Dementia Update: Biomarkers And New Drug Treatments

Professor Christopher Rowe FRACP MD
Director, Molecular Imaging Research, Austin Health
Director, Australian Dementia Network, University of Melbourne

Disclosures:

- Enigma/ Cerveau Technologies – Research grant to institution, Scientific Advisory Board
- Biogen – Research grant to institution, Medical Education Working Group
- Abbvie - Research grant to institution
- Janssen - Research grant to institution
- Prothena – Scientific advisory board
- Merck – Scientific input consultant
- Janssen - Research grant to institution
- Eisai Australia – Medical Advisory Board
- Lilly Australia – Medical Advisory Board
- Roche – speaker honorarium

Correct diagnosis and prognosis of the dementias is hard!

Clinical criteria for Alzheimer's Disease have only
Sensitivity 70-80%, Specificity 70%

- *Knopman DS, Neurology 2001- average of 13 studies with pathological confirmation*
- *Beach TG, J Neuropath Exp Neurol. 2012. NIA AD Centers*

30% of "AD" patients referred to clinical trials are amyloid negative

Clinical diagnosis requires dementia so it is late and only has moderate accuracy!

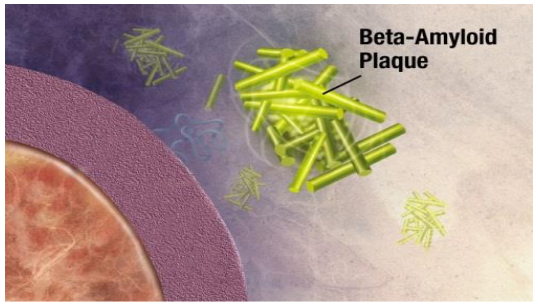
Mild Cognitive Impairment (MCI) precedes dementia but has variable definition and low disease specificity.

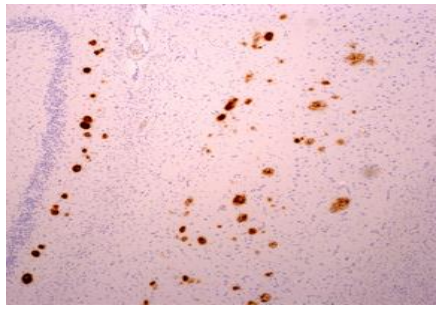
MCI is a symptom not a diagnosis.

- 50% of MCI will progress to AD dementia
- 15-20% have other dementias.
- 35-40% do not develop dementia.

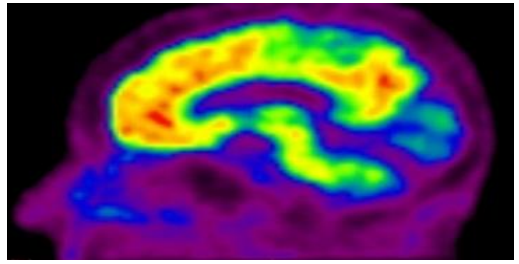
Alzheimer's Pathology

1. Extracellular Beta-amyloid Plaques

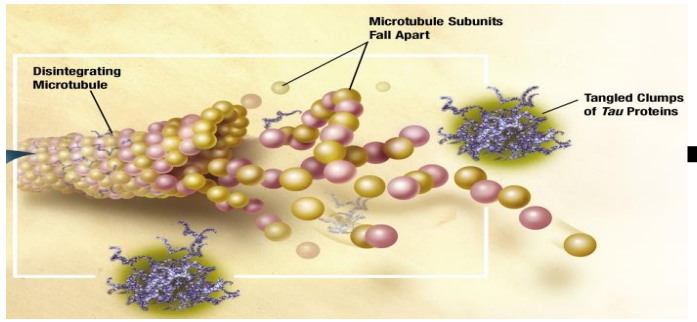


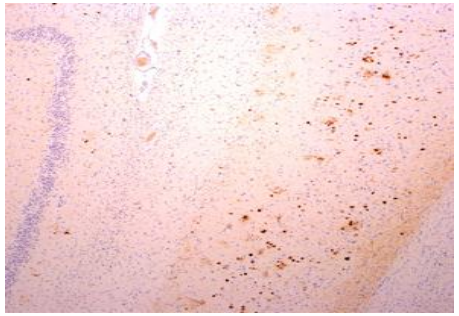


2004

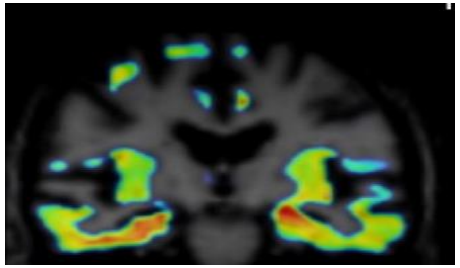


2. Intracellular Neurofibrillary Tangles (tau aggregates)





2013



Australian Dementia Network
REGISTRY. CLINICS. TRIALS.

Blood Diagnostics for Alzheimer's Disease are Coming!

- C_2N through Healius Pathology Australia provide access to PrecivityAD2 blood test (88% accurate for AD) for $1500 AUD
- LabCorp in USA providing Fujirebio Lumipulse pTau217 for $185 USD
- Roche completing international trial of pTau181 and pTau217 on Elecsys platform
- Beckman-Coulter validating pTau217
- pTau217 (ALZpath and Janssen) kits are available for Quanterix SIMOA immunoassay platform in Australia
- "Real world" trials are underway in Australia in memory clinics and primary care run by Australian Dementia Network (ADNeT) and Florey

Amyloid Antibody Therapies are Coming!

- Lecanemab (Eisai) approved and funded in USA, Japan, South Korea and China but not by EMA (Europe). UK approved but not NHS funded. Recent negative TGA decision in Australia under appeal.
- Donanemab (Lilly) approved by FDA.
- Preclinical prevention trials are in progress.
- Both drugs require proof of amyloid by PET or CSF. Amyloid PET at 12 months recommended for Donanemab to determine need for continued dosing.
- Better results at low Tau load (neurofibrillary tangles) on PET.

The need for early accurate diagnosis of AD has never been greater but there are cost and accessibility restrictions on PET and reluctance in many countries to have a lumbar puncture.

How good are the blood biomarkers for AD?

Where can they replace PET?

Medicare rebate for FDG PET for AD available since November 2021
- 17,500 performed in 2023

Medicare Benefits Schedule - Item 61560

Search Results for Item 61560

Category 5 - DIAGNOSTIC IMAGING SERVICES

61560

Group I4 - Nuclear Medicine Imaging

Subgroup 2 - PET

FDG PET study of the brain, performed for the diagnosis of Alzheimer's disease, if:

a. clinical evaluation of the patient by a specialist, or in consultation with a specialist, is equivocal; and

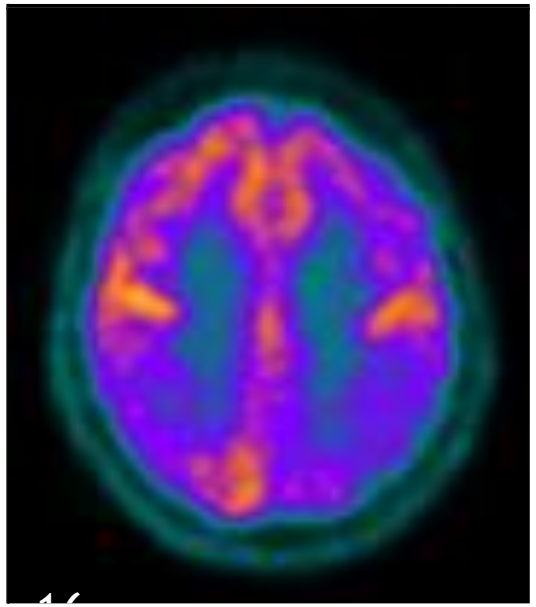
b. the service includes a quantitative comparison of the results of the study with the results of an FDG PET study of a normal brain from a reference database; and

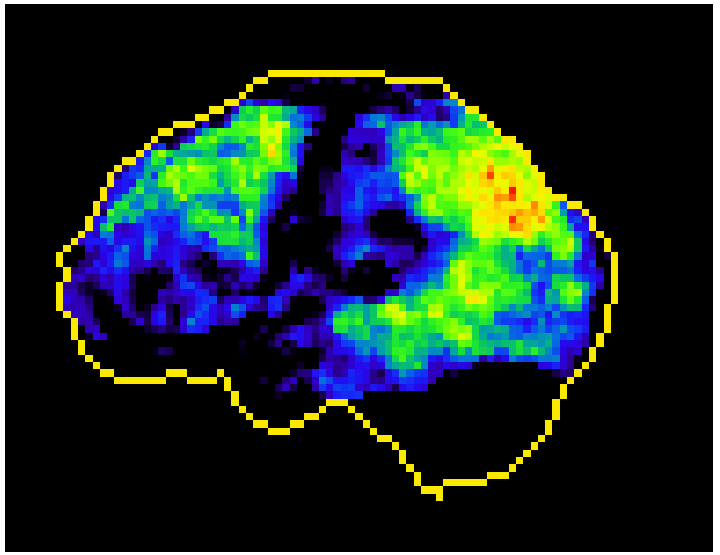
c. a service to which this item applies has not been performed on the patient in the previous 12 months; and

d. a service to which item 61402 applies has not been performed on the patient in the previous 12 months for the diagnosis or management of Alzheimer's disease

