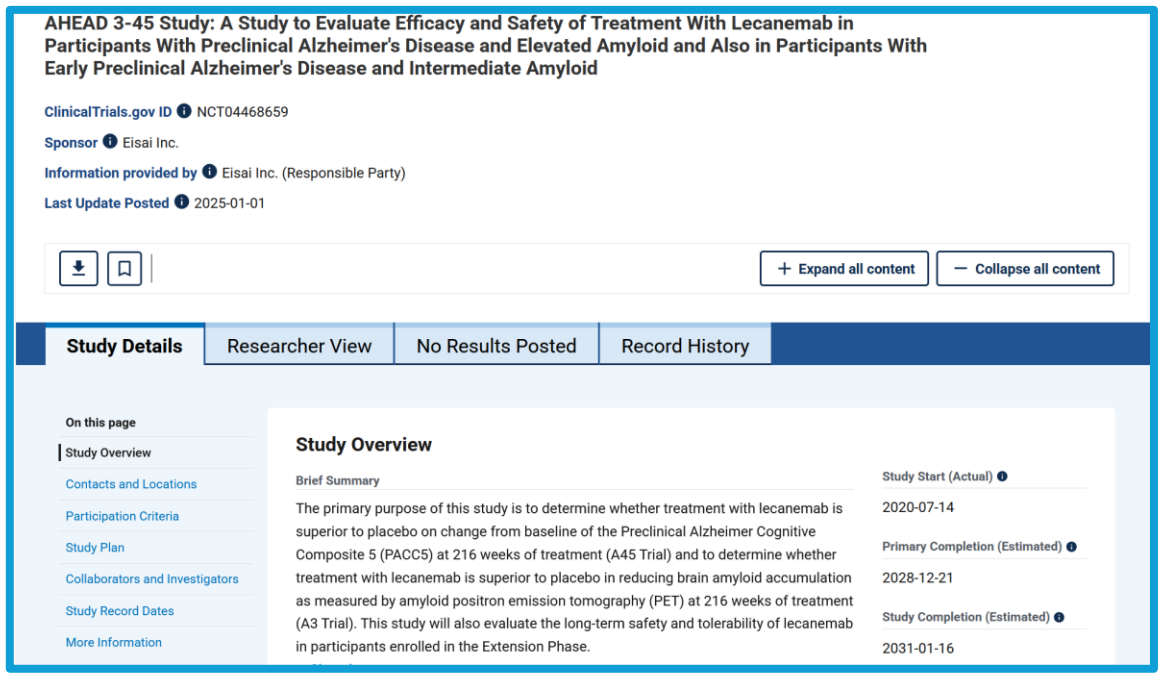


Solanezumab did not stop amyloid accumulation



Collapsed over drug and placebo, rate of decline was related to baseline amyloid level

But we have learned a great deal from A4. Now both lecanemab and donanemab are in prevention trials



AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid

ClinicalTrials.gov ID NCT04468659

Sponsor Eisai Inc.

Information provided by Eisai Inc. (Responsible Party)

Last Update Posted 2025-01-01

+ Expand all content — Collapse all content

Study Details | Researcher View | No Results Posted | Record History

On this page
- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Study Record Dates
- More Information

Study Overview

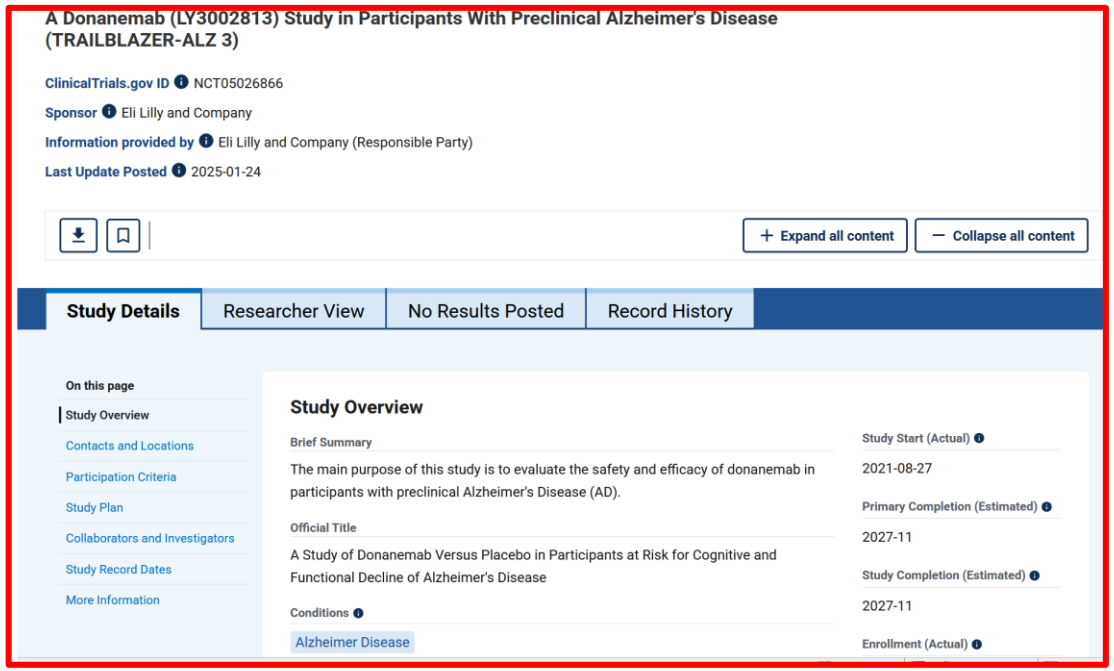
Brief Summary

The primary purpose of this study is to determine whether treatment with lecanemab is superior to placebo on change from baseline of the Preclinical Alzheimer Cognitive Composite 5 (PACC5) at 216 weeks of treatment (A45 Trial) and to determine whether treatment with lecanemab is superior to placebo in reducing brain amyloid accumulation as measured by amyloid positron emission tomography (PET) at 216 weeks of treatment (A3 Trial). This study will also evaluate the long-term safety and tolerability of lecanemab in participants enrolled in the Extension Phase.

Study Start (Actual) 2020-07-14

Primary Completion (Estimated) 2028-12-21

Study Completion (Estimated) 2031-01-16



A Donanemab (LY3002813) Study in Participants With Preclinical Alzheimer's Disease (TRAILBLAZER-ALZ 3)

ClinicalTrials.gov ID NCT05026866

Sponsor Eli Lilly and Company

Information provided by Eli Lilly and Company (Responsible Party)

Last Update Posted 2025-01-24

+ Expand all content — Collapse all content

Study Details | Researcher View | No Results Posted | Record History

On this page
- Study Overview
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- More Information

Study Overview

Brief Summary

The main purpose of this study is to evaluate the safety and efficacy of donanemab in participants with preclinical Alzheimer's Disease (AD).

Official Title

A Study of Donanemab Versus Placebo in Participants at Risk for Cognitive and Functional Decline of Alzheimer's Disease

Conditions

Alzheimer Disease

Study Start (Actual) 2021-08-27

Primary Completion (Estimated) 2027-11

Study Completion (Estimated) 2027-11

Enrollment (Actual)

What's next in AIBL clinical ? 1. assessment of speech and language: (with the USA: ADDF)

SpeechDx

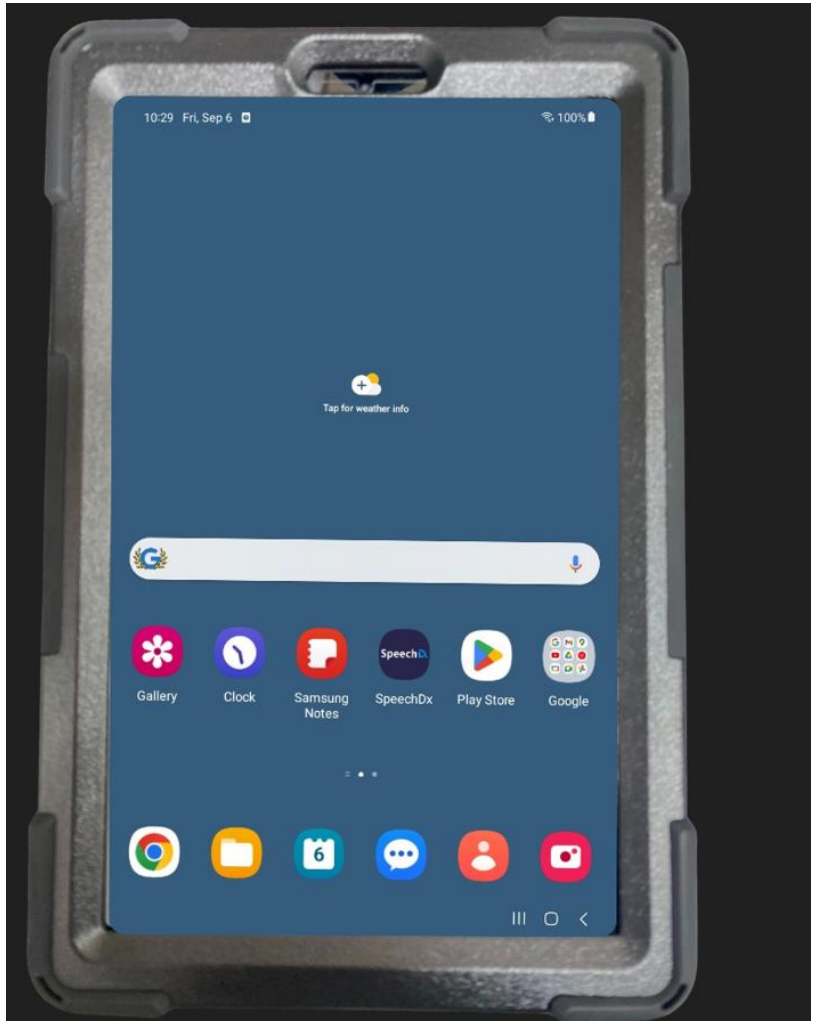
- Collaboration with the Alzheimer's Drug Discovery Foundation.
- Multi-site, observational study of 2,650 participants across several global clinical sites.

Aims

- To build the world's largest repository of longitudinal, harmonized speech and clinical data.
- To assess whether subtle changes in speech patterns can be used to diagnose Alzheimer's disease at a very early stage.

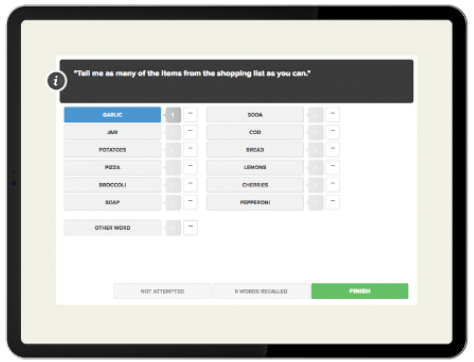
Procedure

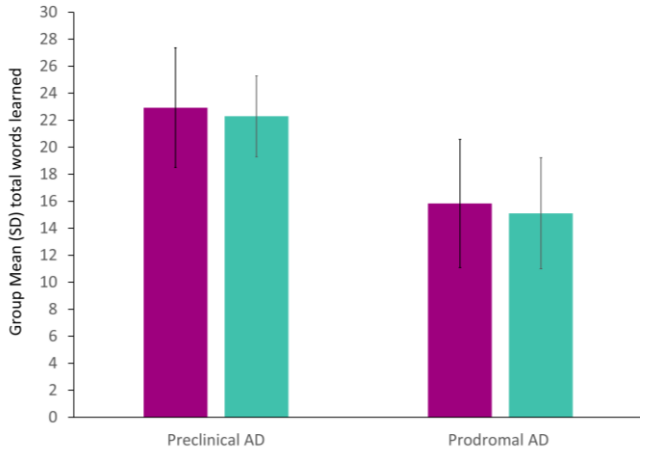
- Speech data to be collected via a study-provided tablet on a quarterly basis for 3 years.
- Participants will complete a practice session at their next AIBL visit, then be provided with a tablet to take home and complete quarterly assessments.
- Assessments take ~20 minutes.
- Tablet can be used recreationally in between assessments and will be gifted to participants upon completion of the study.



What's next in AIBL clinical ? 2. remote assessments

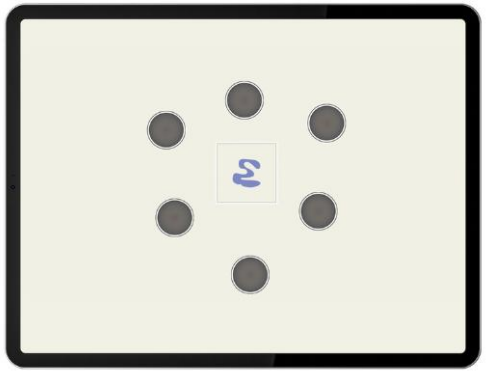
ISLT - Verbal Memory

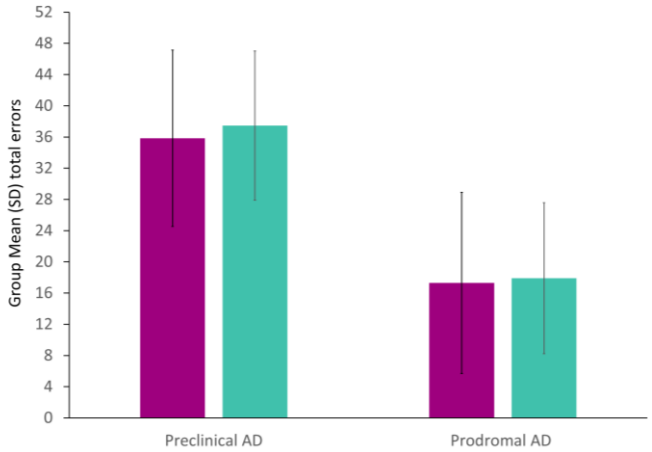




In clinic d = -1.69
Remote d = -1.62

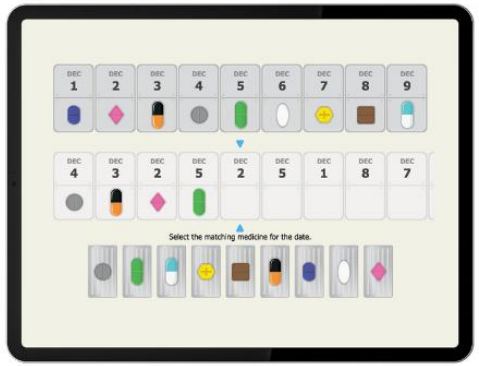
PAL - Visual Memory

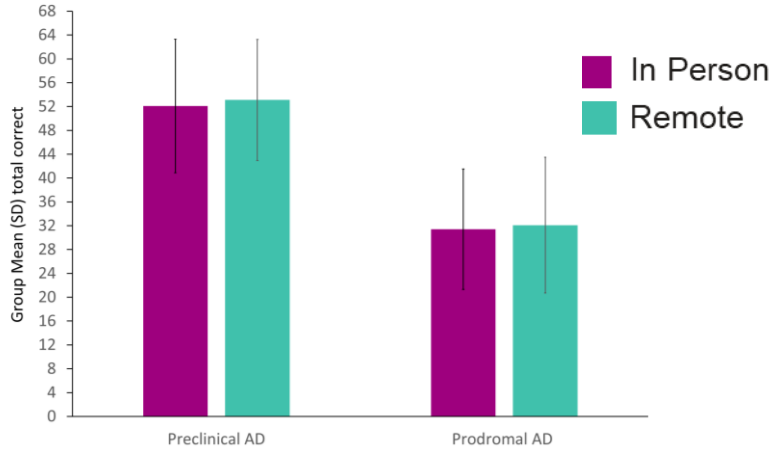




In clinic d = -1.13
Remote d = -1.18

DSST-m - Executive Function





In clinic d = -1.74
Remote d = -1.75

Standardized scores combined into composite score, **Remote PACC**: Preclinical AD = -0.29 (0.33), Prodromal AD = -1.19 (0.41); d **= -2.4**

l Paired Associate Learning Test; DSST-m= Digit-Symbol Substitution Test-Meds (DSST-m); d= Cohen's d effect size.

Maruff et al CTAD Boston 2023

Thank you

Understanding Lumbar Punctures

- Lumbar punctures are performed by **A/Prof Brendan Silbert** MBBS FANZCA
- Bookings and are arranged through the CACF of the Department of Anaesthesia and Acute Pain Medicine at SVHM
- LP research team: **Annemieke Kidd**

  Antonio (Tony) Jimenez

- **Ph:** 9231 2072

Understanding Lumbar Punctures

What to expect

What is a Lumbar Puncture (LP)?

- Procedure to collect cerebrospinal fluid (CSF).
- CSF surrounds the spinal cord and brain.
- Thin needle inserted into lower back (L3-L4 or L4-L5).
- Minimizes risk by avoiding nerves at higher levels.

What to Expect on the Day:

Preparation:

- Fast from midnight; small sips of water allowed.
- Safety call and confirmation the day before.

During the Procedure:

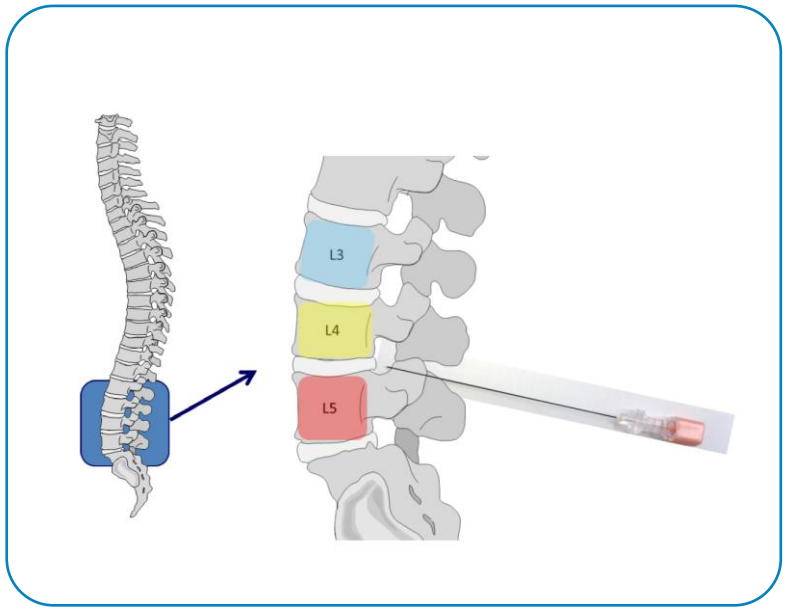
- Asked a few questions during admission
- Change into hospital gown.
- Meet anaesthetist and assistant for any questions and confirm consent.
- Procedure duration: **~20 minutes.**
- Sit still on your side during the procedure.

After the Procedure:

- Rest for at least 30 minutes under supervision.
- Avoid lifting heavy items, vigorous exercise, or driving.
- Ensure someone is available to accompany you home.

Potential Side Effects:

- Minor: Bruising, swelling, or headache (1-2 days typical).
- Rare: Severe headache (treatable with bed rest and medication).
- Very rare:
  - Infection (less risk than a regular blood test).
  - Temporary or permanent nerve damage.
  - Paralysis (1 in a million chance).



All steps are taken to minimize risks and ensure patient safety

ST VINCENT'S
Better and fairer care. Always.

Why Lumbar Punctures matter

Open access Short report

BMJ Neurology Open

Cerebrospinal fluid sampling for research of Alzheimer's disease and other neurodegenerative diseases when lumbar punctures are performed by anaesthetists

Kelly J Atkins,[1,2] Lisbeth Evered,[1,2,3] David A Scott,[1,2] Christopher Fowler,[4] Colin L Masters,[4] Brendan Silbert [1,2]

To cite: Atkins KJ, Evered L, Scott DA, *et al*. Cerebrospinal fluid sampling for research of Alzheimer's disease and other neurodegenerative diseases when lumbar punctures are performed by anaesthetists. *BMJ Neurology Open* 2022;**4**:e000335. doi:10.1136/bmjno-2022-000335

Accepted 11 August 2022

[1]Department of Anaesthesia and Acute Pain Medicine, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia
[2]Department of Critical Care,

ABSTRACT

Objectives An increasing number of people are undergoing lumbar puncture (LP) for the purposes of research. Performing LP for research purposes introduces considerations that differ from LP performed for clinical, diagnostic or therapeutic reasons. The demand for research LP will greatly increase as biomarkers are used to both diagnose and monitor disease progression in clinical trials. Minimising adverse events is paramount because research participants receive no clinical benefit and often need repeat procedures. We describe the experience of performing LP for research by anaesthetists.

Methods We reviewed the clinical protocol and incidence of adverse events in 326 research LP in an anaesthesia department.

Results There was a lower incidence of adverse events compared with previous reports when LP was undertaken for clinical reasons. The incidence of severe post-LP headache was 1.3% when an atraumatic spinal needle with a 27 gauge tip and a 22 gauge shaft was used.

Conclusions We describe the practice to sample cerebrospinal fluid (CSF) by LP for research purposes. Specific practices include the sitting position of the participant, aspiration rather than passive CSF withdrawal, attention to the sterility of the procedure, monitoring of vital signs and importantly the use of 22/27 gauge microtip spinal needle.

Trial registration numbers ACTRN12612000493842, NCT04623242.

than for clinical management,[3] a different informed consent[4] and a requirement for a positive participant experience to facilitate retention. Complications of LP include post-LP headache (PLPH), paraesthesia, back pain, vasovagal events, nerve injury, nausea, vomiting and dizziness.[5 6]

Anaesthetists commonly perform spinal anaesthesia, for which the clinical skills are essentially identical to those required for research LP. We describe the LP for research as distinct from diagnostic or therapeutic indications in an anaesthesia department.

MATERIALS AND METHODS

Between 2011 and 2021, after written informed consent, participants underwent LP by anaesthetists for one of two institutionally approved research studies on Alzheimer's disease:

1. Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL) (ACTRN12612000493842).
2. Dominantly Inherited Alzheimer Network (DIAN) (NCT04623242).

All relevant information pertaining to the LP was recorded on a specific case report

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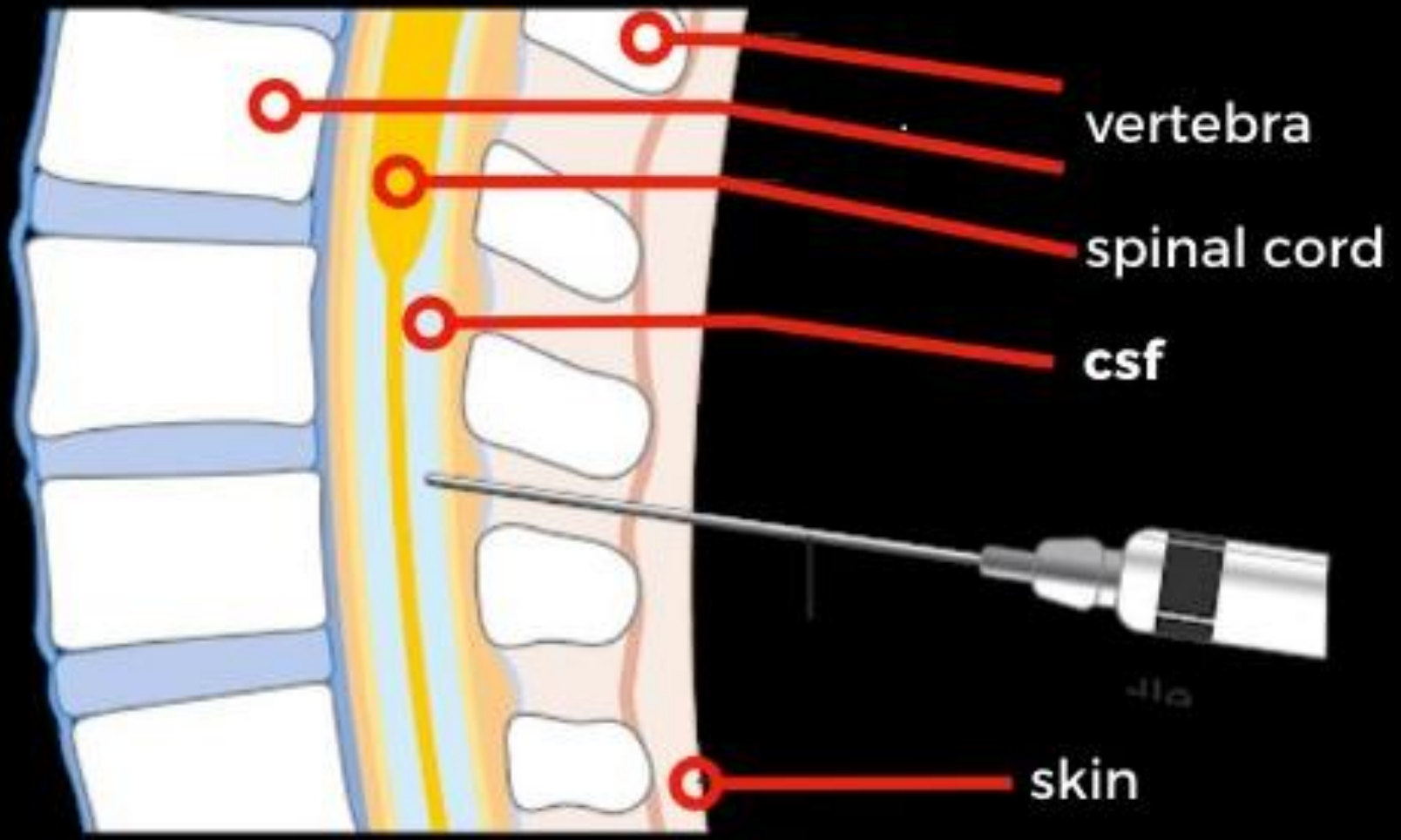
The Lumbar Puncture
detail



ST VINCENT'S
Better and fairer care. Always.

The Lumbar Puncture

detail

ST VINCENT'S
Better and fairer care. Always.

AIBL CSF projects

Chris Fowler

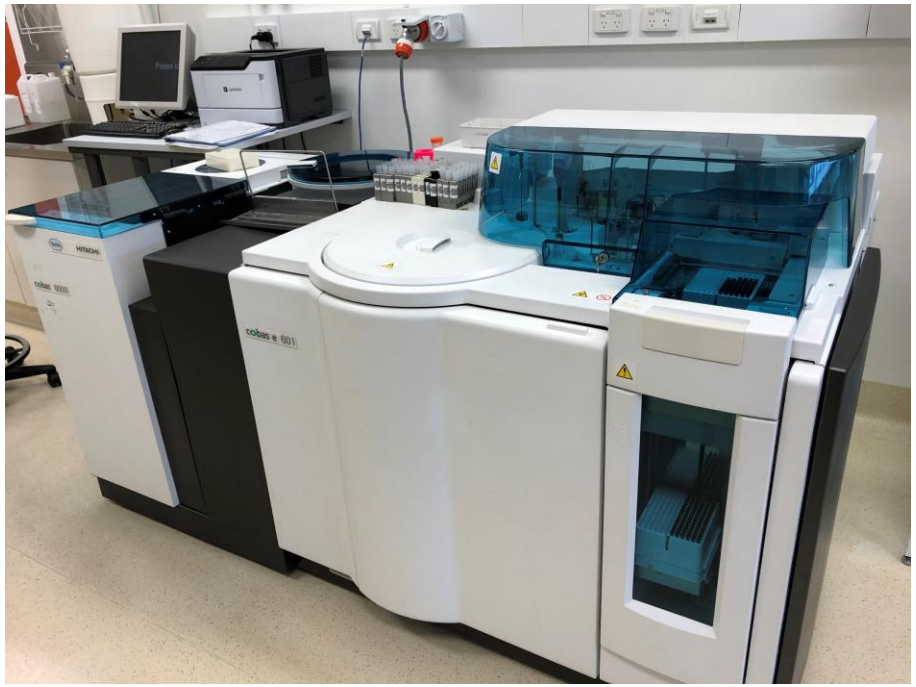
1. Establishment of National Dementia Diagnostic Laboratory at Florey
   - CSF biomarker thresholds and clinical testing

2. Blood Immune Cell populations in CSF
   - *Nature Communications* paper

Clinical testing

- Laboratory established in 2014 to measure Clinical CSF.
- NATA-accredited.
- Only pathology lab in Australia to analyse CSF dementia and CJD biomarkers.
- NDDL tests 30 samples/week. CJD is rare, dementia panel differentiates between CJD and AD.
- 1st generation tests were research kits. Use AIBL samples to generate Australia-specific threshold.
- 2nd generation automated/robotic Roche Elecsys.
  - AIBL contributed to setting cut-off applicable world-wide.
- More markers being introduced for NATA accreditation. NfL helps with identifying MND, MS and AD.
- Next international project is to add another marker to the AD panel.

National Dementia Diagnostics Laboratory



Cobas® e601 (GI)

Research: Blood immune cells entering the brain

nature communications

Article

https://doi.org/10.1038/s41467-024-52396-1

Clearance and transport of amyloid β by peripheral monocytes correlate with Alzheimer's disease progression

Received: 1 November 2023

Accepted: 2 September 2024

Published online: 12 September 2024

Check for updates

Xin Huang[1,2], Chris Fowler[1], Yihan Li[1], Qiao-Xin Li[1,3], Jiaqi Sun[1], Yijun Pan[1], Liang Jin[1], Keyla A. Perez[1], Céline Dubois[1], Yen Y. Lim[4], Candace Drysdale[1], Rebecca L. Rumble[1], Holly R. Chinnery[5,6,7], Christopher C. Rowe[8], Ralph N. Martins[9], Paul Maruff[1,10], James D. Doecke[11], Yong Lin[12], Abdel A. Belaidi[1], Kevin J. Barnham[1], Colin L. Masters[1] ✉ & Ben J. Gu[1,2,12] ✉

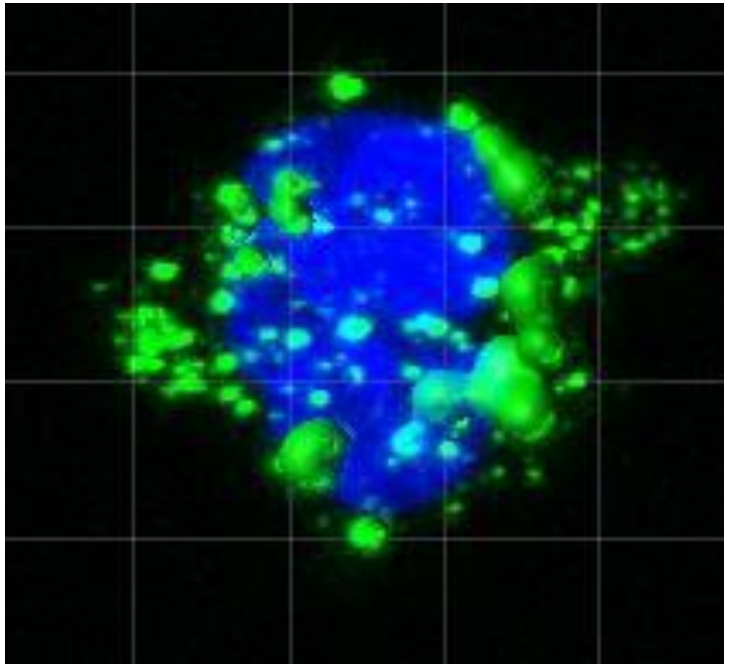
Background

Typically thought that blood immune cells do not enter brain to large extent except during inflammation.

New research

- We characterised a subtype of blood monocyte that binds Abeta.
- This subtype is the main type of monocyte present in the CSF, even in healthy participants. When labelled blood immune cells were injected into animal brain CSF, the cells migrated back into the blood stream.
- In MCI/AD these cells carry less Abeta.

Thus peripheral blood monocytes entering the brain and leaving with Abeta may be another mechanism for controlling Abeta levels in the brain.



Confocal microscope image of monocyte with surface-bound abeta.

Australia's National Science Agency

AIBL:
AI and interpreting data

Jurgen Fripp

Group Leader of Biomedical Informatics

Health & Biosecurity

The Australian e-Health Research Centre

February 2025

Innovative medical technologies for the discovery of meaningful patterns and biomarkers from biomedical data.

THE AUSTRALIAN E-HEALTH RESEARCH CENTRE

AIBL Data

The Australian Imaging Biomarkers and Lifestyle study

Observe evolution and understand Alzheimer's pathology
Define main biomarkers for Alzheimer's pathway
Focus on early detection
Commercial partnerships

aibl The Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing

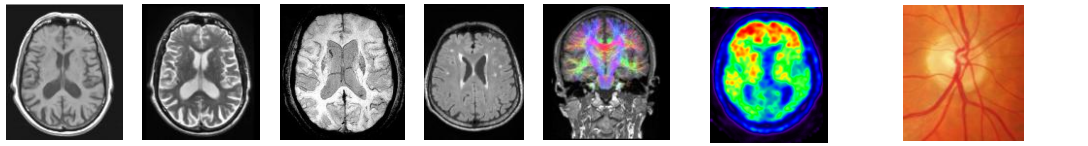
2006 ***2020+***

3000+ subjects over 60 years (HC, MCI, AD)

baseline | 18 months | 36 months | 54 months | 72 months | 90 months | …126 months

Imaging biomarkers

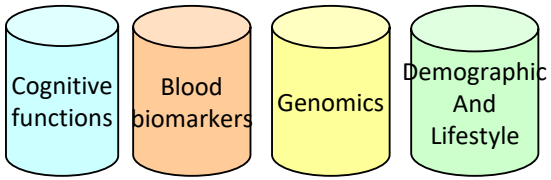
MRI PET Retina



T1W Anatomy | T2W CSF and structures | SWI Venous tree | FLAIR White matter | DWI Connectivity | PET Amyloid ^{11}C and ^{18}F markers | Optical and fluorescent Blood vessel and Amyloid

http://aibl.csiro.au/, large research group 10+ world leading chief investigators

Clinical and biofluid biomarkers



THE FLOREY INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH
THE UNIVERSITY OF MELBOURNE
CSIRO
Austin HEALTH
AUSTRALIA ECU EDITH COWAN UNIVERSITY
NARI NATIONAL AGEING RESEARCH INSTITUTE LTD

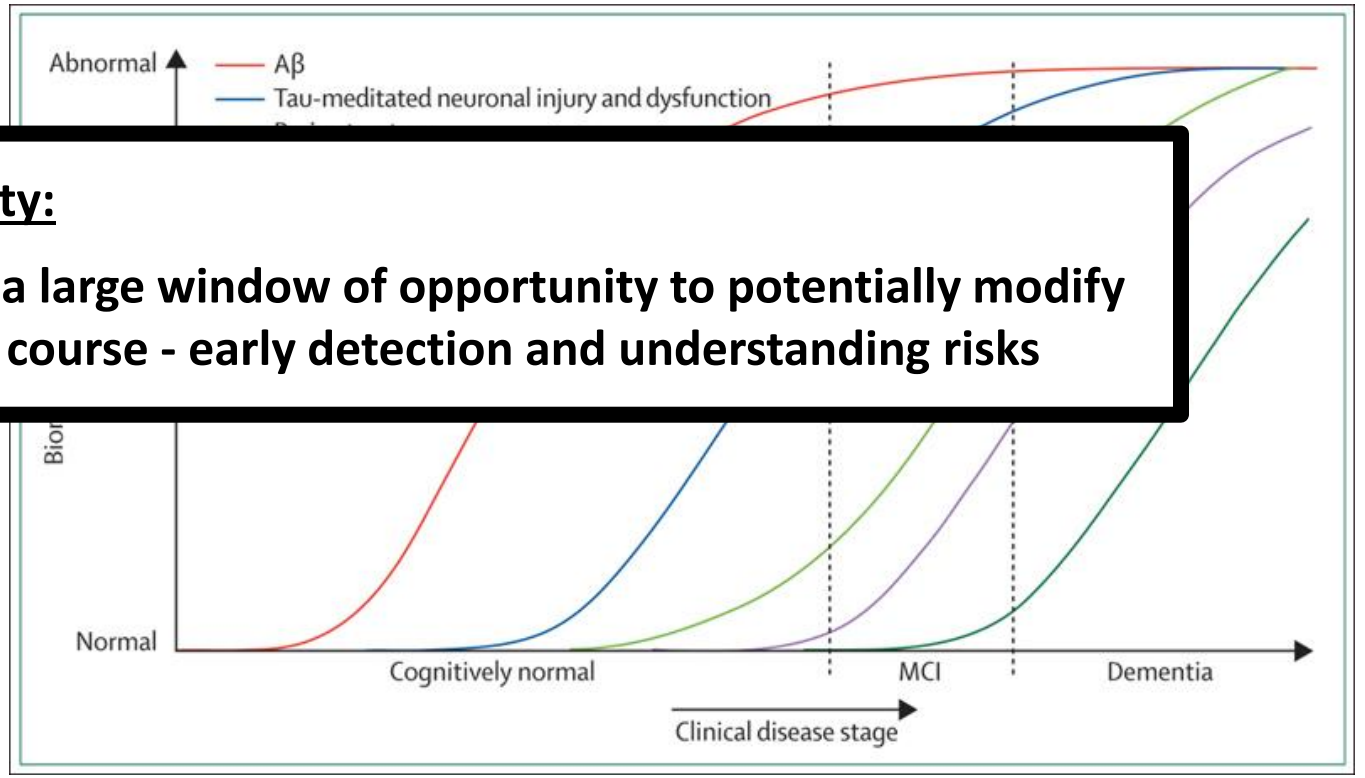
Alzheimer's – hypothetical disease model

aibl ADNI

MRI

Aβ

tau

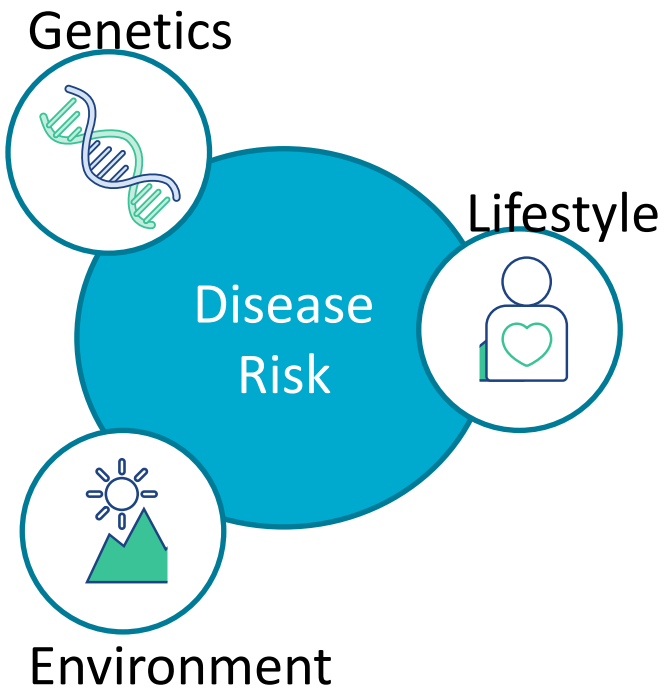


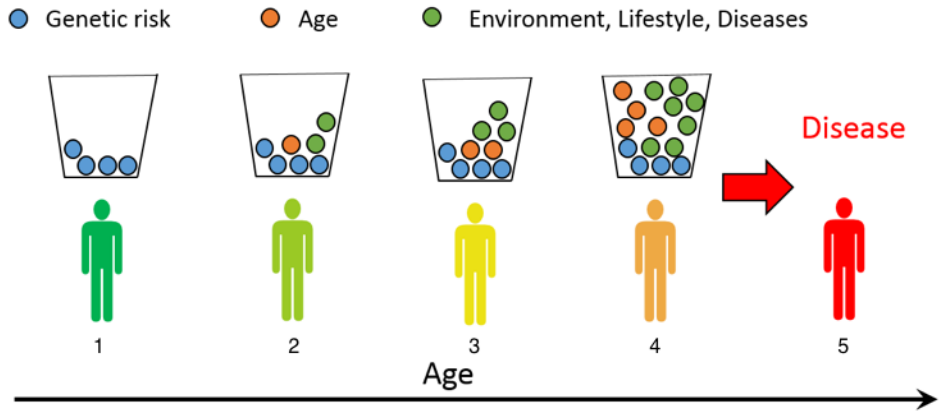
Opportunity:

There's a large window of opportunity to potentially modify disease course - early detection and understanding risks

Rowe, Villemagne, Jack

AIBL long term goal: Precision medicine





Visualisation by Krista Fischer

AI/ML is one approach to address large data problems in precision medicine.