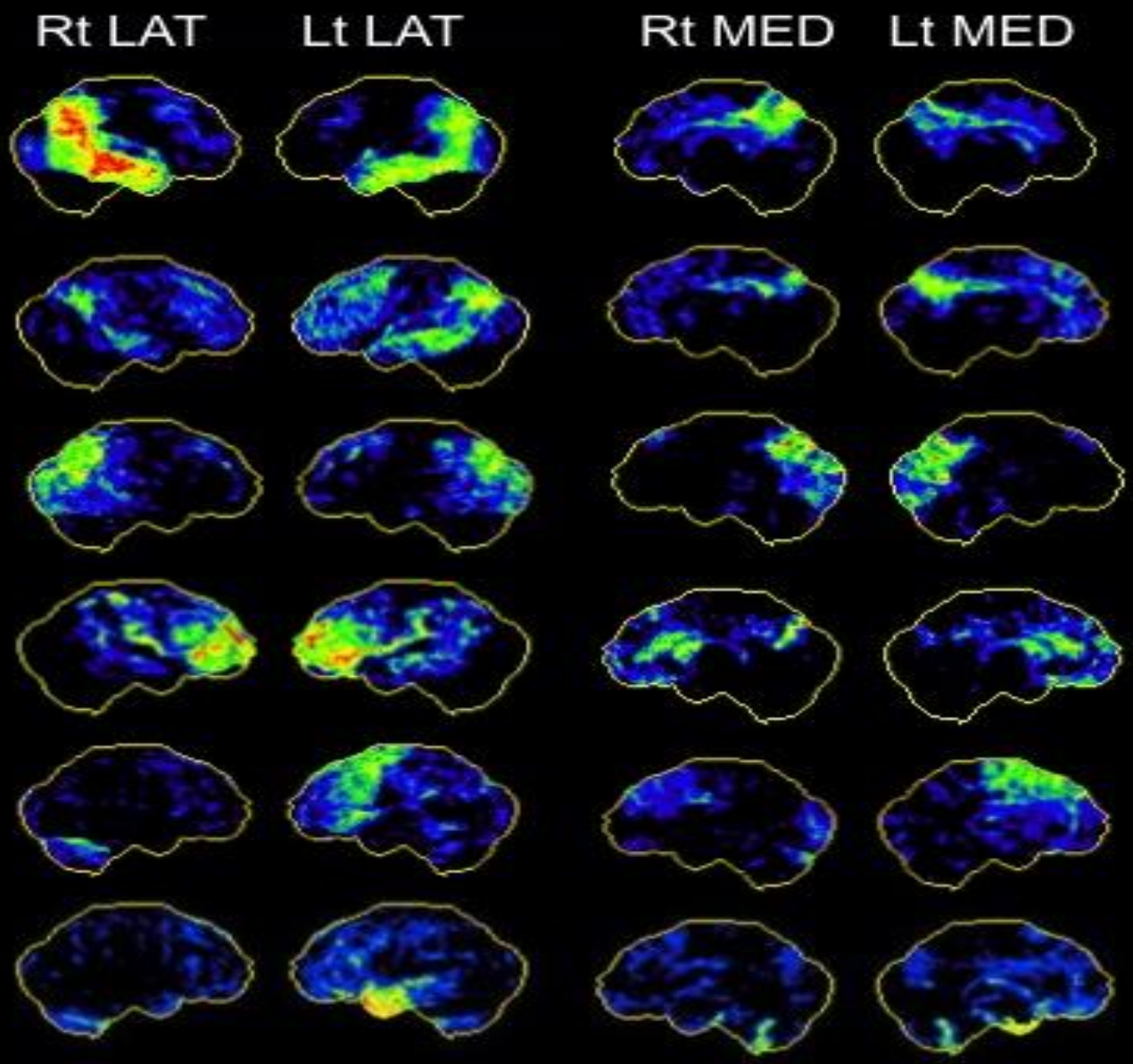
Applicable not more than 3 times per lifetime (R)

Typical AD pattern of hypometabolism





^{18}F-FDG PET Patterns in Dementia



Alzheimer's Disease

Logopenic Aphasia variant of AD

Dementia with Lewy bodies

Behavioural subtype of Frontotemporal Dementia

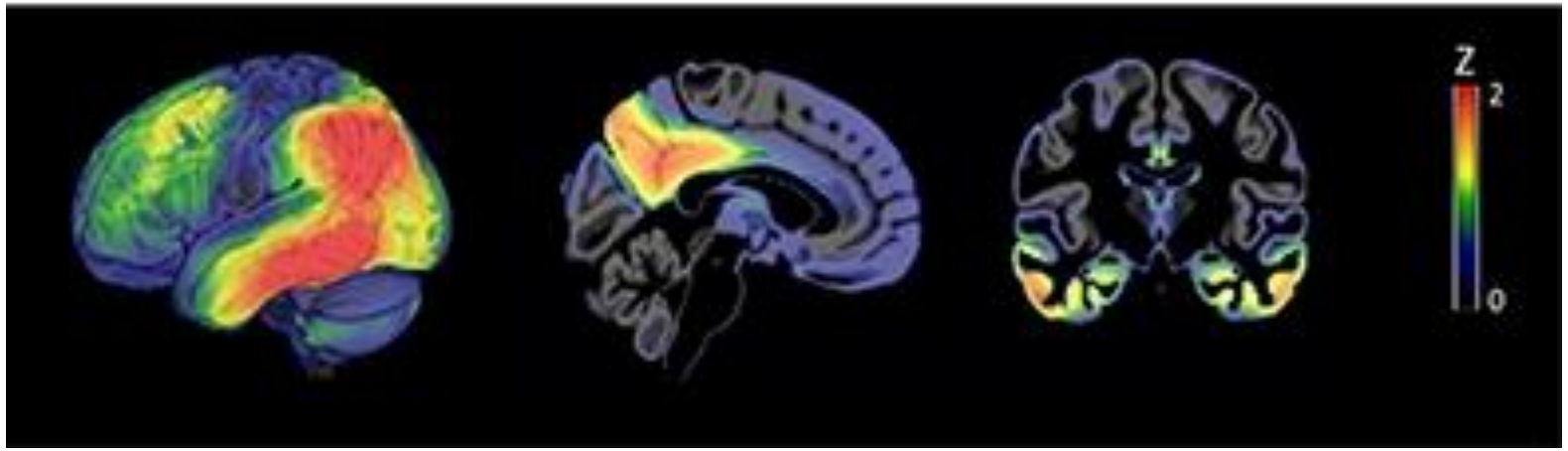
Progressive Non-fluent Aphasia subtype of FTD

Semantic Dementia subtype of FTD

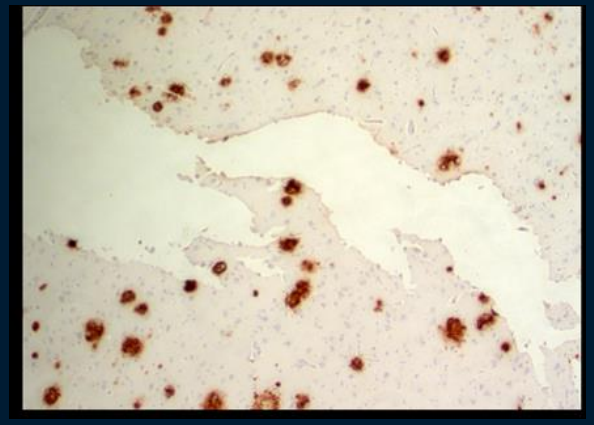
FDG PET Patterns:
Limbic Predominant Age related TDP-43 Encephalopathy (LATE) versus Alzheimer's disease