- Automation of processes (e.g. medical image analysis, omics, digital biomarkers) – may improve sens/spec and reliability
- Diagnosis
- Risk prediction

Australia's National Science Agency

DeepSUVR

Using temporal constraints to improve SUVR and Centiloid quantification

Pierrick Bourgeat, Jurgen Fripp, Ashley Gillman, Leo Lebrat, Tim Cox, Manu Goyal, Duygu Tosun, Pamela LaMontagne, Tammie Benzinger, Michael W. Weiner, Victor L Villemagne, Colin Masters, Christopher C Rowe, Vincent Dore

for the ADOPIC research group (AIBL, ADNI and OASIS3)

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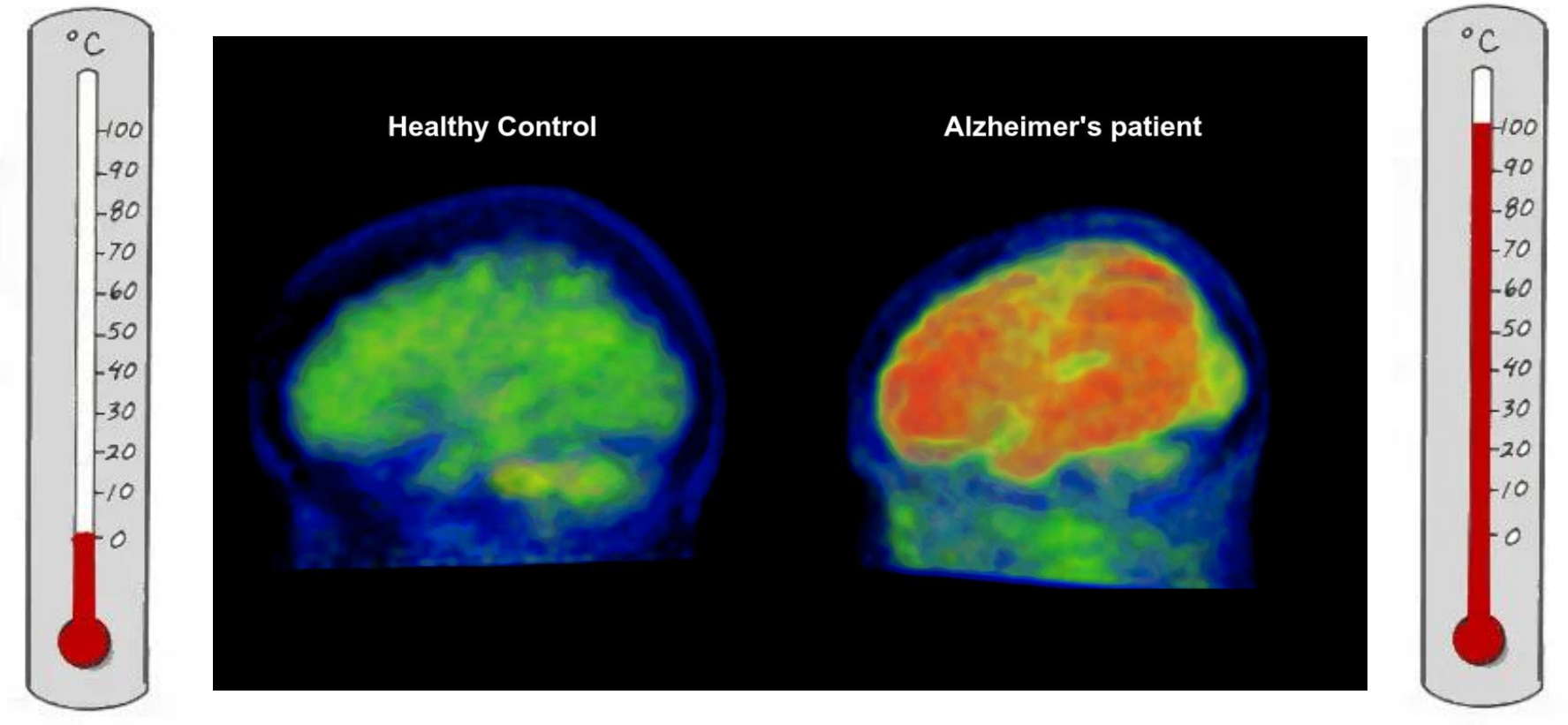
Amyloid PET Imaging: Centiloid measure



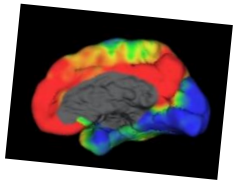
Centiloid measure is calibrated from a set of Young Controls (0 CL) and mild AD (100 CL)

ELSEVIER

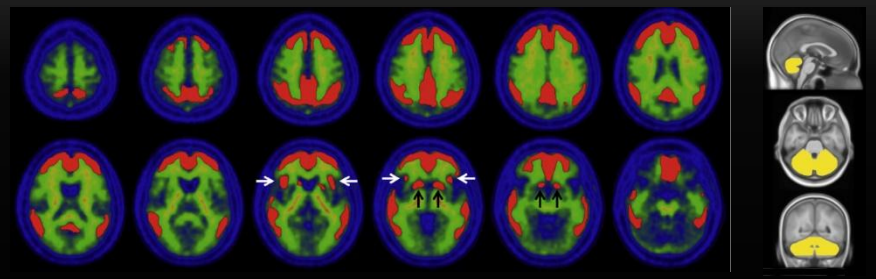
The centiloid project: Standardizing quantitative amyloid plaque estimation by PET

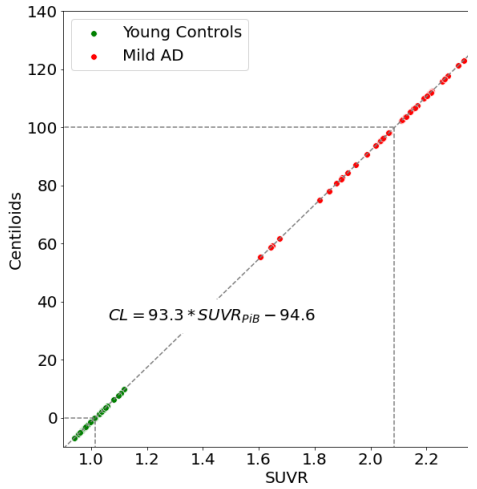
William E. Klunk[a,b,*], Robert A. Koeppe[c], Julie C. Price[d], Tammie L. Benzinger[e,f], Michael D. Devous, Sr.,[g,h], William J. Jagust[i], Keith A. Johnson[e,j], Chester A. Mathis[k], Davneet Minhas[d], Michael J. Pontecorvo[l], Christopher C. Rowe[m], Daniel M. Skovronsky[l], Mark A. Mintun[l]

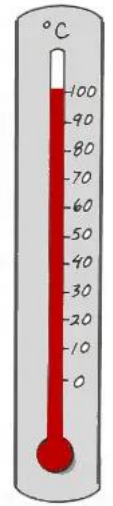
Alzheimer's & Dementia



$$SUVR = \frac{Mean\ Uptake\ (Target\ ROI)}{Mean\ Uptake\ (Reference\ ROI)}$$

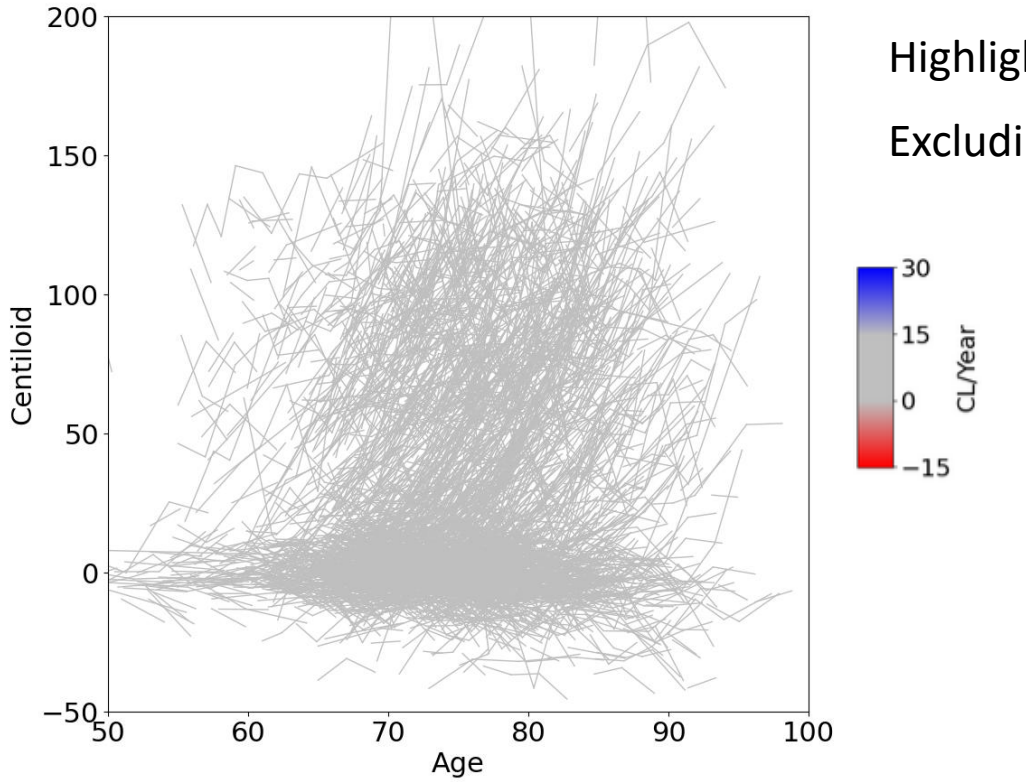






Centiloid measure is calibrated from a set of Young Controls (0 CL) and mild AD (100 CL)

Longitudinal trajectories



Highlighting outliers

Excluding ^{18}F-Florbetapir

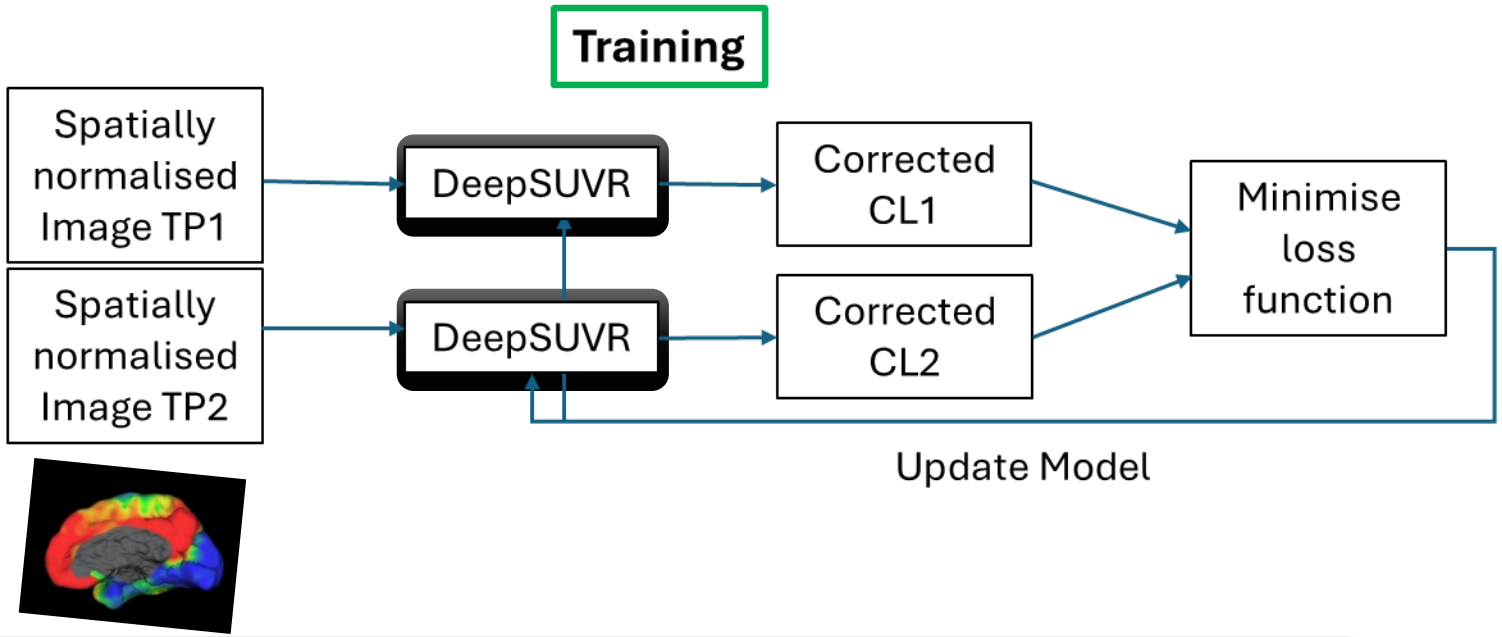
Variability in CL measures (changes in equipment/tracers):

- Reduced reliable across tracers/participants
- Monitoring changes and estimating natural history less accurate

DeepSUVR: AI Solution

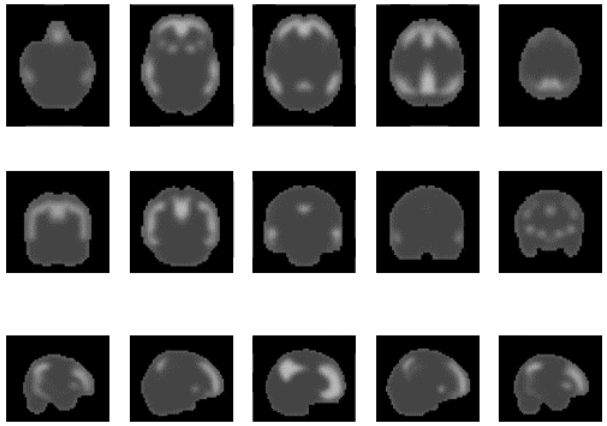
Incorporate longitudinal PET information into the training of our **AI** model (DeepSUVR)

Data: AIBL, ADNI, OASIS (3098 participants), Cross Validation on 2288 participants. Tested on remaining subjects and 4 other international cohorts (6325 participants).

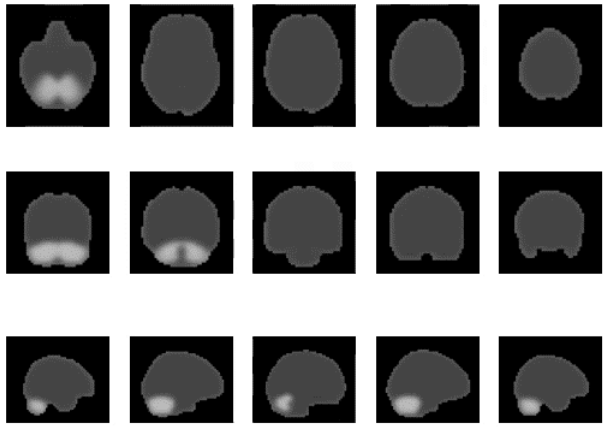


Explainability: What's the black box doing

Optimising Target mask



Optimising Reference mask



AIBL/ADNI – Cross-validation

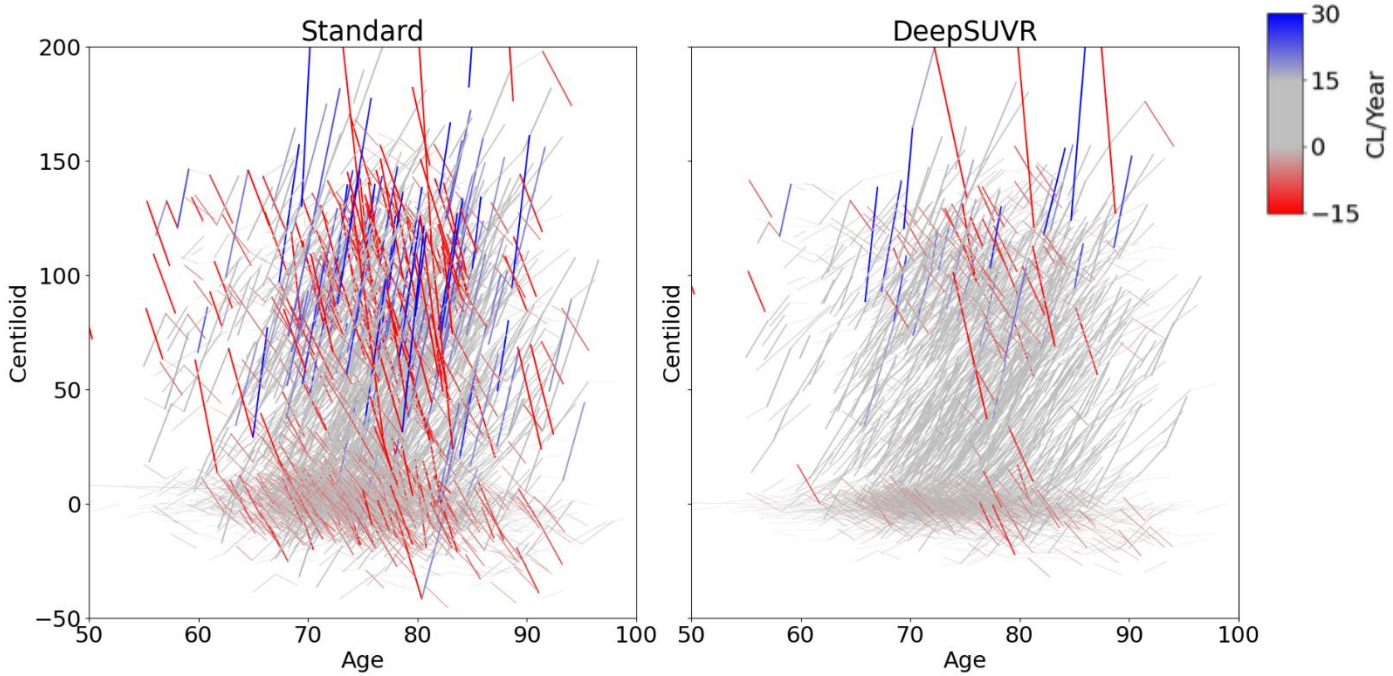
Outliers:

<u>Standard</u>

- 8.1% < -5CL/Y
- 2.5% > 15CL/Y

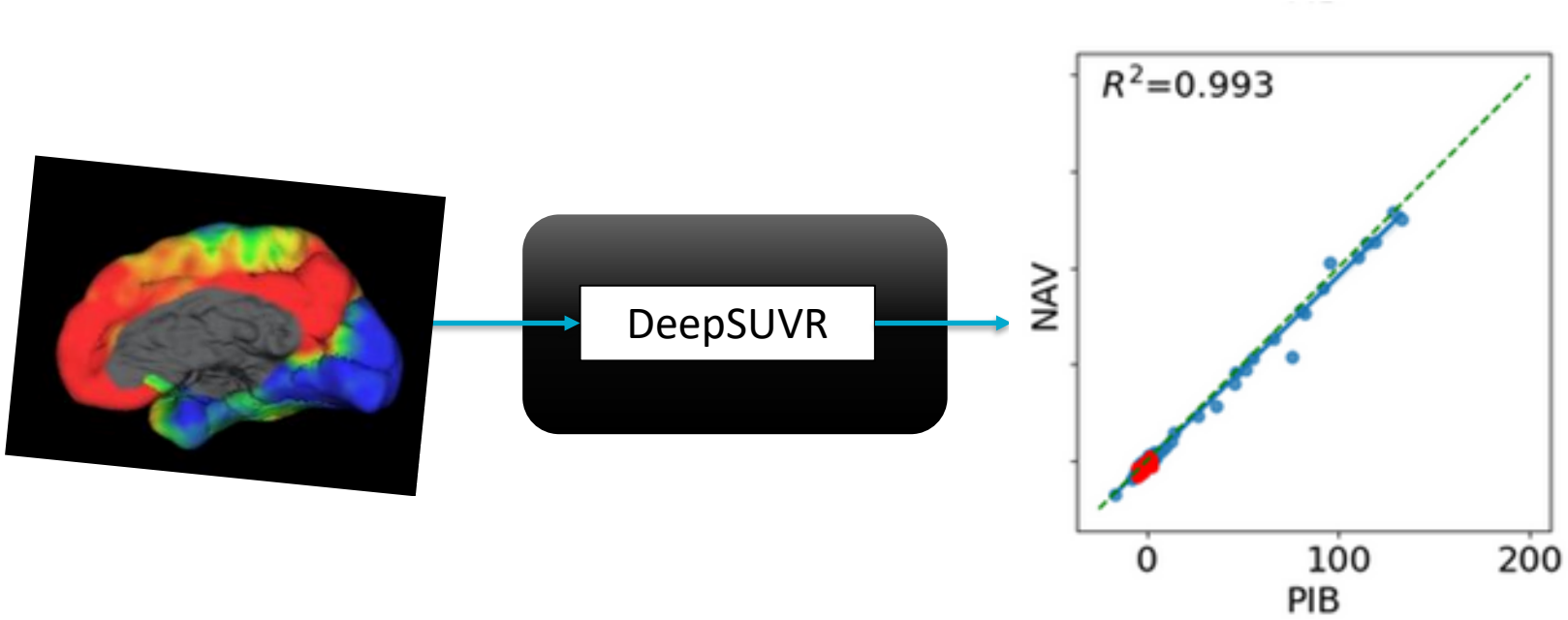
<u>DeepSUVR</u>

- **2.0%** < -5CL/Y
- **0.7%** > 15CL/Y



7403 scans from 2288 participants

Unseen data: GAAIN Head-to-Head Centiloid Calibration



Conclusion

- Developed a robust machine learning technique that
  - Reduces variability in longitudinal trajectories
  - Improves Tracer agreement

- Current research
  - Evaluate DeepSUVR to other PET tracers (Tau, FDG)
  - Better understand what information is used for the correction (Explainability)

Australia's National Science Agency

Natural History Modeling

When does Alzheimer's disease start? Robust estimates based on longitudinal data from three large international cohorts.

Samantha C. Burnham*, Timothy Cox, Tammie Benzinger, Pierrick Bourgeat, Carlos Cruchaga, James D. Doecke, Vincent Doré, Christopher Fowler, Manu S. Goyal, Liang Jin, Simon M. Laws, Jason Hassenstab, Tenielle Porter, Paul Maruff, Rob Williams, Andrew J. Saykin, Rosita Shishegar, Hamid R. Sohrabi, Ronald Petersen, Duygu Tosun, Jurgen Fripp, Christopher C. Rowe, John C. Morr Weiner, Colin L. Masters and Victor L. Villemagne

for the ADOPIC research group (AIBL, ADNI and OASIS3)

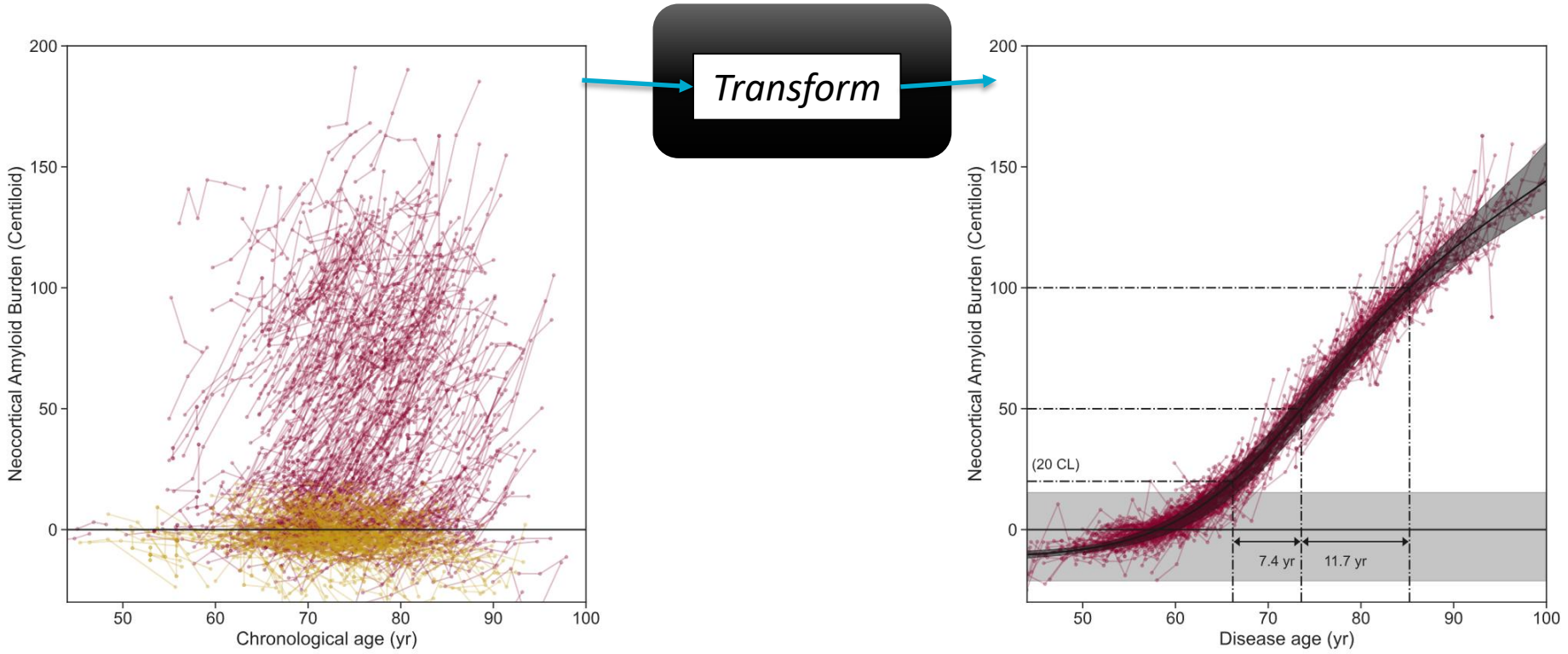
aibl
The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

ADNI
Alzheimer's Disease Neuroimaging Initiative

OASIS
Open Access Series of Imaging Studies

Aβ natural history curve

Natural history modelling characterizes disease onset and progression. Aβ burden abnormal (<20CL) at a mean age of 66.2 years, 19.1 years before reaching level associated with AD (>100CL)

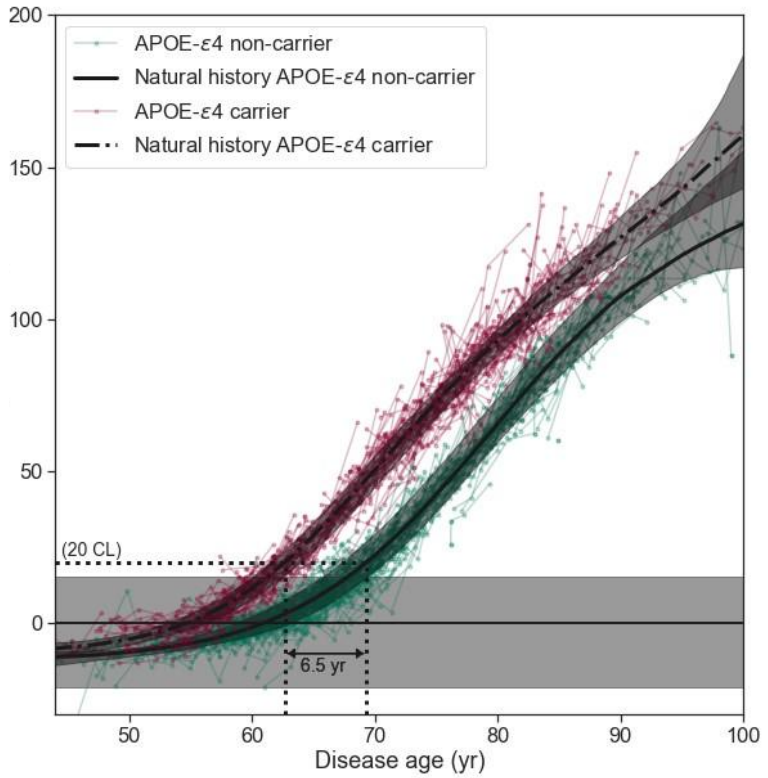


Participants with three or more Amyloid β PET (Aβ PET) scans: AIBL (N=496), ADNI (N=465), OASIS (N=127)

Aβ natural history curve: stratified by e4

May improve individualised staging.

On average APOE- ε4 carriers have detectable abnormal Aβ level 6.5 earlier than non-carriers



Participants with three or more Amyloid β PET (Aβ PET) scans: AIBL (N=496), ADNI (N=465), OASIS (N=127)

Australia's National Science Agency

Risk Models

Identifying an Optimal Cutoff Point for Progression from Mild Cognitive Impairment to Alzheimer's Disease: Comparing Cognitive Performance and Aβ PET Insights

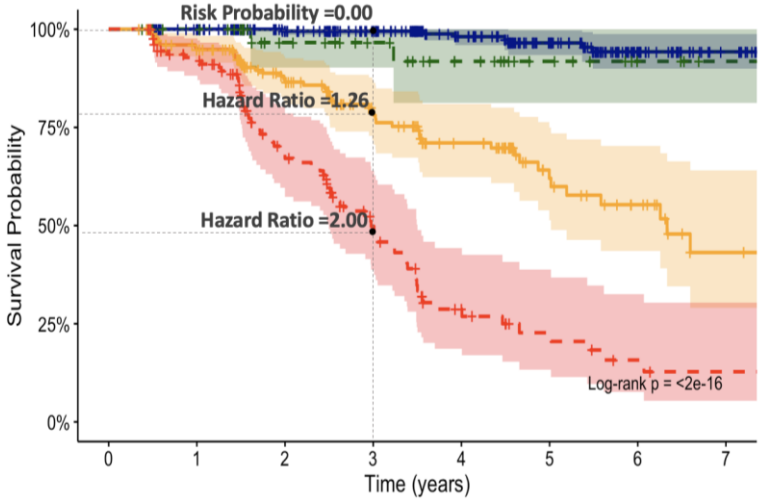
Rosita Shishegar, Pierrick Bourgeat, Vincent Dore, Simon Laws, Tenielle Porter, Michael Weiner, Colin L. Masters, Jurgen Fripp, Victor L. Villemagne, Christopher C. Rowe
for the Alzheimer's Disease Neuroimaging Initiative[8] and the AIBL Research Group

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

MCI-to-AD progression

686 MCI participants (CDR 0.5) from AIBL (N=166) & ADNI (N=520), analysed using Cox models

Optimal thresholds: Aβ **44 CL** & MMSE **27** selected for maximum hazard ratio (HR) at 3 years



Combining Aβ & MMSE improves prediction

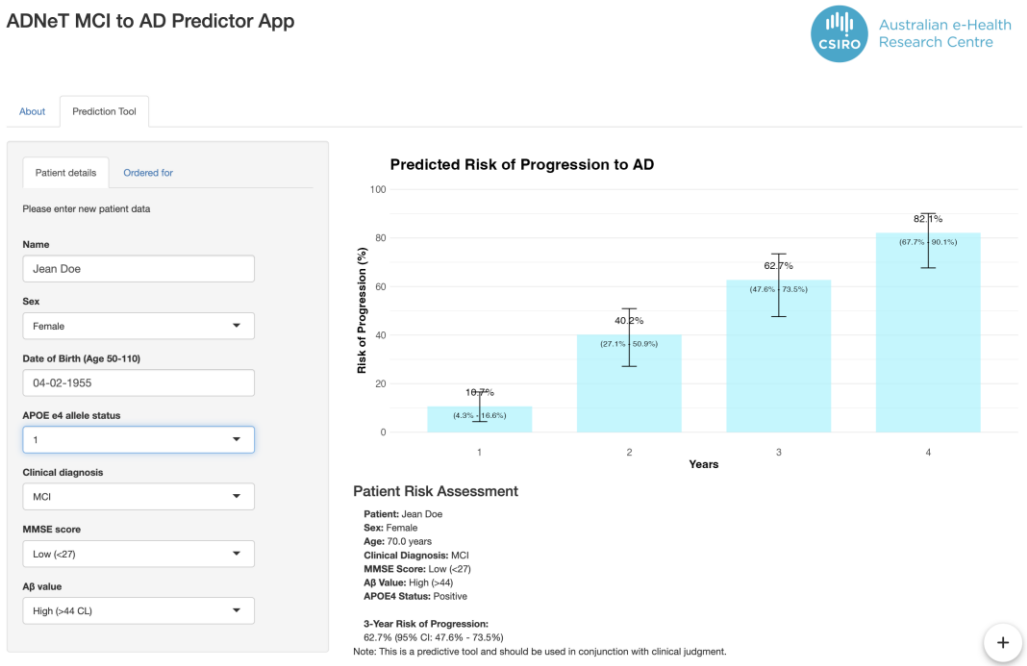
Low-cognition, high-Aβ MCI had highest risk (50% progressed in 3 years).

High-cognition, low-Aβ MCI had low risk of progressing

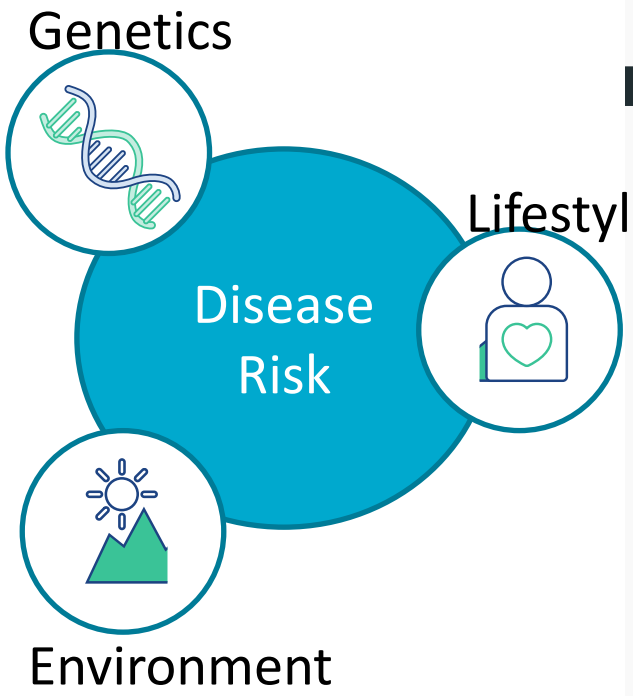
Conclusion: MCI-to-AD progression

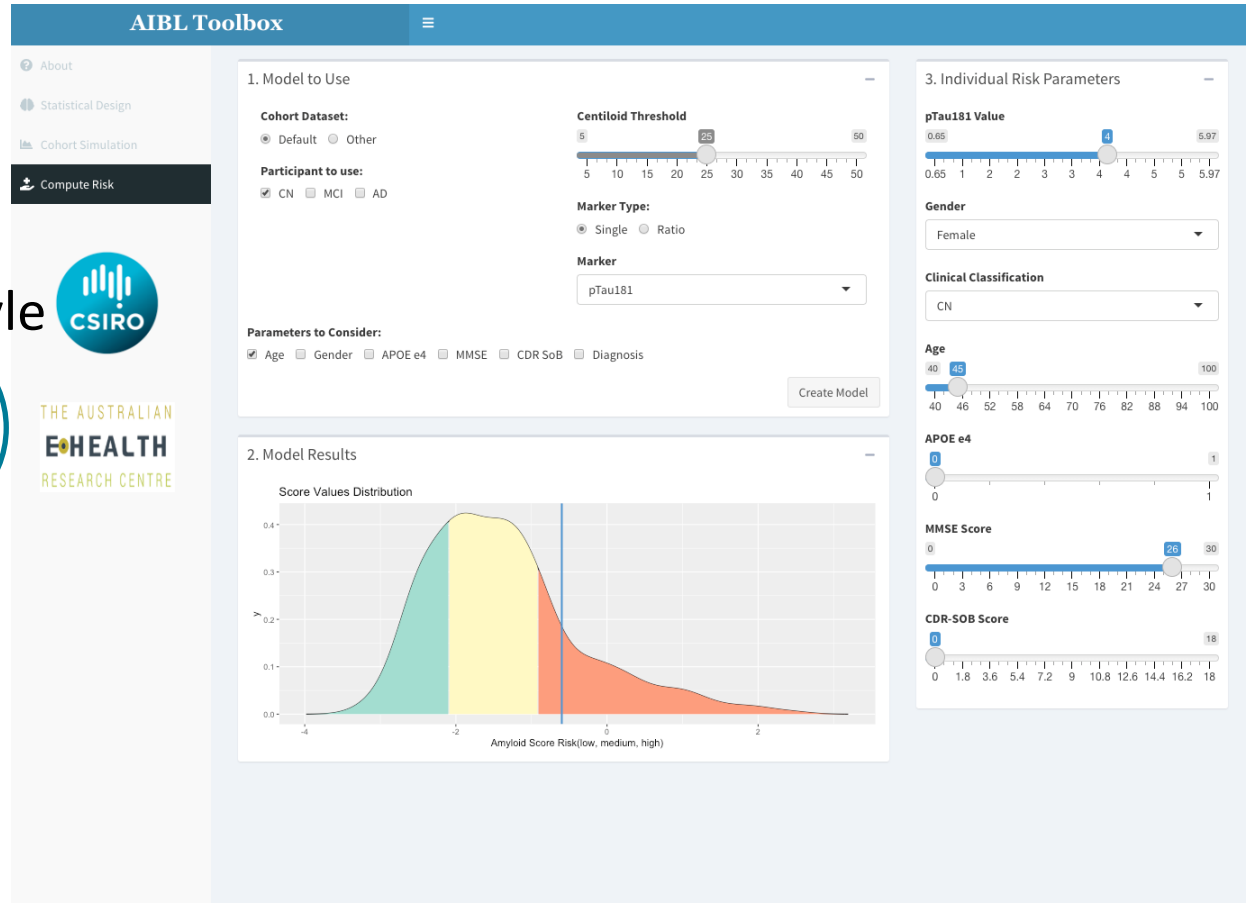
Aβ PET (CL > 44) plus MMSE enhances risk stratification, aiding clinical trials & interventions.