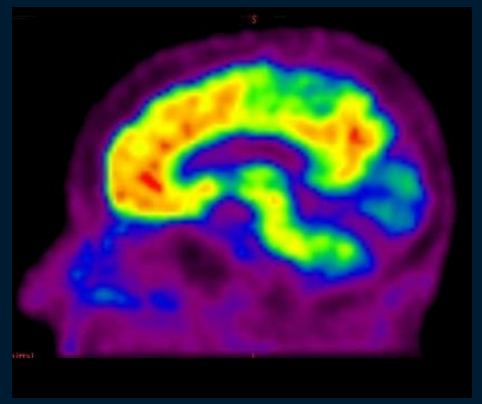
LATE

AD



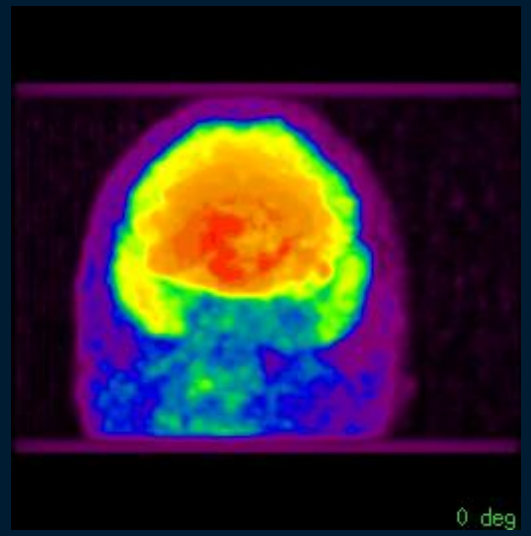
2004: *Beta-amyloid PET Begins*





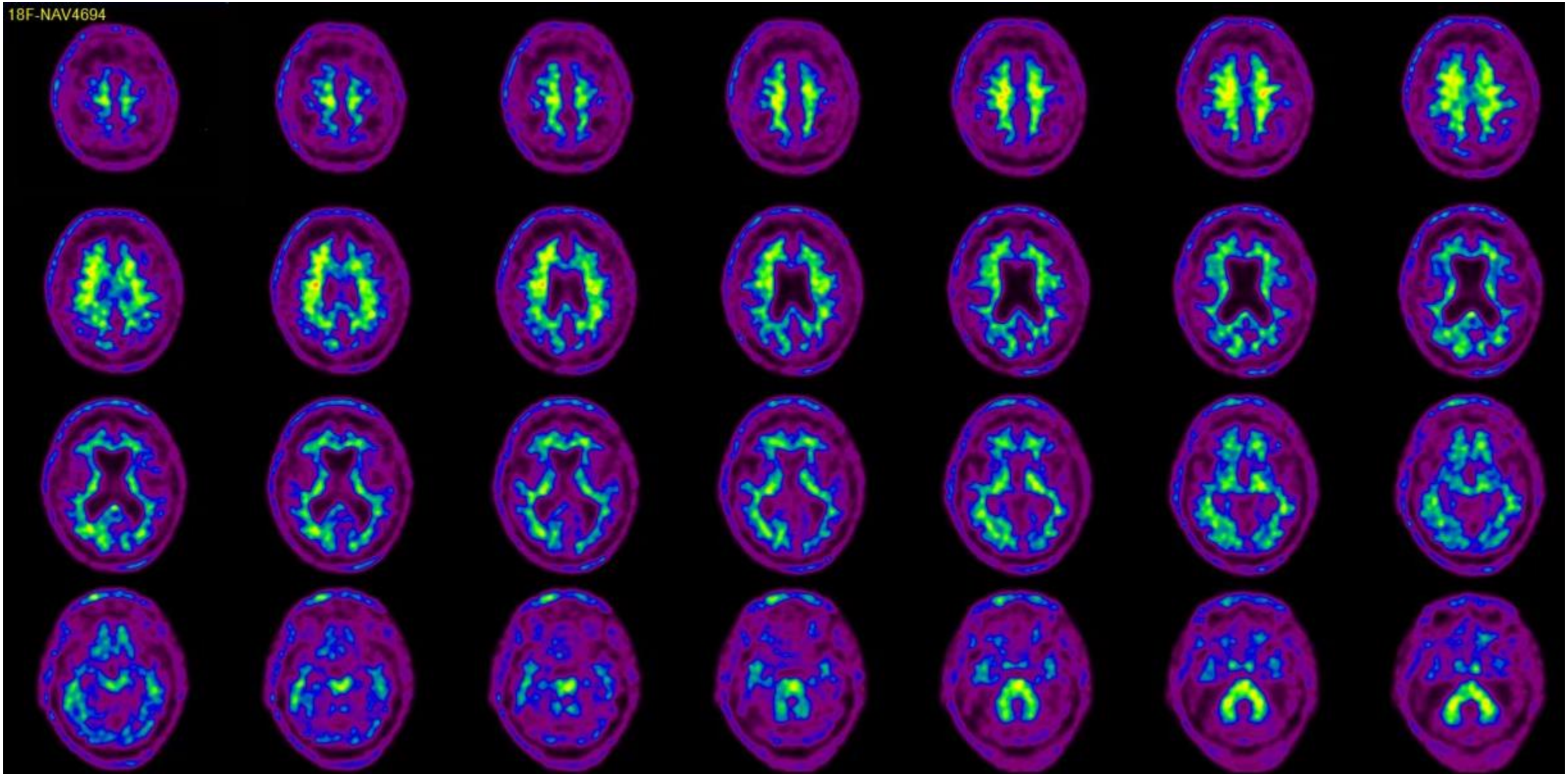
^{11}C-PiB

Inventors:
Chet Mathis
William Klunk
University of Pittsburgh

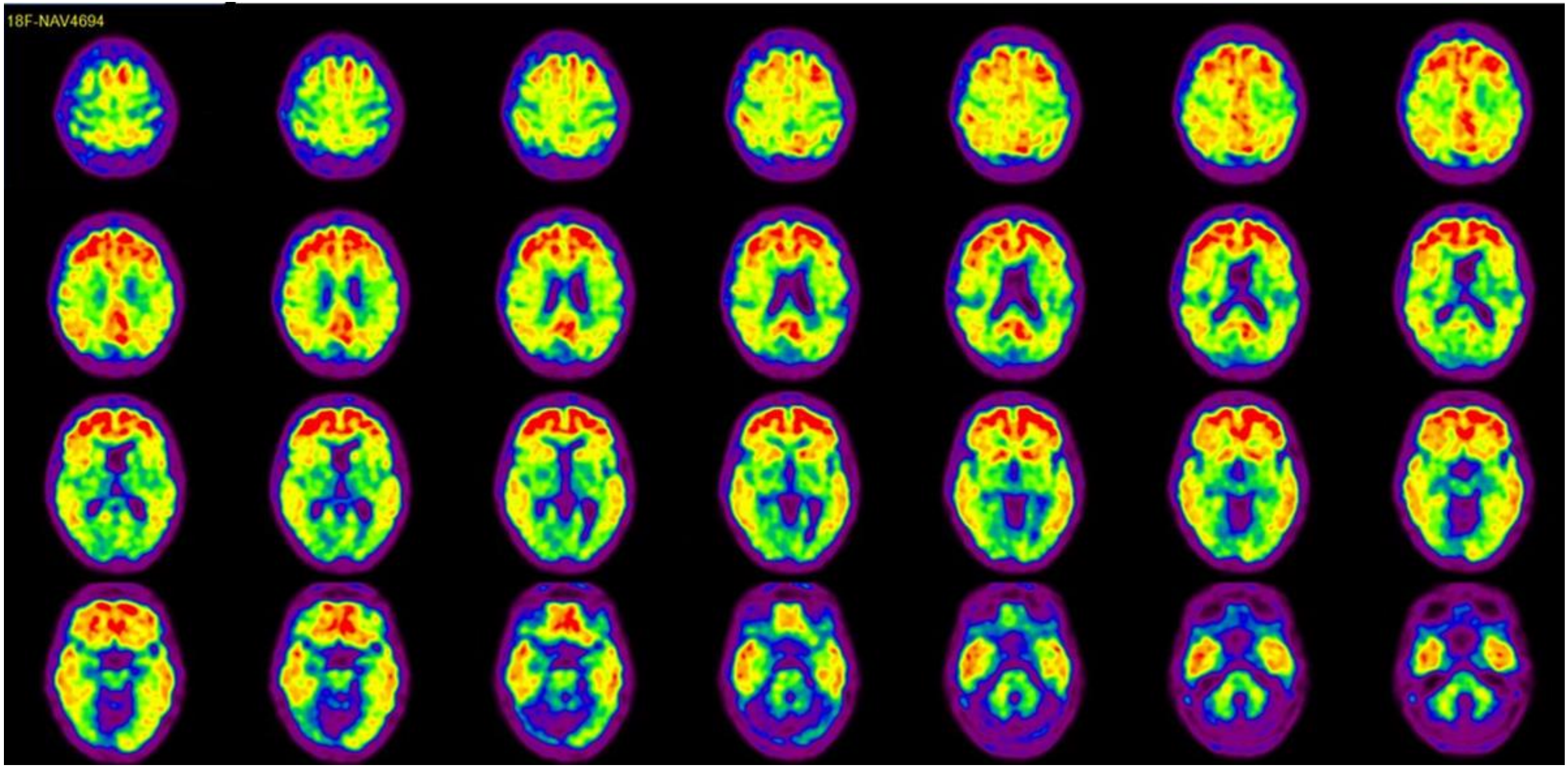


Alzheimer's Disease