The model informs personalized prediction of conversion risk for new patients



Risk Models: Blood biomarkers





ACKNOWLEDGEMENTS

AIBL would like to thank the study participants and their families

AIBL Study team:

David Ames
Alex Barac
Mary Barnes
Kevin Barnham
Pierrick Bourgeat
Sveltana Bozinovski (nee Pejoska)
Belinda Brown
Samantha Burnham
Lesley Cheng
Steven Collins
James Doecke
Josie Domingo
Vincent Dore
Denise El-Sheikh
Kathryn Ellis
Binosha Fernando
Christopher Fowler
Jurgen Fripp
Shaun Frost
Sam Gardener
Simon Gibson
Rob Grenfell
Rodney Guzman
Bronwyn Hall
David Hanson
Elise Harrison
Jacqui Hayem
Andy Hill
Eugene Hone
Maryam Hor
Jill Hwang
Yogi Kanagasingam
Neil Killeen
Fiona Lamb
Nicola Lautenschlager
Simon Laws
Hugo Leroux
Qiao-Xin Li
Yen Ying Lim
Florence Lim
Lucy Lim
Kathy Lucas
Lucy Mackintosh
Ralph Martins
Georgia Martins
Paul Maruff
Colin Masters
Simon McBride
Tash Mitchell
Amanda Niu
Steve Pedrini
Kayla Perez
Kelly Pertile
Tenielle Porter
Stephanie Rainey-Smith
Malcolm Riley
Blaine Roberts
Jo Robertson
Mark Rodrigues
Christopher Rowe
Rebecca Rumble
Ian Saunders
Greg Savage
KaiKai Shen
Brendan Silbert
Harmid Sohrabi
Kevin Taddei
Tania Taddei
Christine Thai
Philip Thomas
Brett Trounson
Regan Tyrell
Jacquie Uren
Victor Villemagne
Irene Volitakis
Larry Ward
Mike Weinborn
Rob Williams
Michael Woodward
Paul Yates
Luz Fernanda Yevenes Ugarte
George Zisis

AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au

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THE FLOREY INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH
CRC for Mental Health
AUSTRALIA ECU EDITH COWAN UNIVERSITY
Austin Health
McCusker ALZHEIMER'S RESEARCH Foundation
CSIRO
YULGILBAR The Yulgilbar Foundation

Collaborators

COGSTATE ASSESS · MONITOR · IMPROVE
NARI
THE UNIVERSITY OF MELBOURNE
THE UNIVERSITY OF WESTERN AUSTRALIA
DCRC Dementia Collaborative Research Centres
janssen
Pfizer
Alzheimer's Australia Living with dementia
Navidea BIOPHARMACEUTICALS

Thank you

Built on AIBL Foundations

Australian Dementia Network

REGISTRY. CLINICS. TRIALS.

OBJECTIVES

- Establish Australia's first dementia clinical quality registry to track, benchmark, and report on the clinical care of people with dementia
- Establish consistent best practice guidelines for dementia diagnosis and treatment
- Facilitate development of effective therapies by screening patients suitable for clinical trials

Our Partners

The University of Melbourne · UNSW Sydney · Monash University · Austin Health · CSIRO · Australia ECU Edith Cowan University · Flinders University · The Florey · Macquarie University · NeuRA · QIMR Berghofer Medical Research Institute · SAHMRI · The University of Newcastle Australia · The University Of Queensland Australia · The University of Sydney · University of Tasmania · NARI National Ageing Research Institute

Supported by

Australian Government NHMRC National Institute for Dementia Research · The Wicking Trust · Yulgilbar · Dementia Australia

Aus

CLINICAL QUALITY REGISTRY

57 participating sites

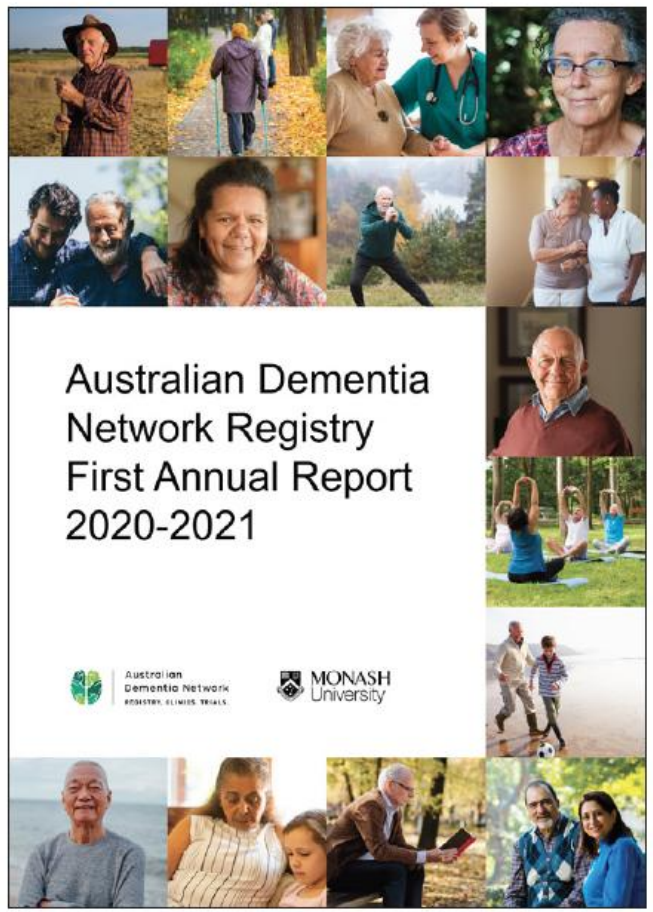
3,247 participants recruited

38% born overseas

2% First Nation people

as of May 2023

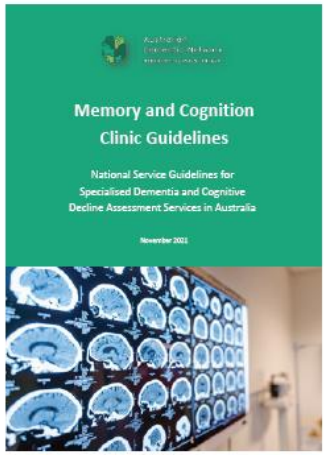
- Collects data to benchmark clinical practice in the diagnosis, management and care of people with dementia or mild cognitive impairment
- Incorporates voice of people living with dementia and their care partners
- Drives improvement
- Measures the impact of new treatments for Alzheimer's disease



MEMORY CLINICS

Harmonises diagnostic and post-diagnostic support pathways so Australians have access to high-quality dementia assessments.

- Published Australia's first National Service Guidelines for MC Clinics
- Nationwide cognitive interventions and risk assessment
- Pioneered management impact study on implementing blood-based biomarkers into Clinics
- Improved diagnosis via training, harmonised assessments and neuropsychological testing tool
- Published national map of dementia services (150 clinics)



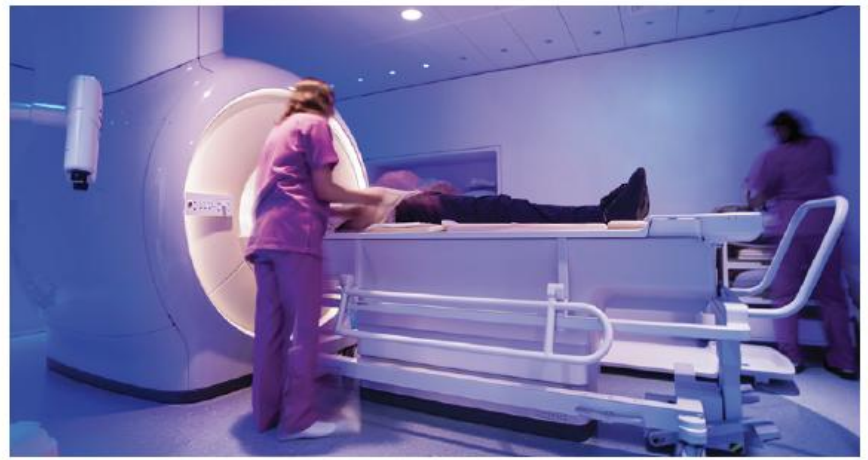
Established leading presence in Australian health and research community

- Leads the Australia Dementia Research Forum
- Home to Early Mid-Career Researchers and Young Onset Dementia Special Interest Groups

SCREENING AND TRIALS

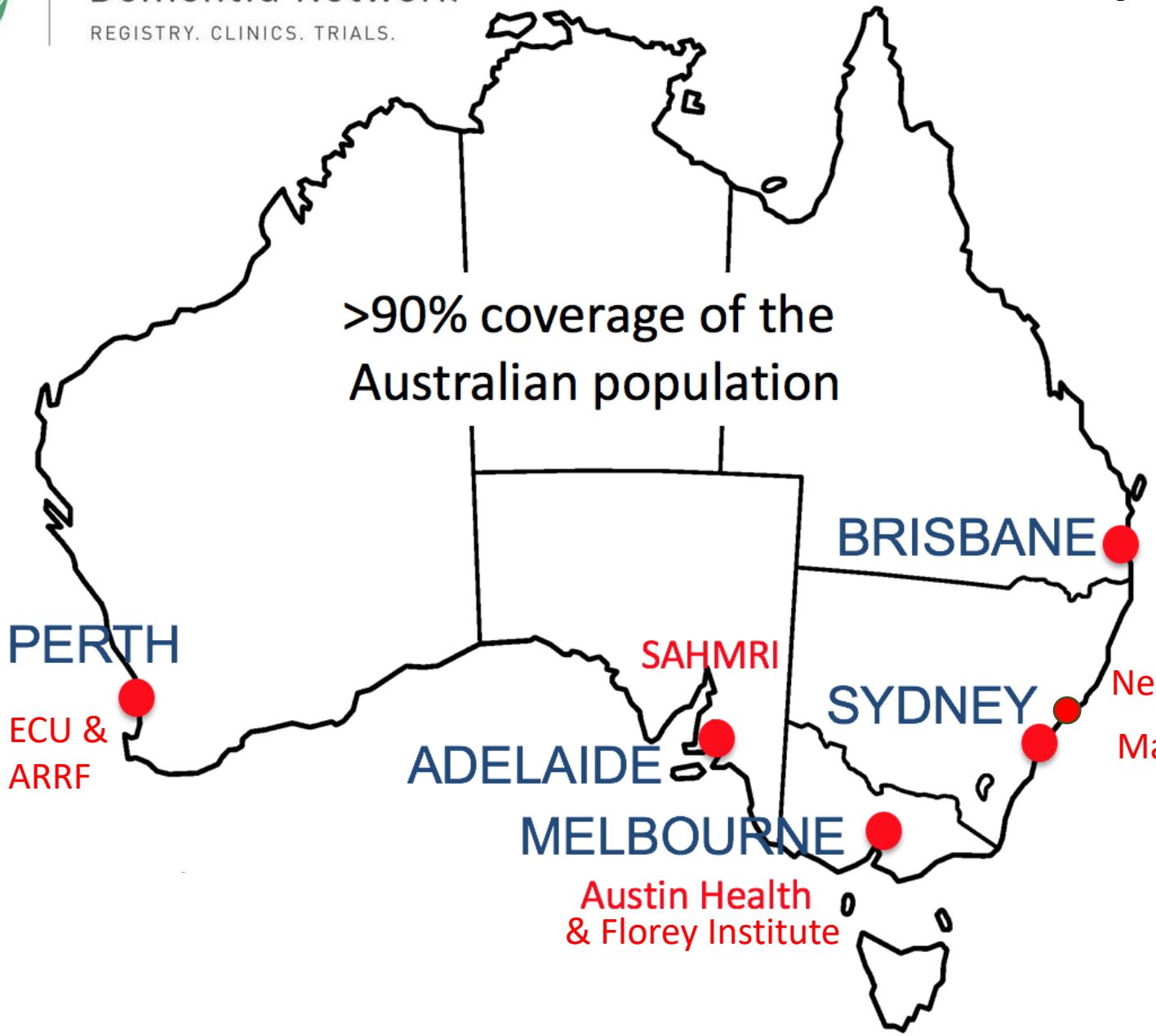
ADNeT Screening centres established to shorten trial recruitment times and increase access to emerging therapies.

- Facilitated international clinical trials in Australia (Eisai **CLARITY** and AHEAD 3-45 studies, Biogen EMERGE trial, Novo Nordisk EVOLVE trial, Roche trial)
- Completed 1,158 screenings for the trial ready cohort
- Recruited 3,439 registrants into ADNeT Volunteer Portal
- Secured significant grant funding from industry partners
- Introduced blood pTau and genetic testing prescreening for early Alzheimer detection



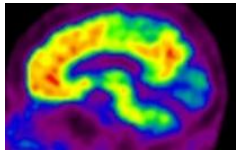
Australian Dementia Network
REGISTRY. CLINICS. TRIALS.

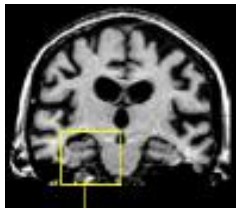
ADNeT/AIBL Trial Screening Sites

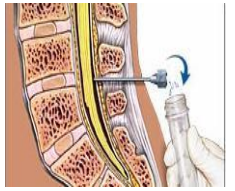


Testing


Cognition

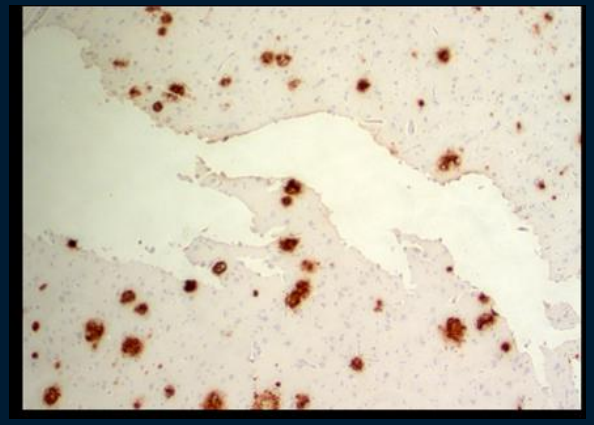

Aβ & tau PET

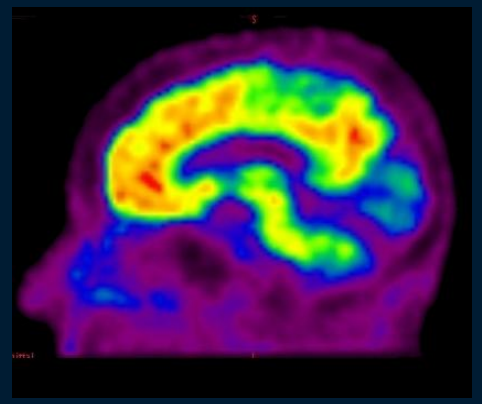

MRI


CSF


Blood

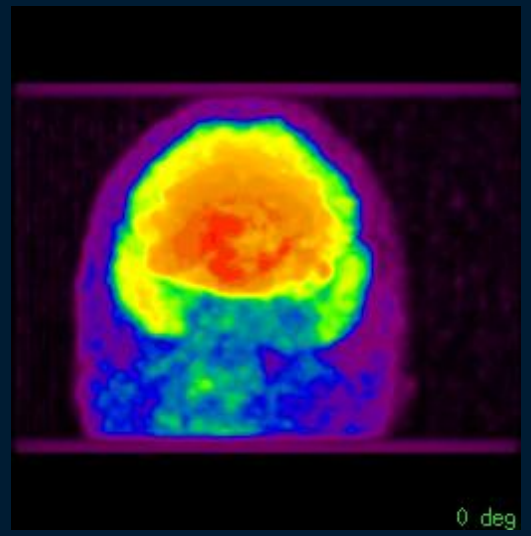
2004: *Beta-amyloid PET Begins*





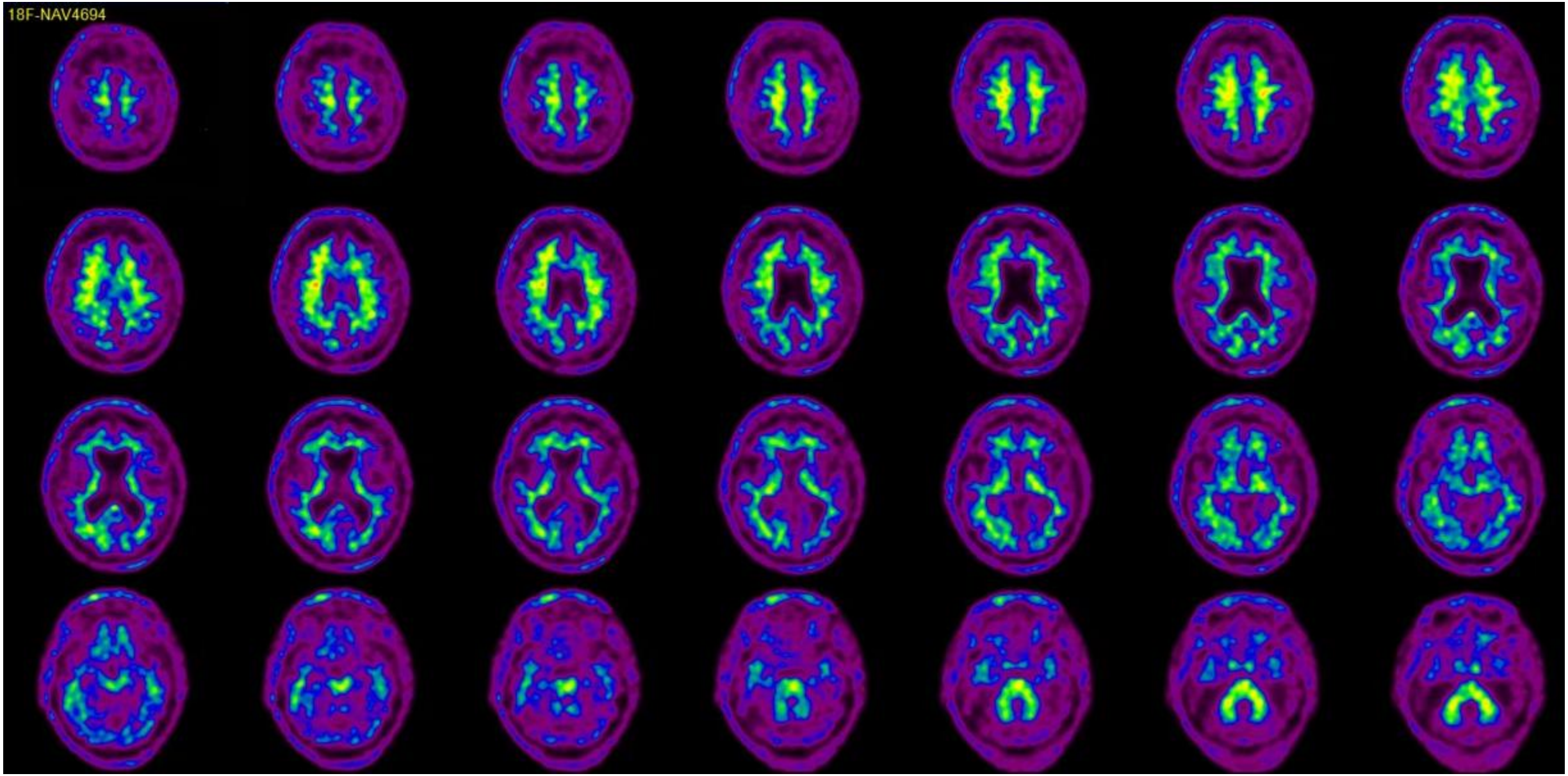
^{11}C-PiB

Inventors:
Chet Mathis
William Klunk
University of Pittsburgh

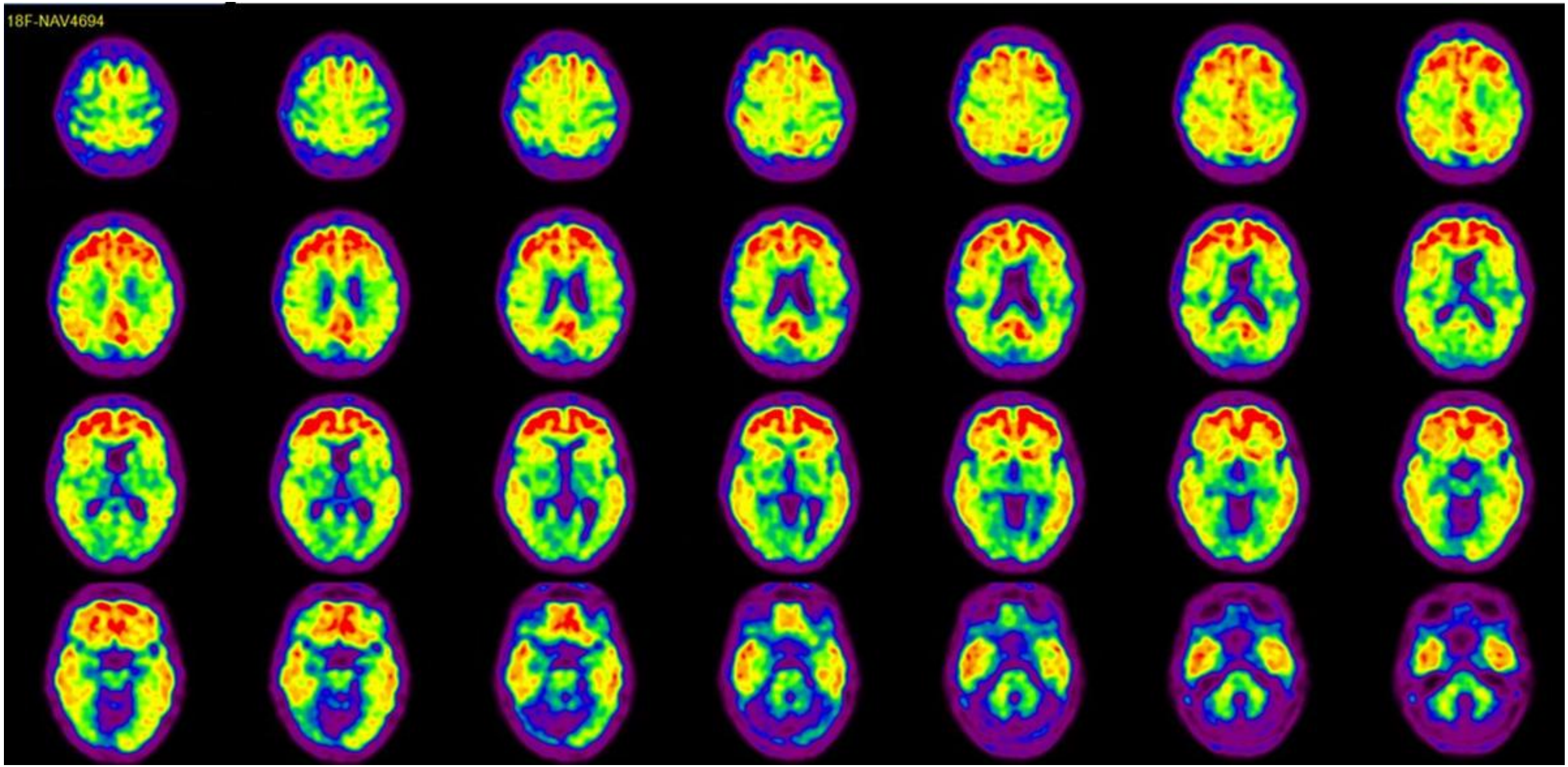


Alzheimer's Disease

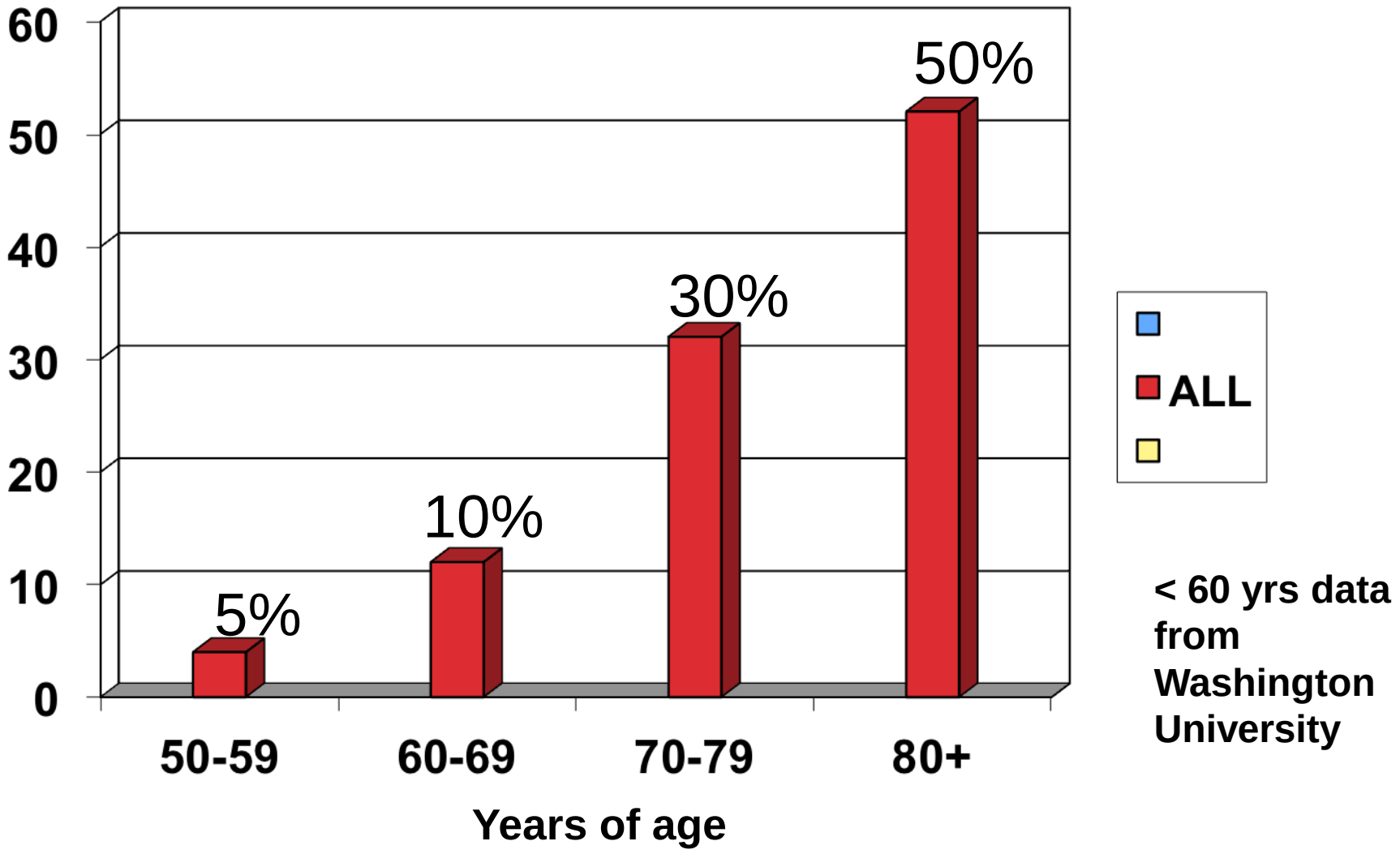
Amyloid scan : Negative



Amyloid scan : Positive



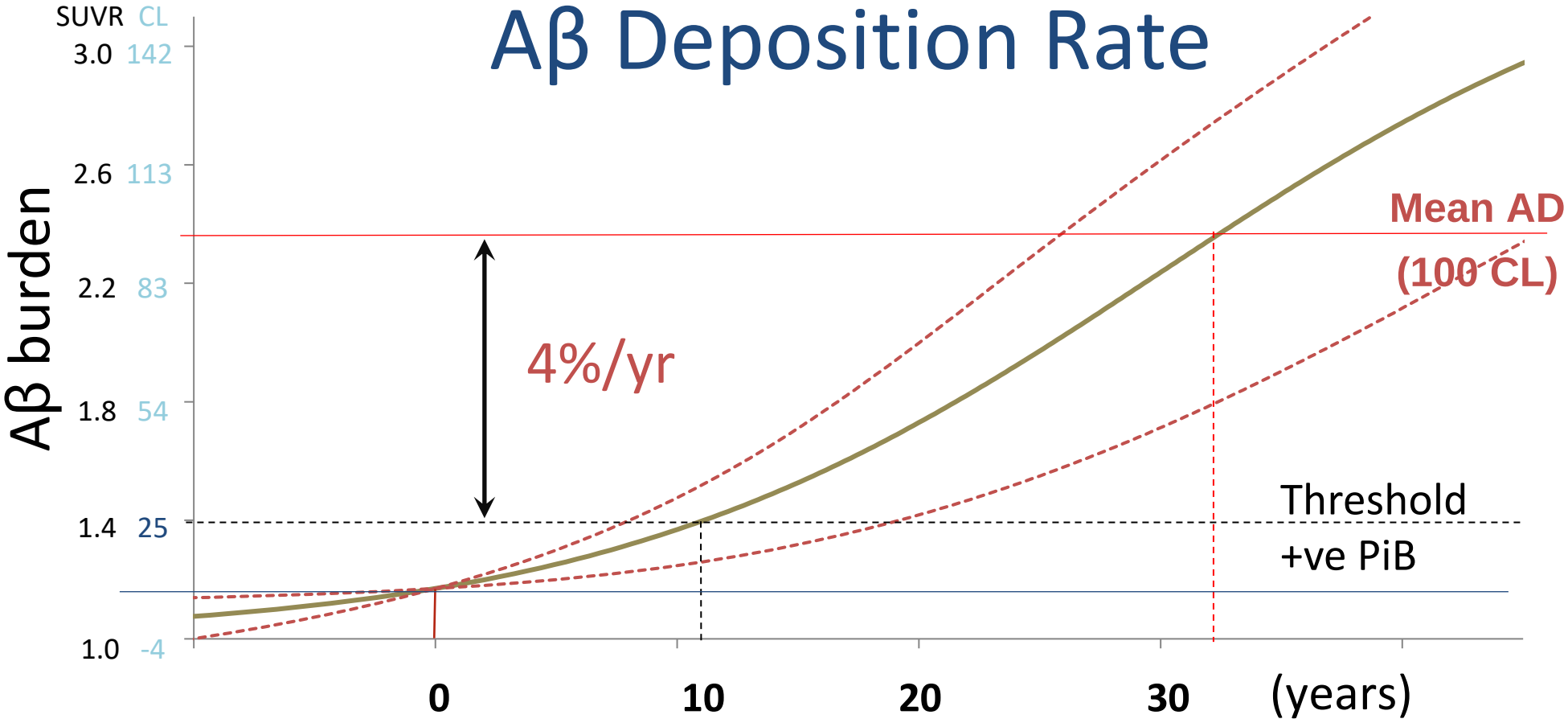
% Healthy Population Amyloid PET +ve



< 60 yrs data from Washington University

Rowe CC, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, Neurobiology of Aging 2010. Citations 1,127

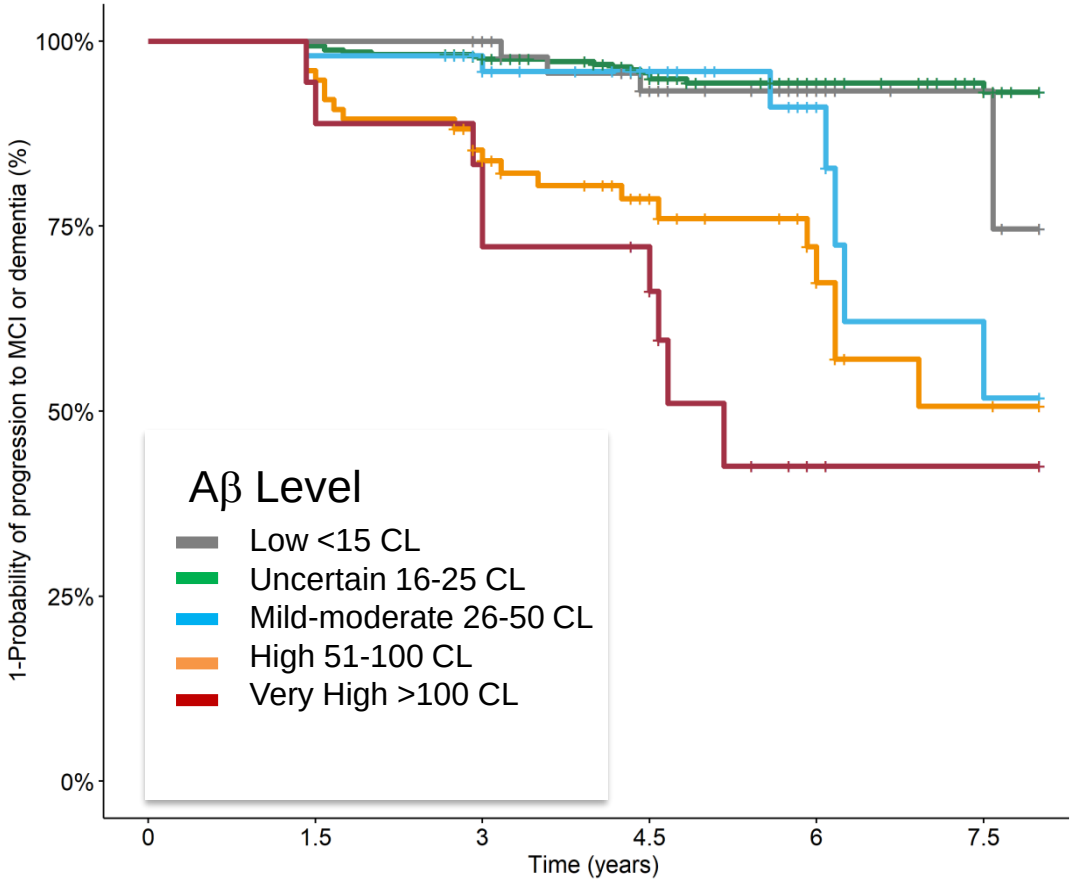
Aβ Deposition Rate



Lancet Neurol. 2013. cites 2,300

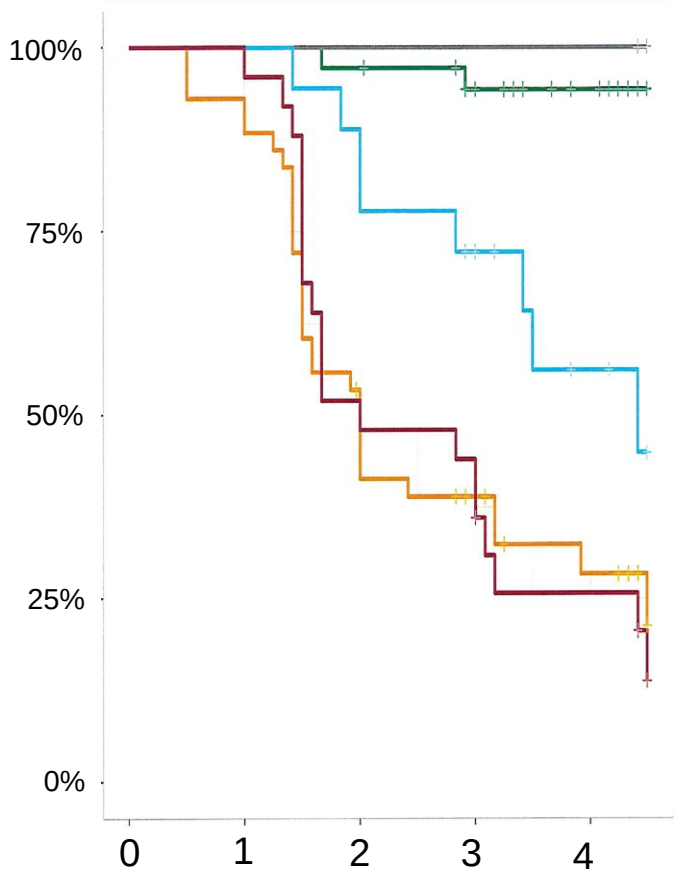
Aβ level vs disease progression

Normal to Mild Cognitive Impairment:



Time (Years)

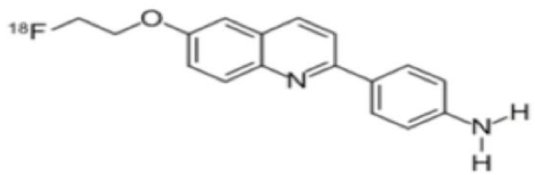
MCI to dementia:

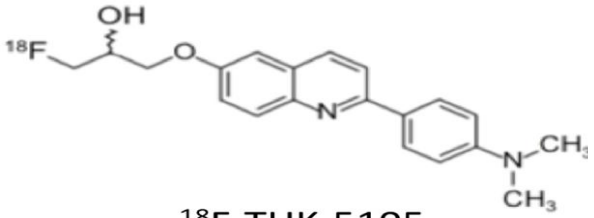


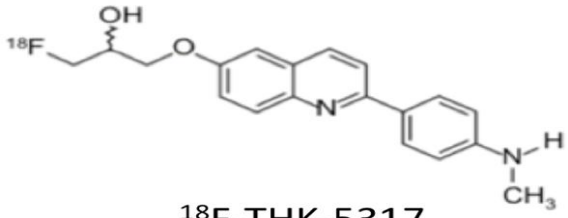
Time (Years)

van der Kall LM, … Rowe CC. Association of β-Amyloid level, clinical progression and longitudinal cognitive change in normal older individuals. **Neurology** 2021

Selective tau imaging tracers


^{18}F-THK-523


^{18}F-THK-5105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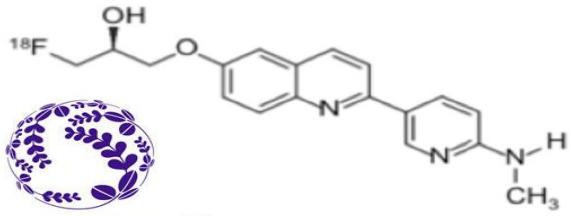
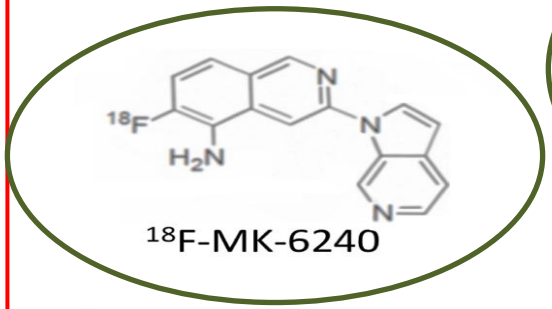
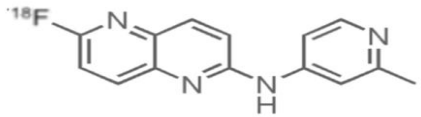
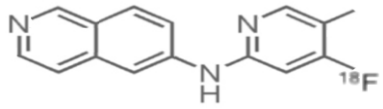