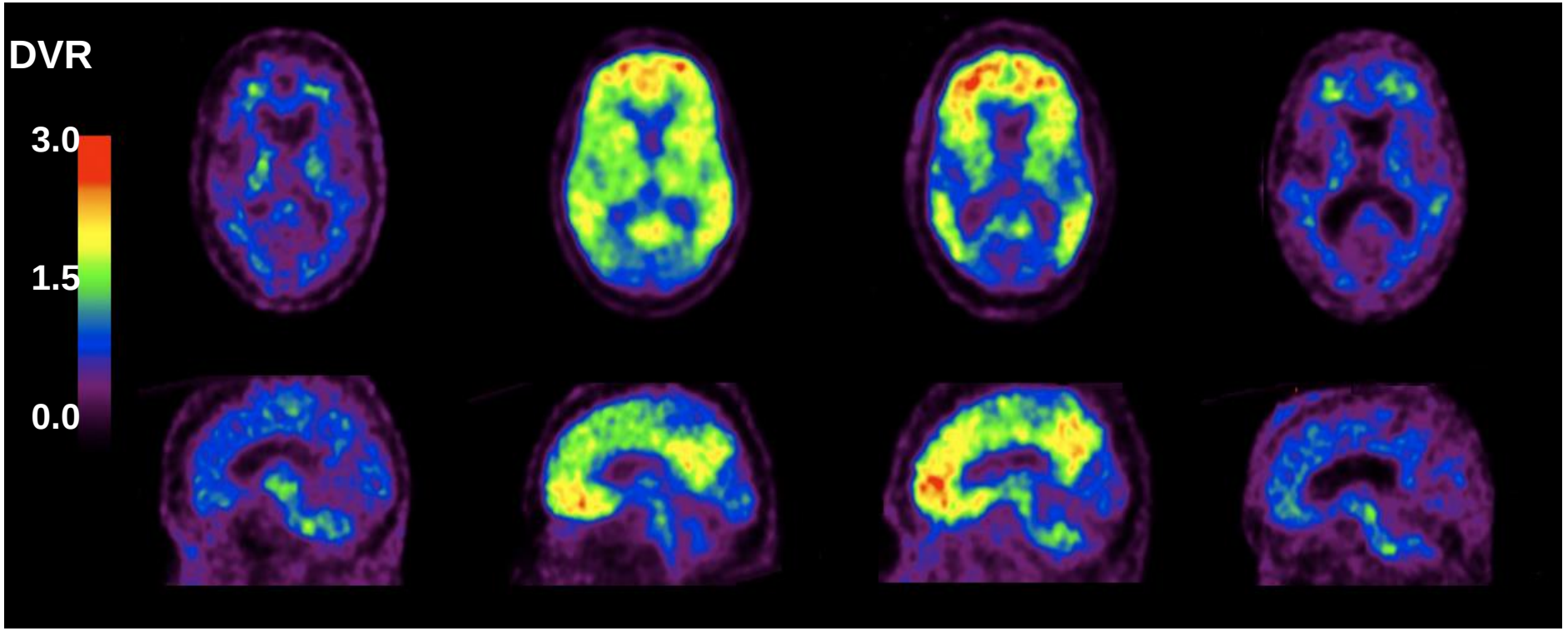
Amyloid scan : Negative



Amyloid scan : Positive



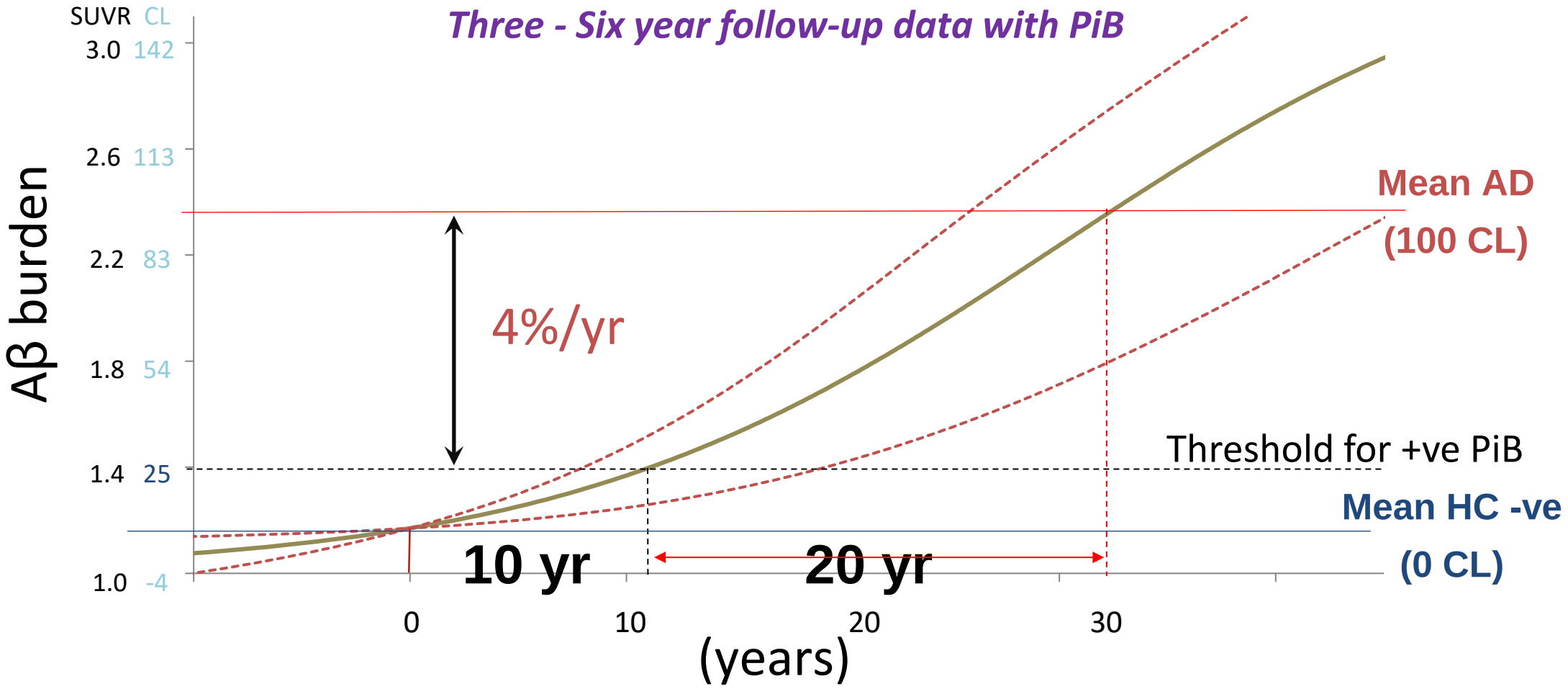
Aβ PET: Dementia Specific Patterns



HC DLB AD FTD

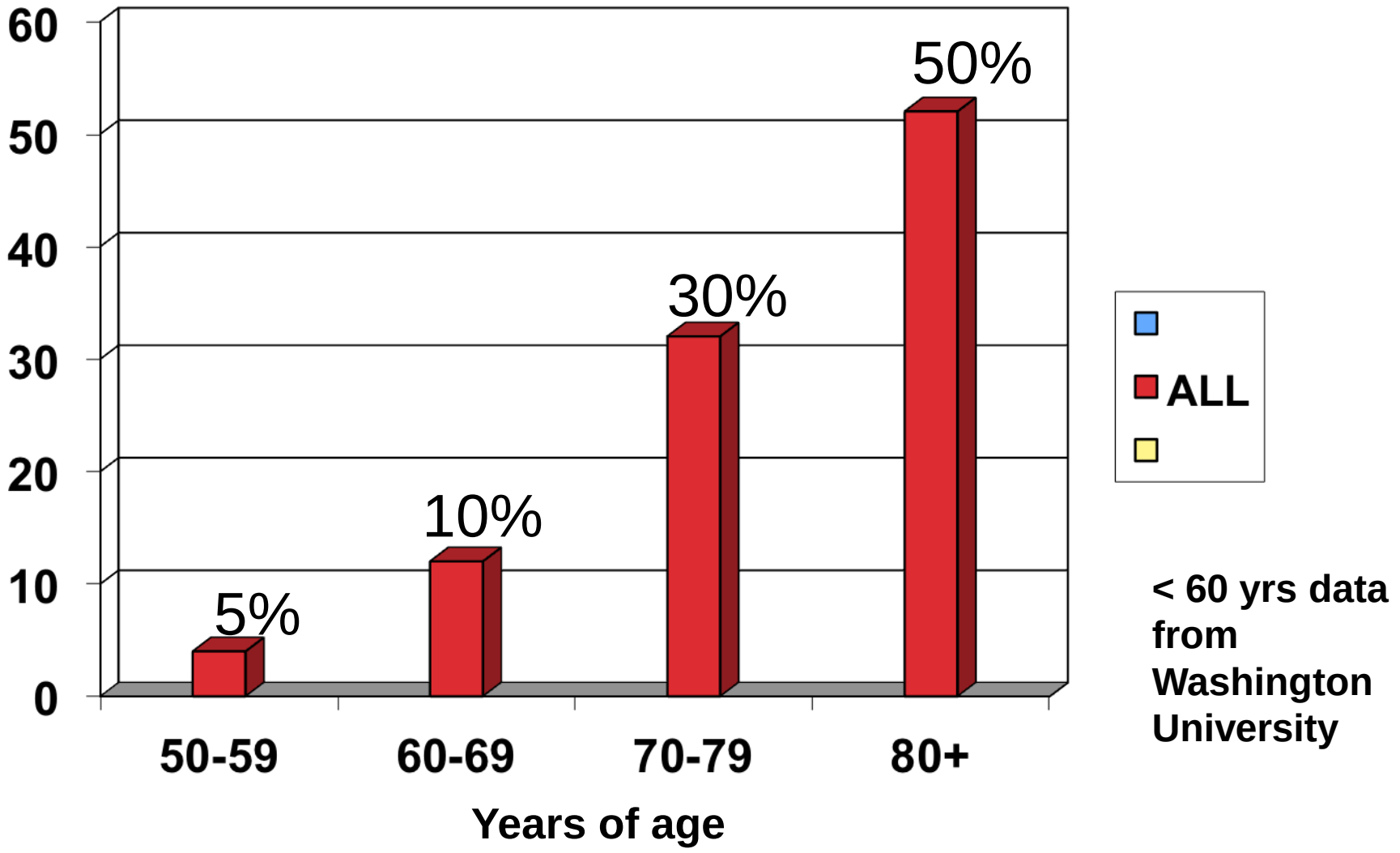
Rowe CC, et al. ***Neurology*** *2007.*

Aβ Deposition Rate



Villemagne VL, et al. Lancet Neurol. 2013.

% Healthy population PiB+ve

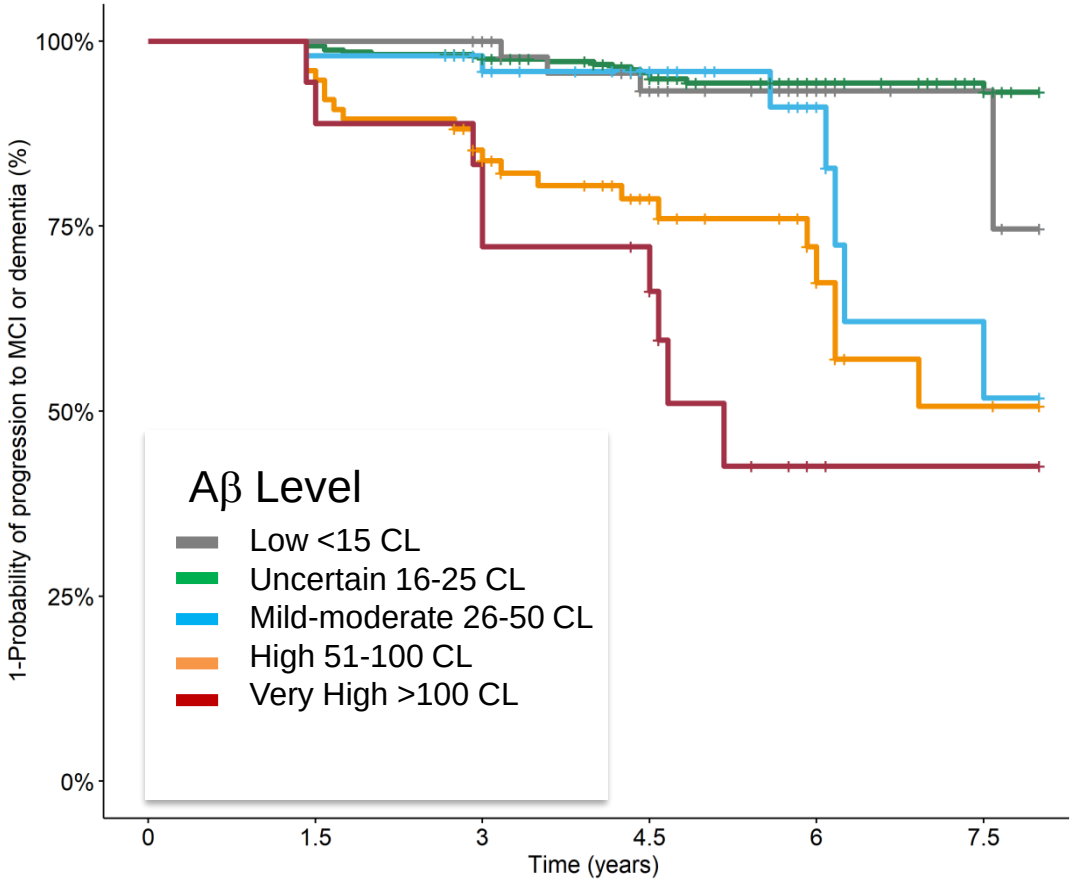


< 60 yrs data from Washington University

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

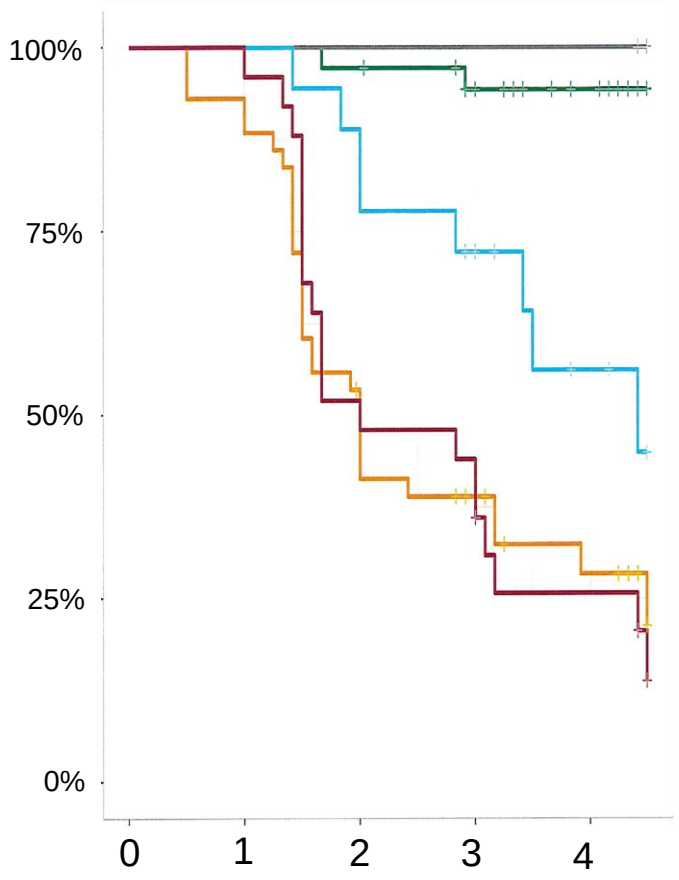
Aβ level vs disease progression

Normal to Mild Cognitive Impairment:



Time (Years)

MCI to dementia:

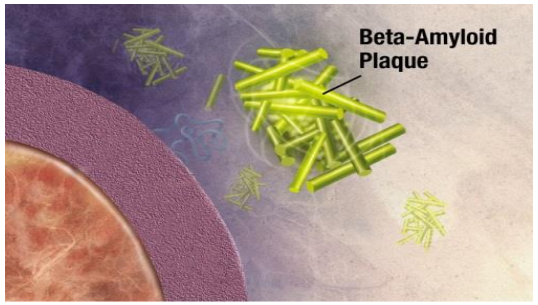


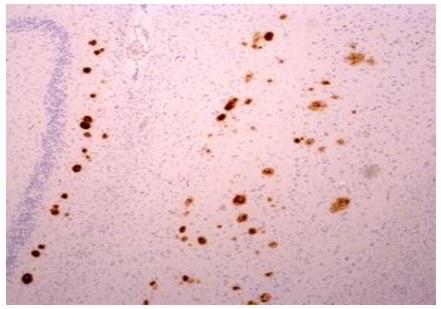
Time (Years)

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

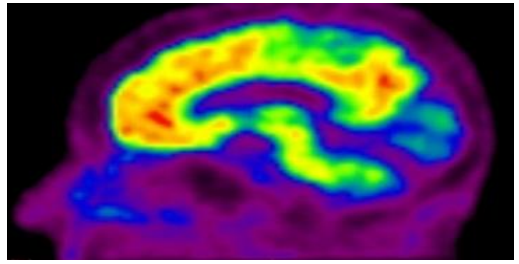
Alzheimer's Pathology

1. Extracellular Beta-amyloid Plaques

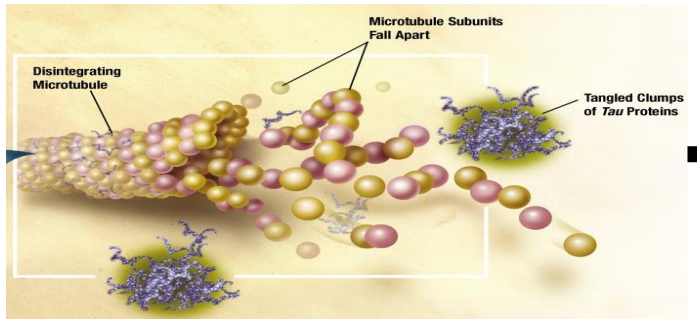


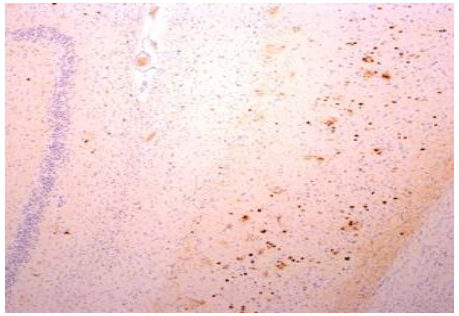


2004

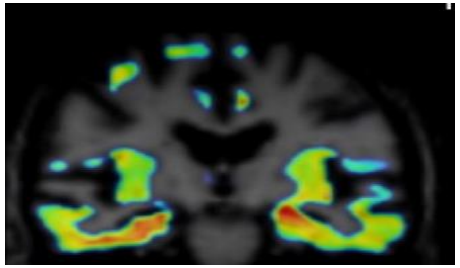


2. Intracellular Neurofibrillary Tangles (tau aggregates)

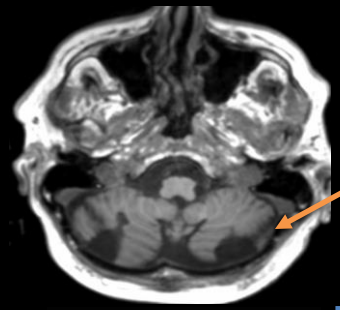




2013

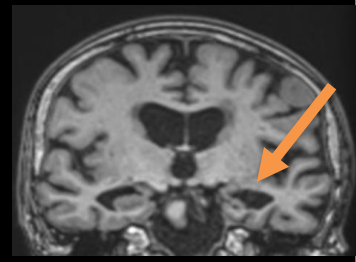


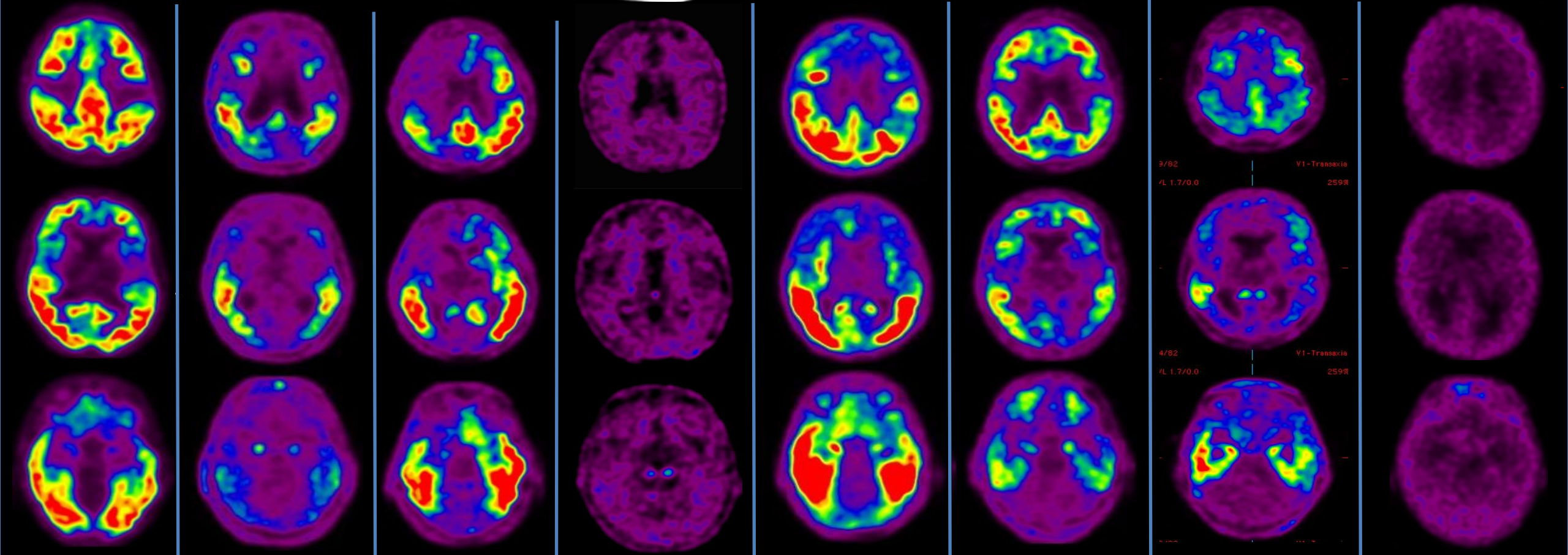
Tau PET in “AD”