^{18}F-THK-5351


^{18}F-MK-6240


^{18}F-JNJ311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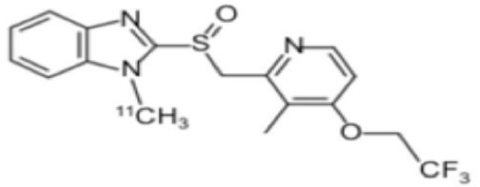
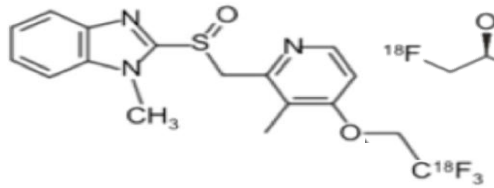
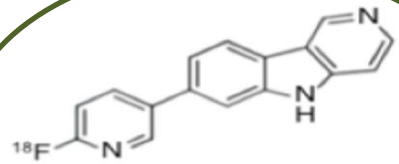
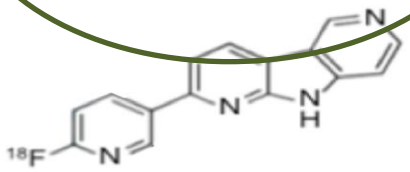

^{11}C-N-Methyl Lansoprazole


^{18}F-N-Methyl Lansoprazole


^{18}F- AV1451 (a.k.a. T807)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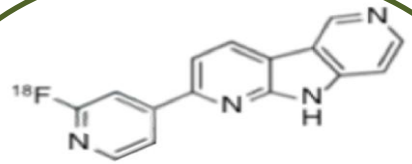
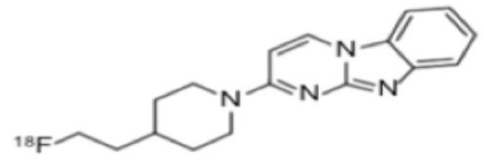
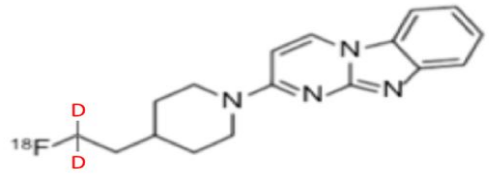
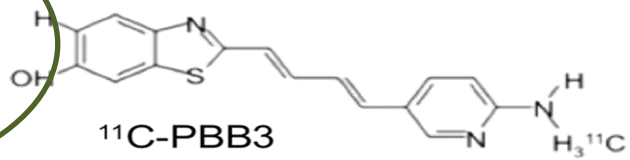
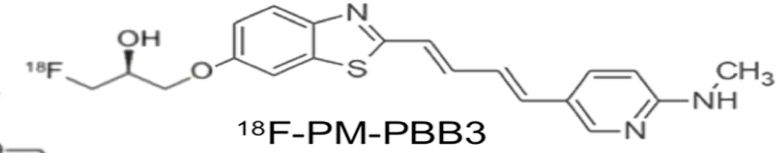

^{18}F-PI-2620


^{18}F-T808

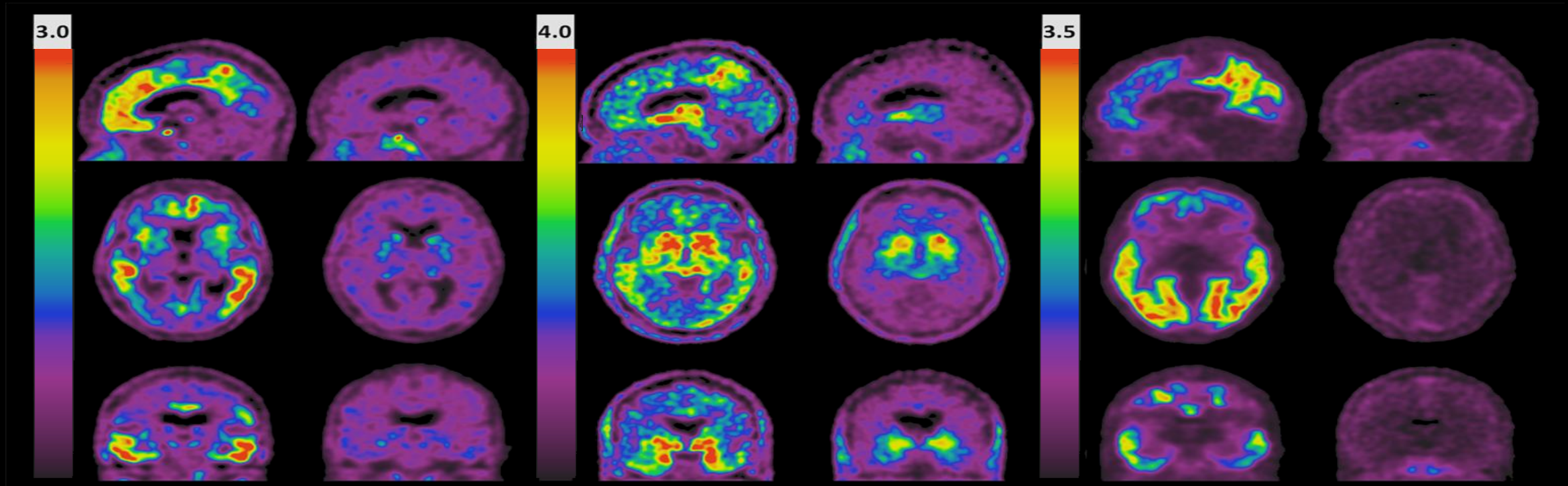

^{18}F-GTP1


^{11}C-PBB3


^{18}F-PM-PBB3

Three Tau Tracers - Examples

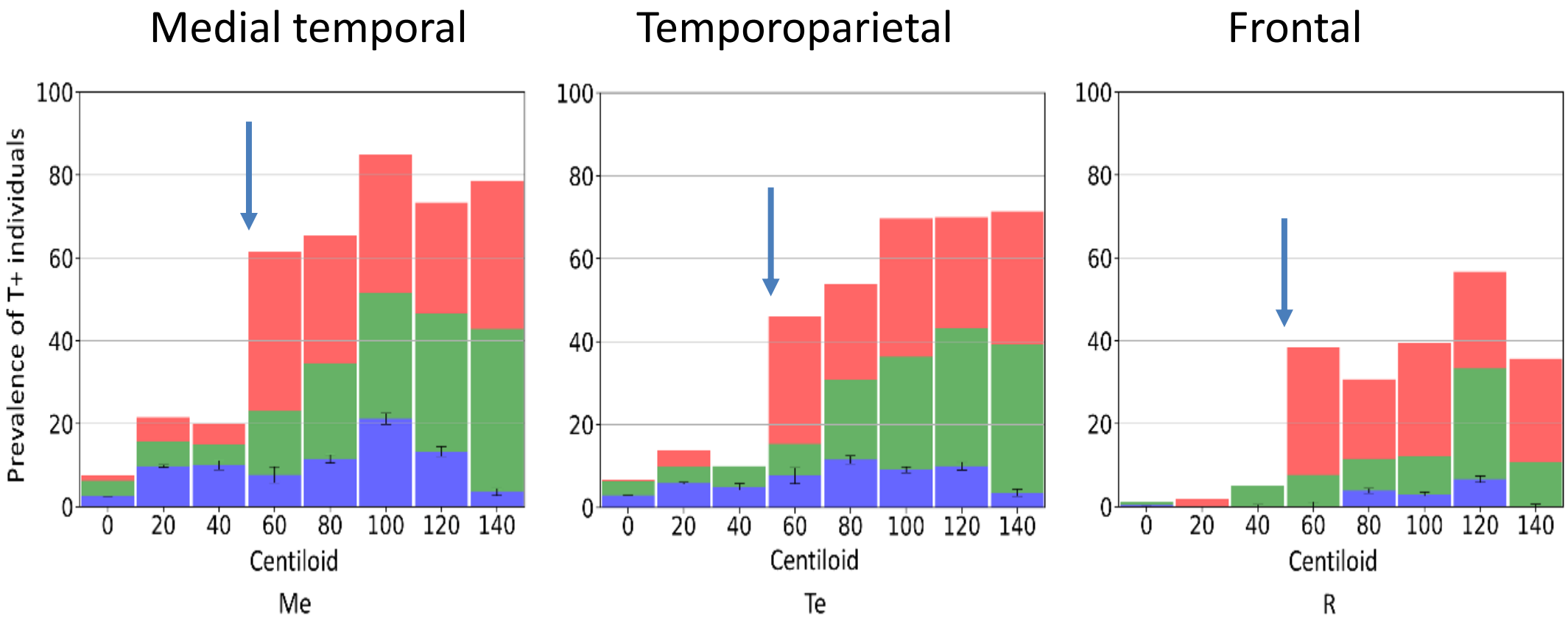
^{18}F-AV1451 ^{18}F-THK5351 ^{18}F-MK6240



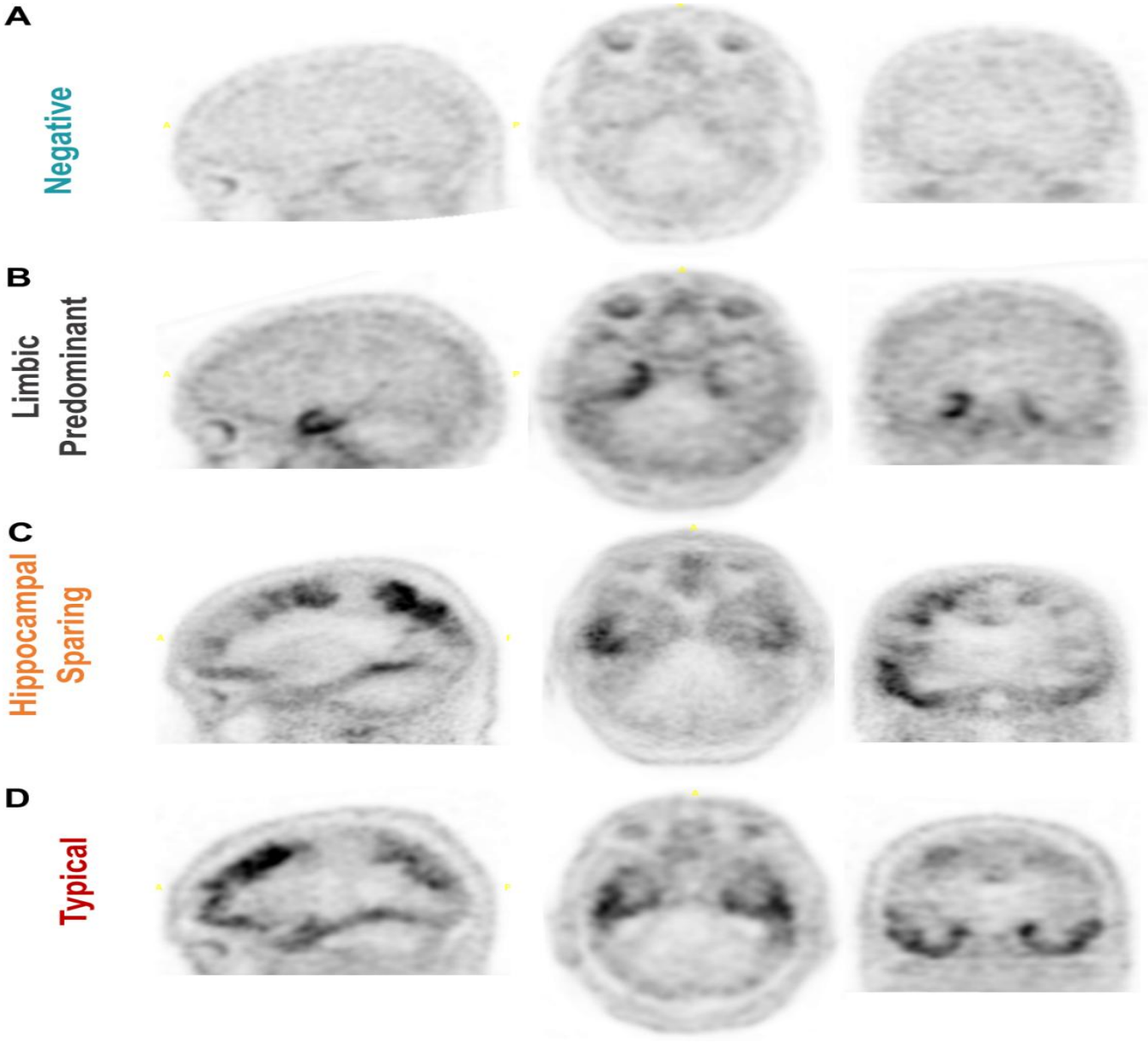
AD HC AD HC AD HC

Amyloid Cascade Hypothesis for AD
confirmed by PET: Tau PET usually negative below 50 CL of amyloid

N=475 MK6240.



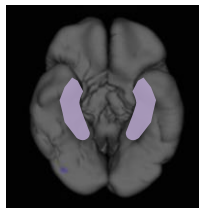
Blue – CN; Green – MCI; Red - Dementia

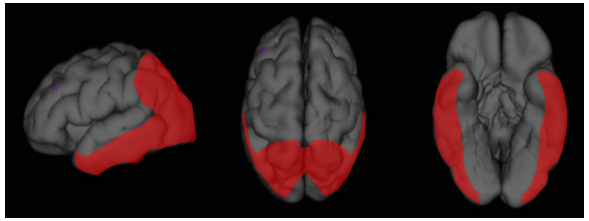


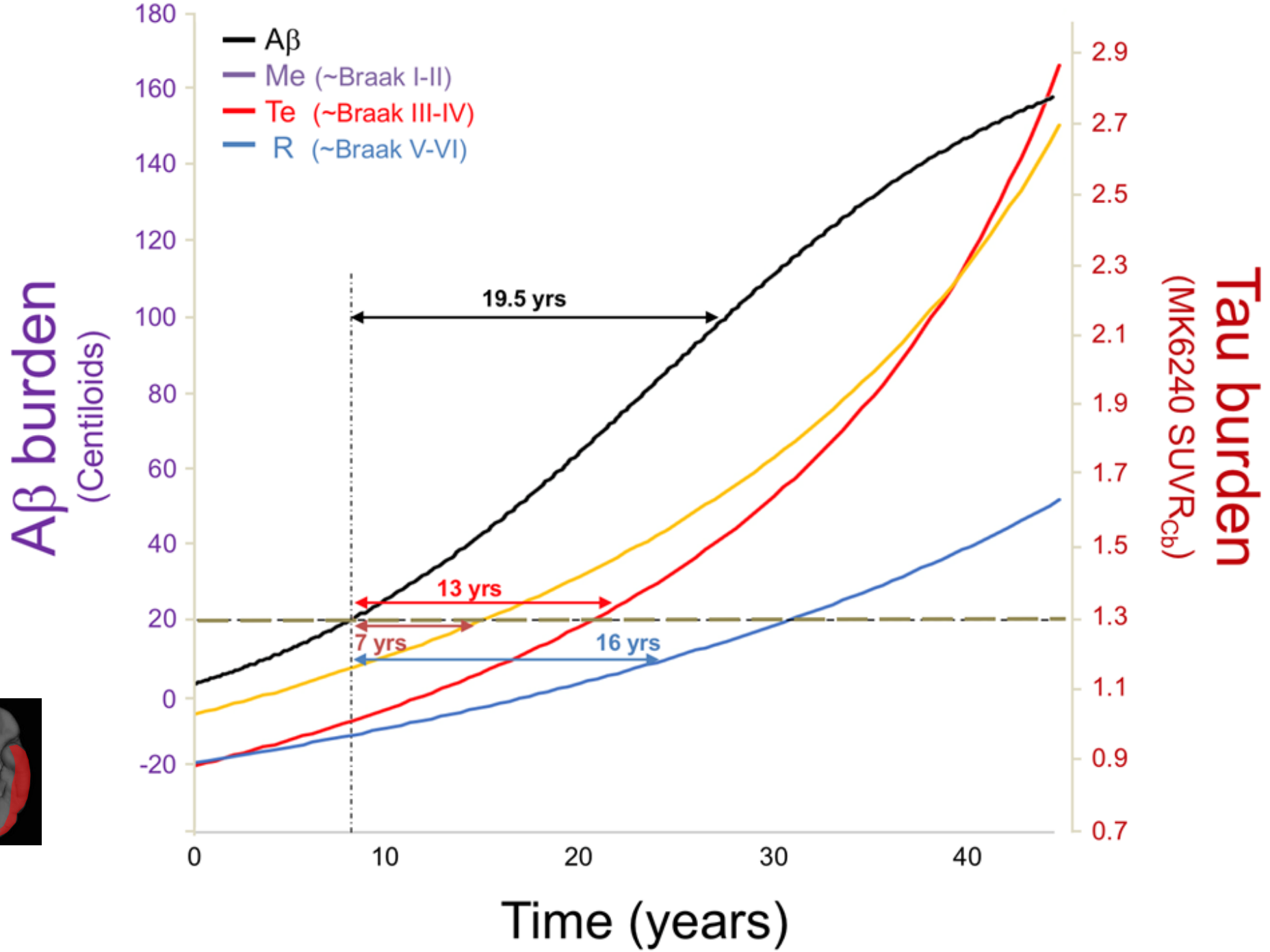
Patterns of MK-6240

A is an Older Control,
B-D are MCI/early AD

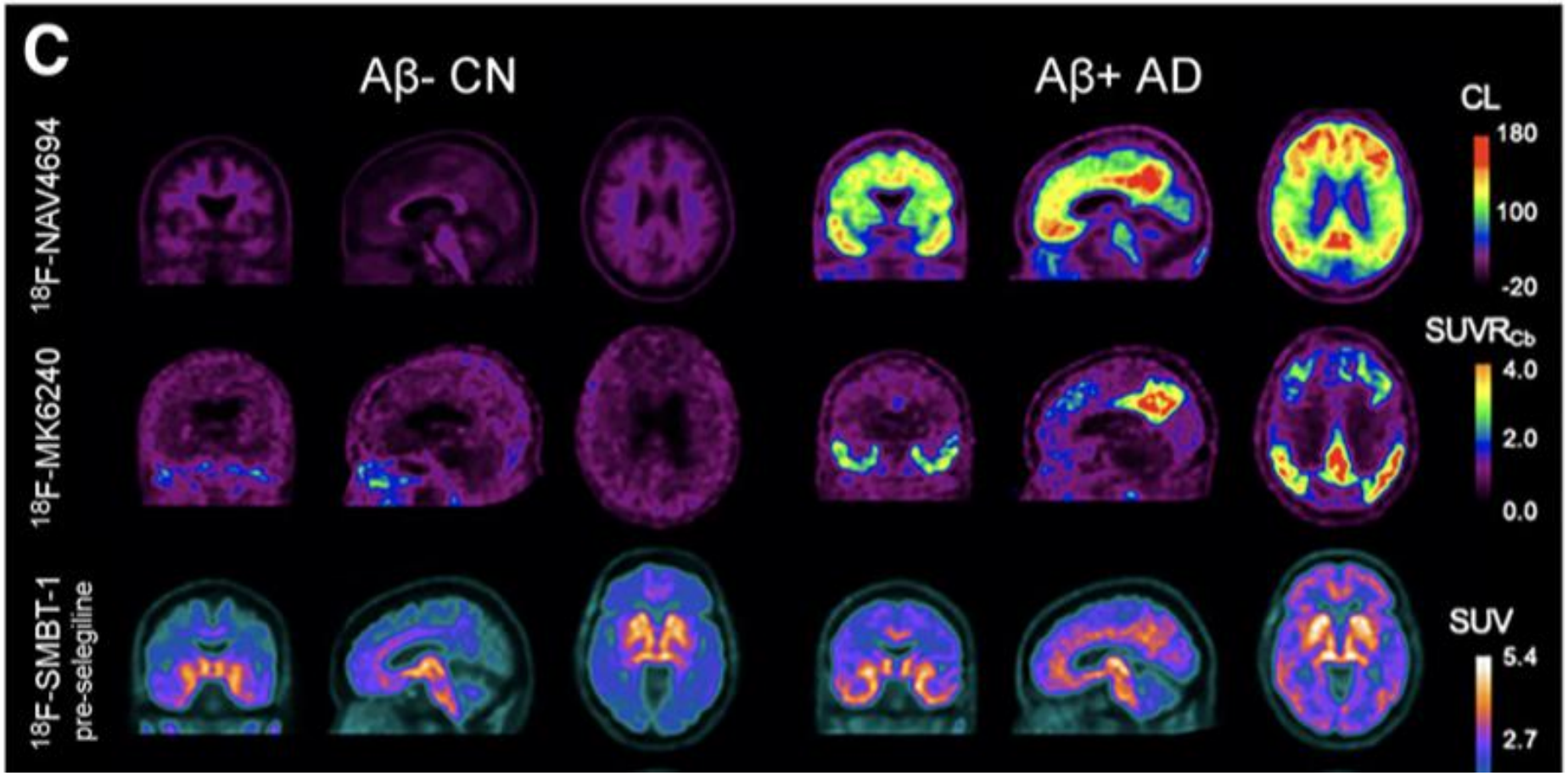
Aβ curve (longitudinal) with paired cross sectional tau