Cerebellar Cognitive Affective Syndrome

LATE (TDP-43)

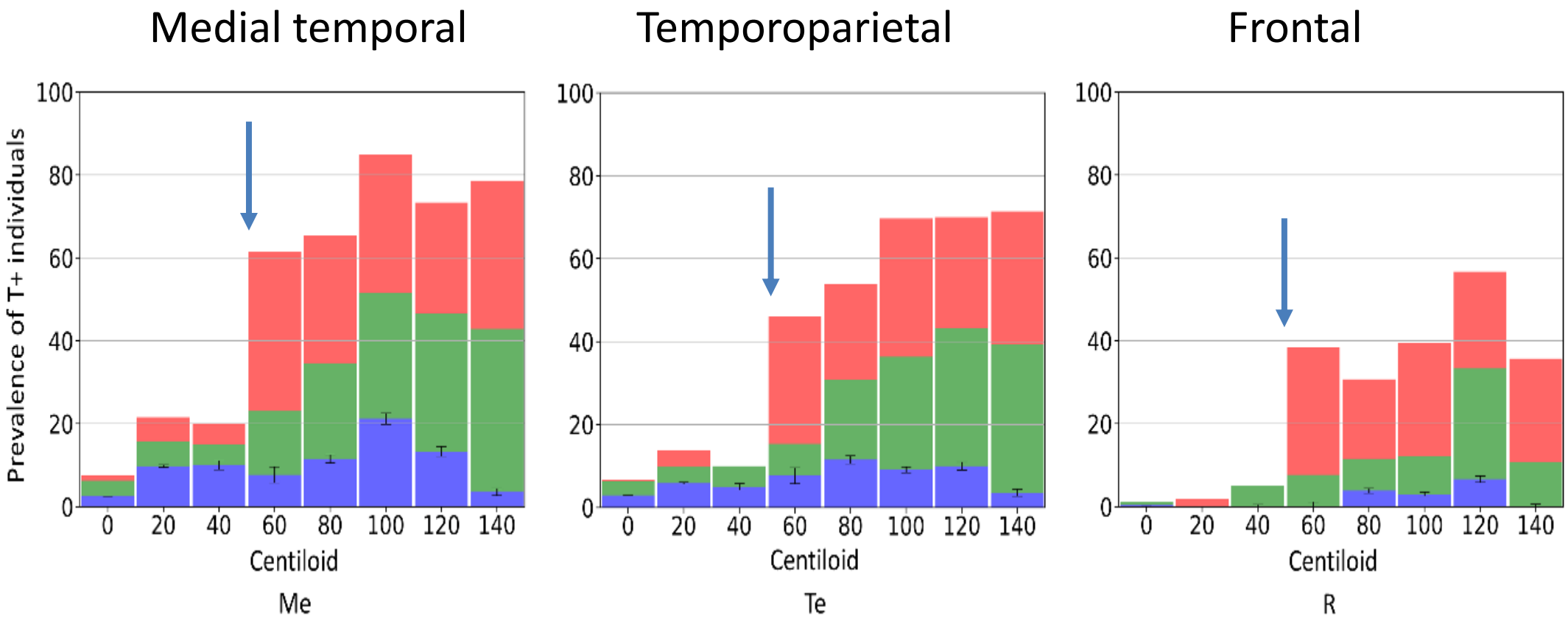




29	23	26	24	24	17	25	25 **MMSE**
52	67	68	69	73	74	75	88 **AGE**

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

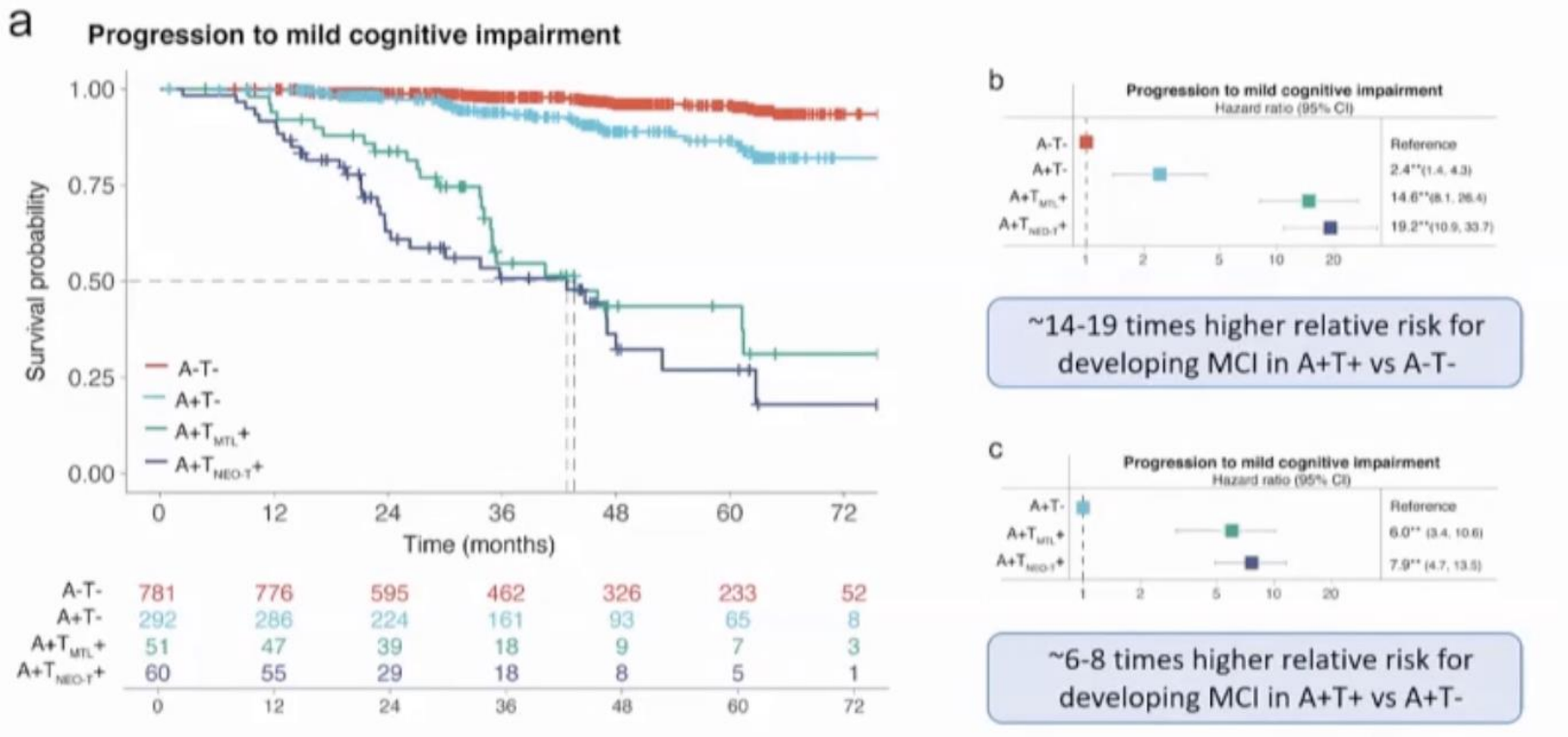
N=475 MK6240.



Blue – CN; Green – MCI; Red - Dementia

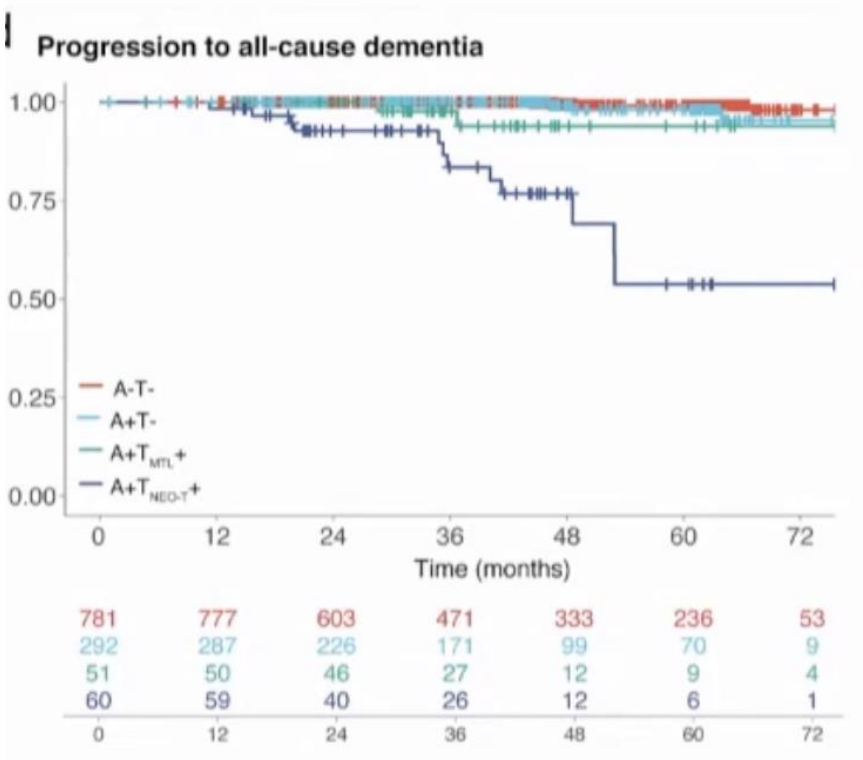
MCI and Dementia Risk in Older Persons

Negative amyloid scan – red
Positive amyloid but Negative tau scans – blue
Positive amyloid and positive tau scans – green & black



~14-19 times higher relative risk for developing MCI in A+T+ vs A-T-

~6-8 times higher relative risk for developing MCI in A+T+ vs A+T-



Current Uses of Amyloid and Tau PET

1. Selection for AD trials
2. Monitoring amyloid and tau clearance in AD trials
3. Validation of blood biomarkers and other new diagnostics for AD
4. Clinical Diagnosis

AD Biomarker Tests in Melbourne Available for Clinical Use

- Amyloid PET at Department of Molecular Imaging & Therapy, Austin Health, Heidelberg. Patient co-payment of $1000 required.
- *Phone: **9496 5718**. Fax: 9457 6605.*

  Email: enquiriesmit@austin.org.au
- CSF analysis at the National Dementia Diagnostics Laboratory, Florey Institute of Neuroscience and Mental Health, Parkville. Patient co-payment of $400 required.
- *Phone: **9035 7243.** Fax: 9349 5105*

  Email: enquiries-nddl@unimelb.edu.au

Healius Pathology network

dorevitch pathology | healius

1761_DOR_C2N_PrecivityAD2_DrBrochure_V2_Mar01

Introducing the

PrecivityAD2™ Blood Test

The PrecivityAD2™ blood test aids assessments of Alzheimer's disease in patients presenting with mild cognitive impairment or dementia

AD Protein Biomarkers included in the PrecivityAD2™ blood test

Amyloid beta (Aß)
- Aß40
- Aß42

Tau
- phosphorylated-tau217 (p-tau217)
- non-phosphorylated-tau217 (np-tau217)

PrecivityAD2™ Blood Test Performance Metrics

Test Performance Characteristics[a]	
Positive Percent Agreement (Sensitivity)[b]	88%
Negative Percent Agreement (Specificity)[b]	89%
Positive Predictive Value - PPV[c]	90%
Negative Predictive Value - NPV[c]	87%
AUC-ROC[c]	0.94
Overall Accuracy[c]	88%

JAMA | Original Investigation

Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlgren, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Calling, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD

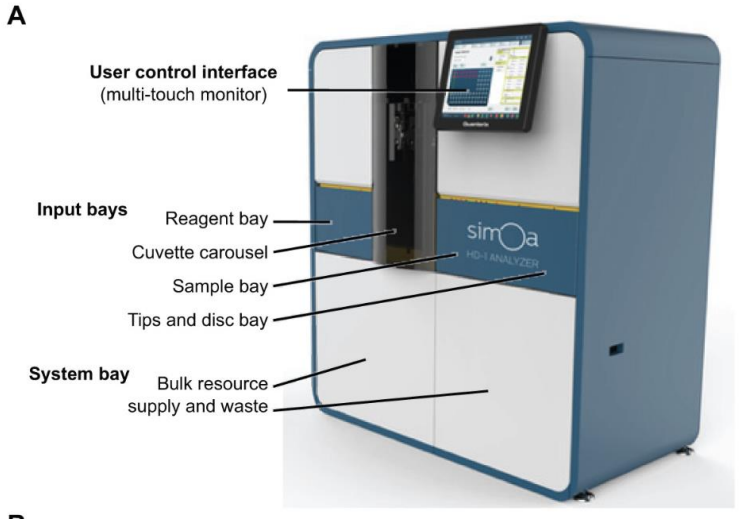
On-line July 28, 2024

1,213 patients undergoing cognitive evaluation in primary and secondary care in Sweden

The accuracy of predicting the presence of Alzheimer disease pathology based on clinical evaluation alone was 61% in primary care and 73% in specialty care compared with 91% for the C2N APS2 blood test in both settings. The performance of the APS2 in these real world clinical cohorts was largely driven by the percentage of p-tau217 measure.

Throughput

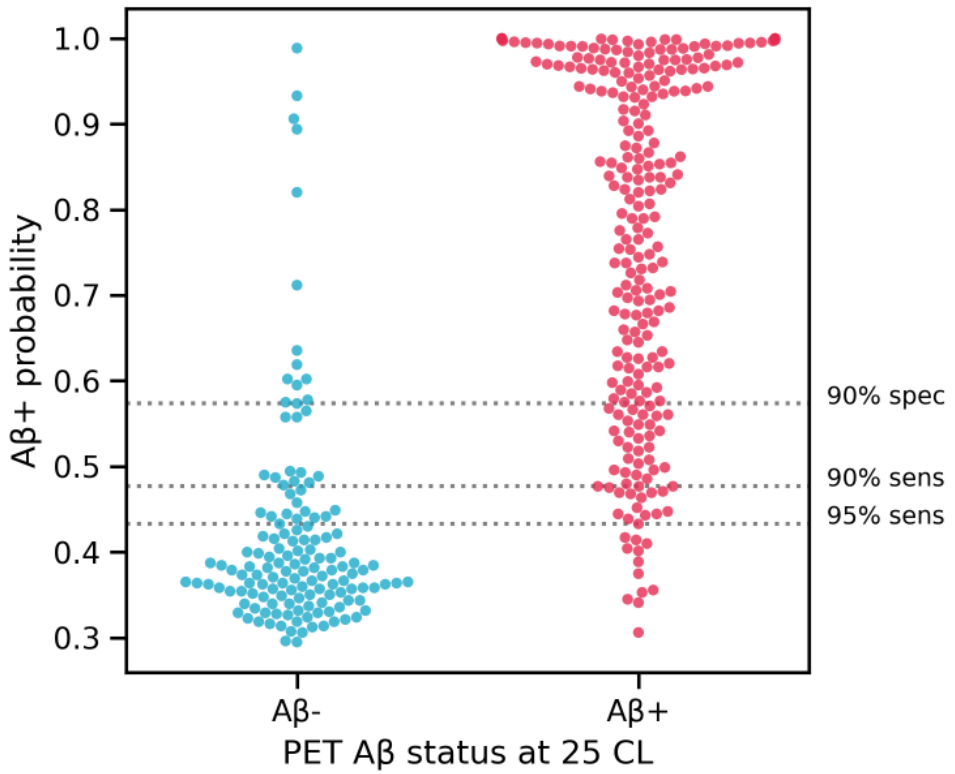
- Simoa – 35 tests per 3 hours. Research installations world-wide.
- Fujirebio Lumipulse G – 120 tests per hour – international clinical installation base. FDA approved CSF AD biomarkers.
- C_2N – warehouse full of mass spec machines only in St. Louis.



Simoa HD-X

Lumipulse G 1200

plasma pTau217 vs Amyloid PET



Single threshold at 0.18 pg/ml gave 87% accuracy while applying a two-threshold approach set for 95% sensitivity and 90% specificity, pTau217 had 92% accuracy for correct classification to Aβ- vs Aβ+ excluding the 18% indeterminant.

Accurate Detection and Staging of Alzheimer's Disease by Plasma pTau217 on a High Throughput Immunoassay Platform. eBioMedicine 2024:109: 105405

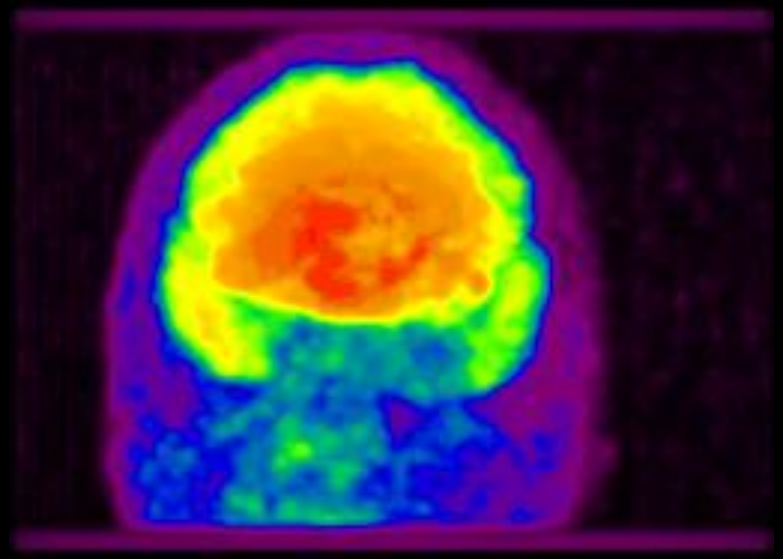
Barriers to Blood Testing for AD in Australia

- Regulatory – not a TGA approved in-vitro diagnostic device
- Reimbursement – no Medicare rebate
- “Real world” evaluation yet to be completed
- Clinician education – clinical guidance documents needed for specialists and GPs
- Expense of C_2N test

Anti Aβ monoclonal antibody therapy aims to slow progression by removing Aβ plaques