PET for amyloid plaques, tau tangles and now also neuroinflammation research in AIBL



Amyloid plaques

Tau tangles

Activated Astrocytes

ImmunoPrecipitation Mass Spectroscopy

LETTER

doi:10.1038/nature25456

High performance plasma amyloid-β biomarkers for Alzheimer's disease

Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[1,5], James Doecke[6], Vincent Doré[3,6], Chris Fowler[4], Qiao-Xin Li[4], Ralph Martins[7], Christopher Rowe[3,4], Taisuke Tomita[8], Katsumi Matsuzaki[9], Kenji Ishii[10], Kazunari Ishii[11], Yutaka Arahata[5], Shinichi Iwamoto[2], Kengo Ito[1,5], Koichi Tanaka[2], Colin L. Masters[4] & Katsuhiko Yanagisawa[1]

NATURE 2018 doi:10.1038/nature25456
(1,555 citations)

Phospho-tau Blood Biomarkers

Tatebe et al. Molecular Neurodegeneration (2017) 12:63
DOI 10.1186/s13024-017-0206-8

Molecular Neurodegeneration

RESEARCH ARTICLE Open Access

Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome

2017

Harutsugu Tatebe[1,2], Takashi Kasai[1], Takuma Ohmichi[1], Yusuke Kishi[3], Tomo
Masaki Kondo[1], David Allsop[5] and Takahiko Tokuda[1,6*]

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Blood-based biomarkers might improve the diagnostic work-up of AD

Featured Article

Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography

Michelle M. Mielke, Clinton E. Hagen, Jing Xu, Xiyun Chai, Prashanthi Vemuri, Val J. Lowe, David C. Airey, David S. Knopman, Rosebud O. Roberts, Mary M. Machulda, Clifford R. Jack Jr., Ronald C. Petersen, Jeffrey L. Dage, ... See fewer authors

JAMA | Original Investigation

Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

2020

Sebastian Palmqvist, MD, PhD; Shorena Janelidze, PhD; Yakeel T. Quiroz, PhD; Henrik Zetterberg, MD, PhD; Francisco Lopera, MD; Erik Stomrud, MD, PhD; Yi Su, PhD; Yinghua Chen, MSc; Geidy E. Serrano, PhD; Antoine Leuzy, PhD; Niklas Mattsson-Carlgren, MD, PhD; Olof Strandberg, PhD; Ruben Smith, MD, PhD; Andres Villegas, MD; Diego Sepulveda-Falla, MD; Xiyun Chai, MD; Nicholas K. Proctor, BS; Thomas G. Beach, MD, PhD; Kaj Blennow, MD, PhD; Jeffrey L. Dage, PhD; Eric M. Reiman, MD; Oskar Hansson, MD, PhD

Title	Publication Year	First Author	Last Author	Journal	Volume
Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome	2017	Tatebe	Tokuda	Mol Neurodegener	12(1)
Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography	2018	Mielke	Dage	Alzheimers & Dem	14(8)
Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease	2019	Palmqvist	Hansson	EMBO Mol Med	11(12)
Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia	2020	Janelidze	Hansson	Nat Med	26(3)
Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration	2020	Thijssen	Bower	Nat Med	26(3)
Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts	2020	Karikari	Blennow	Lancet Neurol	19(5)
Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders	2020	Palmqvist	Hansson	JAMA	324(8)
Plasma Phospho-Tau Identifies Alzheimer's Co-Pathology in Patients with Lewy Body Disease	2020	Hall	Hansson	Mov Disord	Epub
Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease	2020	Janelidze	Hansson	JAMA Neurol	78(2)
Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease	2020	Mattsson Carlgren	Hansson	Brain	143(11)
Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease	2020	Mattsson Carlgren	Hansson	Sci Adv	6(16)
Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease	2020	Janelidze	Hansson	Nat Commun	11(1)
Plasma p-tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterisation of cognitive decline	2020	Lantero Rodriguez	Ashton	Acta Neuropathol	140 (3)
Plasma phospho-tau181 in presymptomatic and symptomatic familial Alzheimer's disease: a longitudinal cohort study	2020	O'Connor	Fox	Mol Psychiatry	Epub
Diagnostic and prognostic value of serum NfL and p-Tau 181 in frontotemporal lobar degeneration	2020	Benussi	Borroni	Neurol Neurosurg Psychiat	91(9)
Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease	2020	Barthelemy	Bateman	J Exp Med	217(11)
Cerebrospinal fluid phospho-tau T217 outperforms T181 as a biomarker for the differential diagnosis of Alzheimer's disease and PET amyloid-positive patient identification	2020	Barthelemy	Bateman	Alzheimers Res Ther	12(1)
A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease	2020	Barthelemy	Bateman	Nat Med	26(3)
Sleep Deprivation Affects Tau Phosphorylation in Human Cerebrospinal Fluid	2020	Barthelemy	Lucey	Ann Neurol	87(5)
Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations	2021	Cullen	Hansson	Nature Aging	1
Soluble P-tau217 reects amyloid and tau pathology and mediates the association of amyloid with tau	2021	Mattsson Carlgren	Hansson	ResearchSquare	
Plasma biomarkers of Alzheimer's disease predict cognitive decline and could improve clinical trials in the cognitively unimpaired elderly	2021	Cullen	Hansson	medRxiv	
				ResearchSquare	
The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease	2021	Simren	Ashton	Alzheimers & Dem	Epub
Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology	2021	Ashton	Blennow	Acta Neuropathol	Epub
Population-based blood screening for preclinical Alzheimer's disease in a British birth cohort at age 70	2021	Keshavan	Ashton	Brain	Epub
Longitudinal Associations of Blood Phosphorylated Tau181 and Neurofilament Light Chain With Neurodegeneration in Alzheimer Disease	2021	Moscoso	Scholl	JAMA Neurol	Epub
Association between polygenic risk score of Alzheimer's disease and plasma phosphorylated tau in individuals from the Alzheimer's Disease Neuroimaging Initiative	2021	Zettergren	Blennow	Alzheimers Res Ther	13(1)
Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum	2021	Moscoso	Scholl	Brain	144(1)
Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative	2021	Karikari	Zetterberg	Mol Psychiatry	26(2)
Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study	2021	Brickman	Mayeux	Alzheimers Dement	Epub
Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures	2021	Palmqvist	Hansson	Nat Med	Epub
Soluble P-tau217 reflects amyloid and tau pathology and mediates the association of amyloid with tau	2021	Mattsson Carlgren	Hansson	EMBO Mol Med	Epub

Recent AIBL/ADNeT Publications on Blood-Based Biomarkers for Alzheimer's Disease

Detection and staging of Alzheimer's disease by plasma pTau217 on a high throughput platform
eBioMedicine, November 2024

Plasma p217+tau vs NAV4694 amyloid and MK6240 tau PET across the Alzheimer continuum.
Alzheimer's and Dementia, DADM 2022

Two-year prognostic utility of plasma p217+tau across the Alzheimer's continuum.
J Prevention of Alzheimer's Disease, 2023


Detection and staging of Alzheimer's disease by plasma pTau217 on a high throughput immunoassay platform

Alzheimer's Disease biological PET staging using plasma p217+tau.
Communications Medicine, 2024 under review

Head-to-head comparison of plasma biomarkers across the AD continuum in an Australian population
Alzheimer's Association, June 2023

Plasma biomarkers in chronic single moderate-severe traumatic brain injury
Brain- Oxford Academic, November 2024

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Blood-Based Biomarkers in the News

High media interest:
Page one Herald Sun,
4 radio and 4 TV interviews
in response to release of
latest AIBL/ADNeT blood
biomarker paper.

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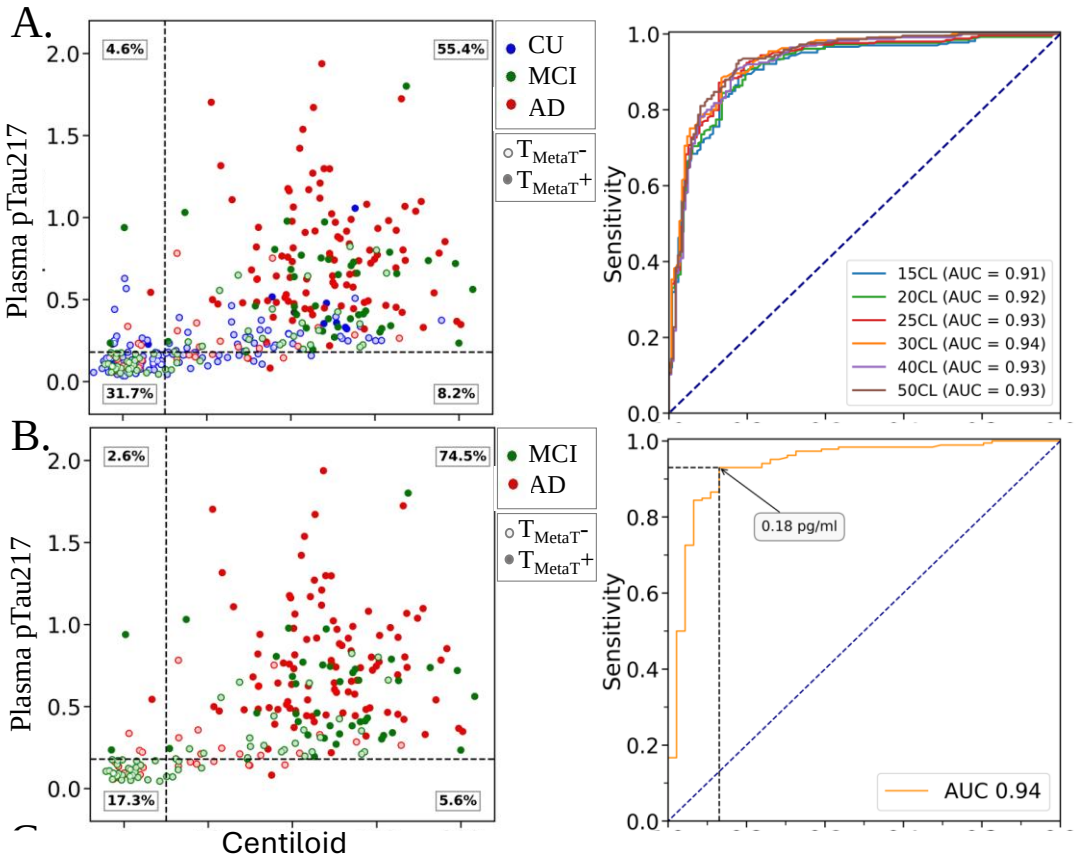
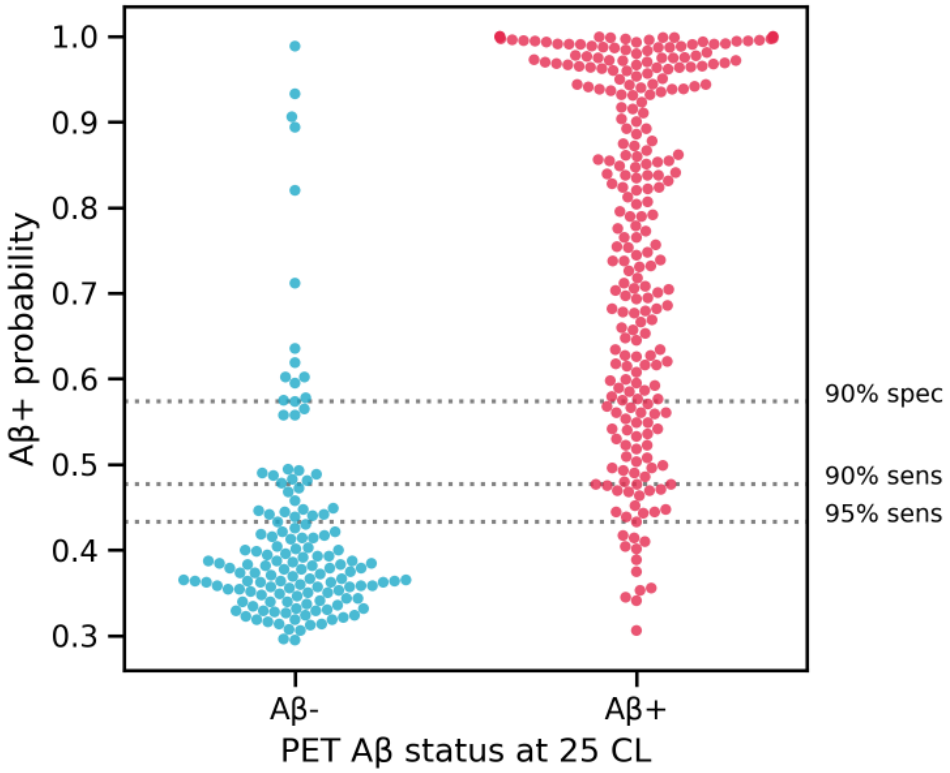
Herald Sun, pg 1 & 3
November 1, 2024

Seven News, 6pm, Metro Melbourne & syndicated nationally
November 1, 2024

Fujirebio Lumipulse plasma pTau217 vs Amyloid PET



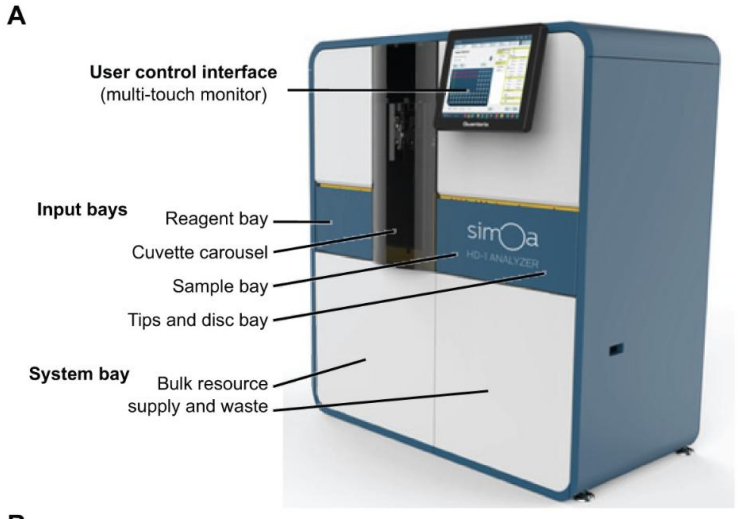


Single threshold gave **87% accuracy.**
Two-threshold approach set for 95% sensitivity and 90% specificity, give **92% accuracy** excluding the 18% indeterminant.
In MCI/mild dementia PPV was >95%.

Accurate Detection and Staging of Alzheimer's Disease by Plasma pTau217 on a High Throughput Immunoassay Platform. Feizpour A,… Rowe CC. eBioMed 2024

Throughput

- Simoa – 35 tests per 3 hours. Research installations world-wide.
- Fujirebio Lumipulse G – 120 tests per hour – international clinical installation base. FDA approved CSF AD biomarkers.
- C_2N – warehouse full of mass spec machines only in St. Louis.



Simoa HD-X

Lumipulse G 1200

AD Blood-Based Biomarkers

Project Rationale

- Address need for early diagnosis for improved patient health outcomes
- Aligns with NDAP Obj 3: Improving dementia diagnosis and post diagnostic care
- Accurate AD diagnosis relies on cerebrospinal fluid (CSF) testing or amyloid PET scans
- CSF collection requires lumbar puncture and amyloid PET scans are costly and not widely accessible

Blood-Based Biomarkers

- **Accuracy**
  - pTau217 high correlation with AD pathology seen on PET scans
  - **92% accuracy** (compared to 75% with current practice specialist diagnosis)
- **Affordability**
  - Cost-effective (~$250)
    - compared to $1,500 existing blood test available to Australians and processed in the US
    - compared to CSF (~$650) and amyloid PET (~$2000)
- **Accessibility**
  - GP or specialist orders test, bloods collected at local pathology, assays run in Australia

AIBL/ADNeT goal is to create world-first, wide access to a Blood Test for AD

National blood-based biomarker testing infrastructure

- Equip and operate a high capacity, national demonstration site that will give Australians immediate access to this “breakthrough” plasma pTau217 diagnostic test while collecting data on appropriate use and diagnostic and management impact.
- Efficiently utilise an existing fully NATA accredited testing laboratory at the Florey Institute

KPIs

- Up to 50,000 Australians with possible early dementia tested (including CALD and First Nations) in the first 3 years
- Improved GP and specialist confidence in AD diagnosis
- Reduced delay in diagnosis and earlier referral for specialist treatment

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Capacity Building & Blood Test Diagnosis in Primary Care

National GP education in Alzheimer's Prevention and Early Diagnosis

- Delivery of the validated and scalable ADNeT online **GP education program**
- Incentivise and empower GPs as education program is delivered in partnership with **accurate diagnostic blood test** for AD
- Provide **guidelines** to make this diagnosis with accuracy and confidence
- Foster communities of practice and GP dementia leaders
- Provide advice on evidence-based drug and non-drug MCI and dementia interventions (cognitive training, exercise, OT)

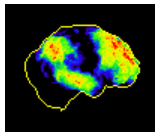
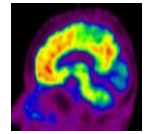
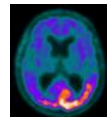
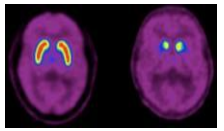
Future Diagnostic Practice

Clinical assessment
+ MRI/CT/bloods
+ plasma assay

-ve

Tailored Imaging

- FDG PET
- Beta-amyloid PET
- DAT/VMAT imaging
- Tau PET

+ve

Alzheimer's Disease

Lumipulse pTau217 had 97% PPV in MCI/mild AD