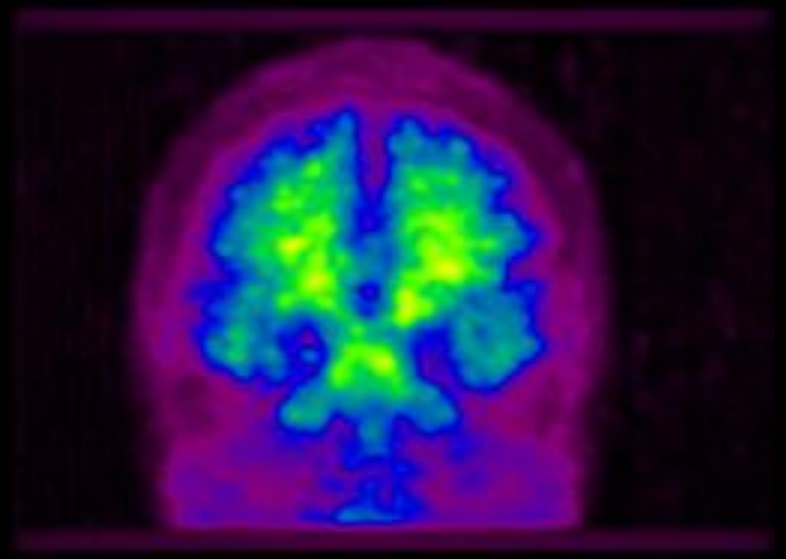
β-amyloid PET

ALZHEIMER'S DISEASE



Anti-amyloid Monoclonal Antibody Treatment

Aβ NEGATIVE SCAN



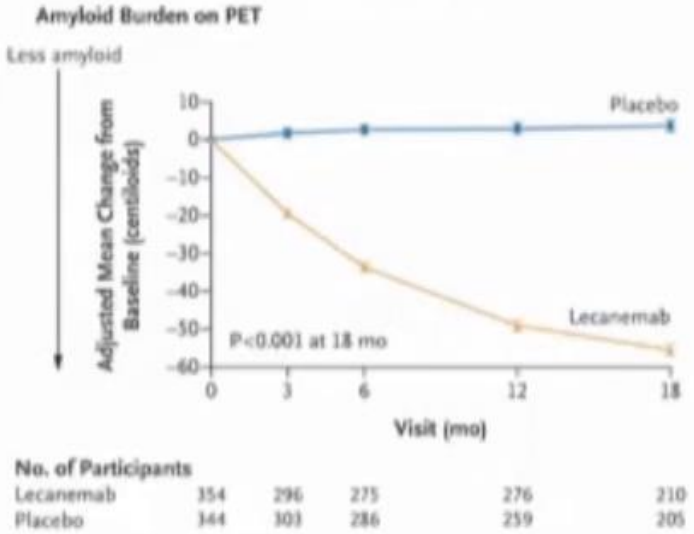
Amyloid Antibody Therapy Clears Amyloid Plaques!

Dose- and time-dependent amyloid depletion in clinical trials with a total of more than 6000 patients

Amyloid removal down to amyloid-negative levels within 12 to 18 months

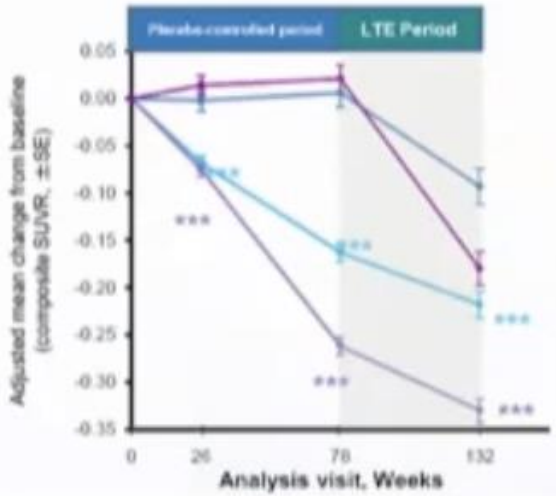
Lecanemab

CLARITY AD

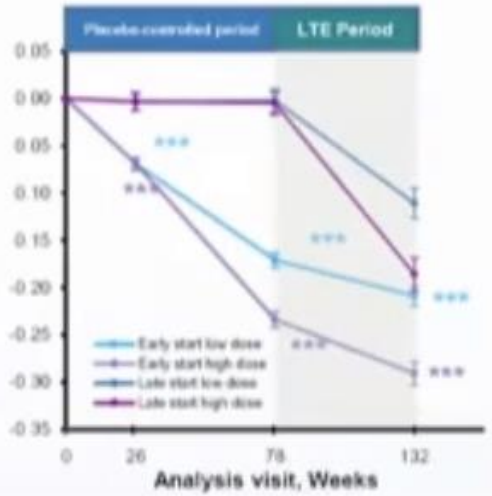


Aducanumab

EMERGE

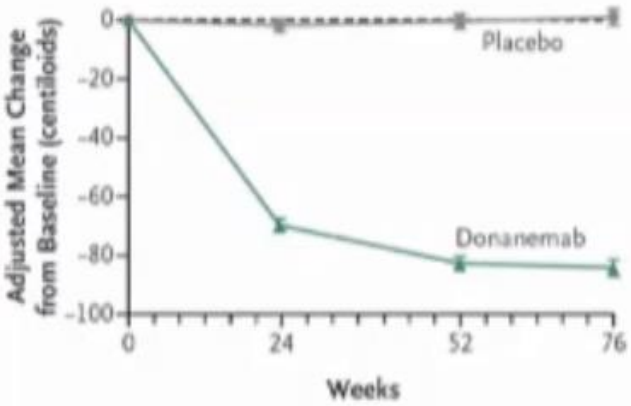


ENGAGE



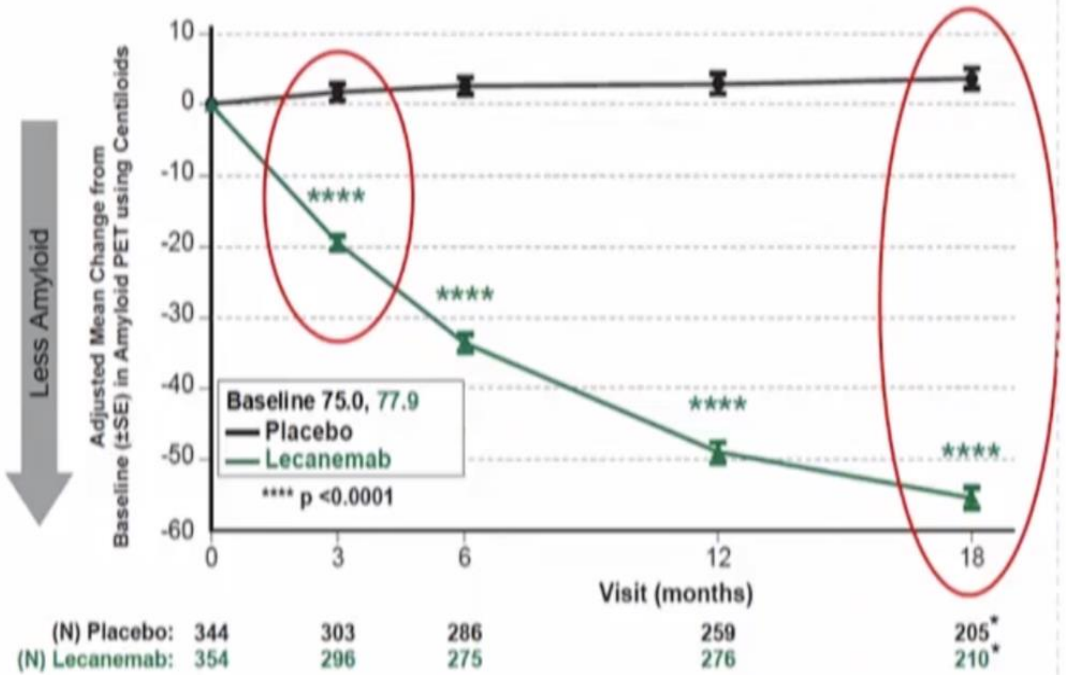
Donanemab

TRAILBLAZER-ALZ



PET Centiloids and Amyloid PET SUVr Images at Baseline and 18 Months

Highly Significantly Reduced Amyloid Plaque (Centiloids) at All Time Points; Mean at 18 Months of 23 Centiloids (Below 30 Centiloid Threshold of Positivity)



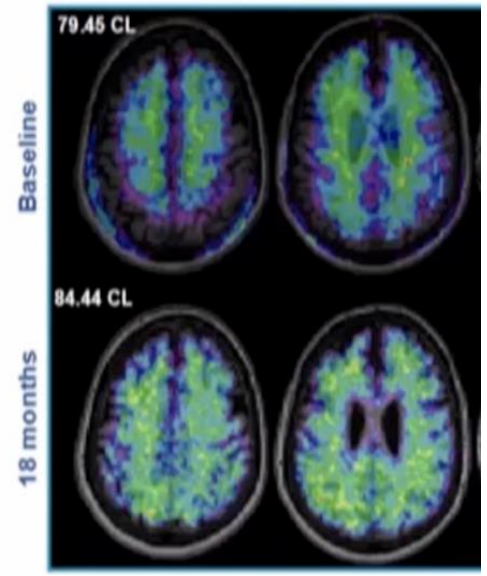
(N) Placebo:	344	303	286	259	205*
(N) Lecanemab:	354	296	275	276	210*

% Amyloid Negative (<30 CL)				
Placebo	15	14	15	16
Lecanemab	24	36	54	68

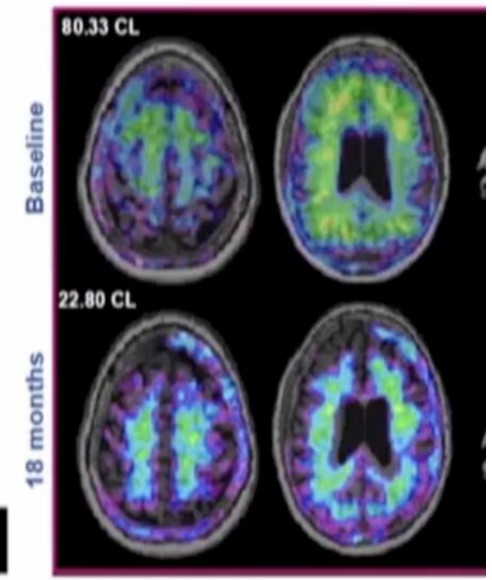
* 73 subjects were not included at 18 months (per SAP) since their PET assessments were performed after receiving lecanemab in the extension phase.

Note: Based on PD analysis population (PET substudy population). Adjusted mean change from baseline, SE and p-value are derived using MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *ApoE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Placebo

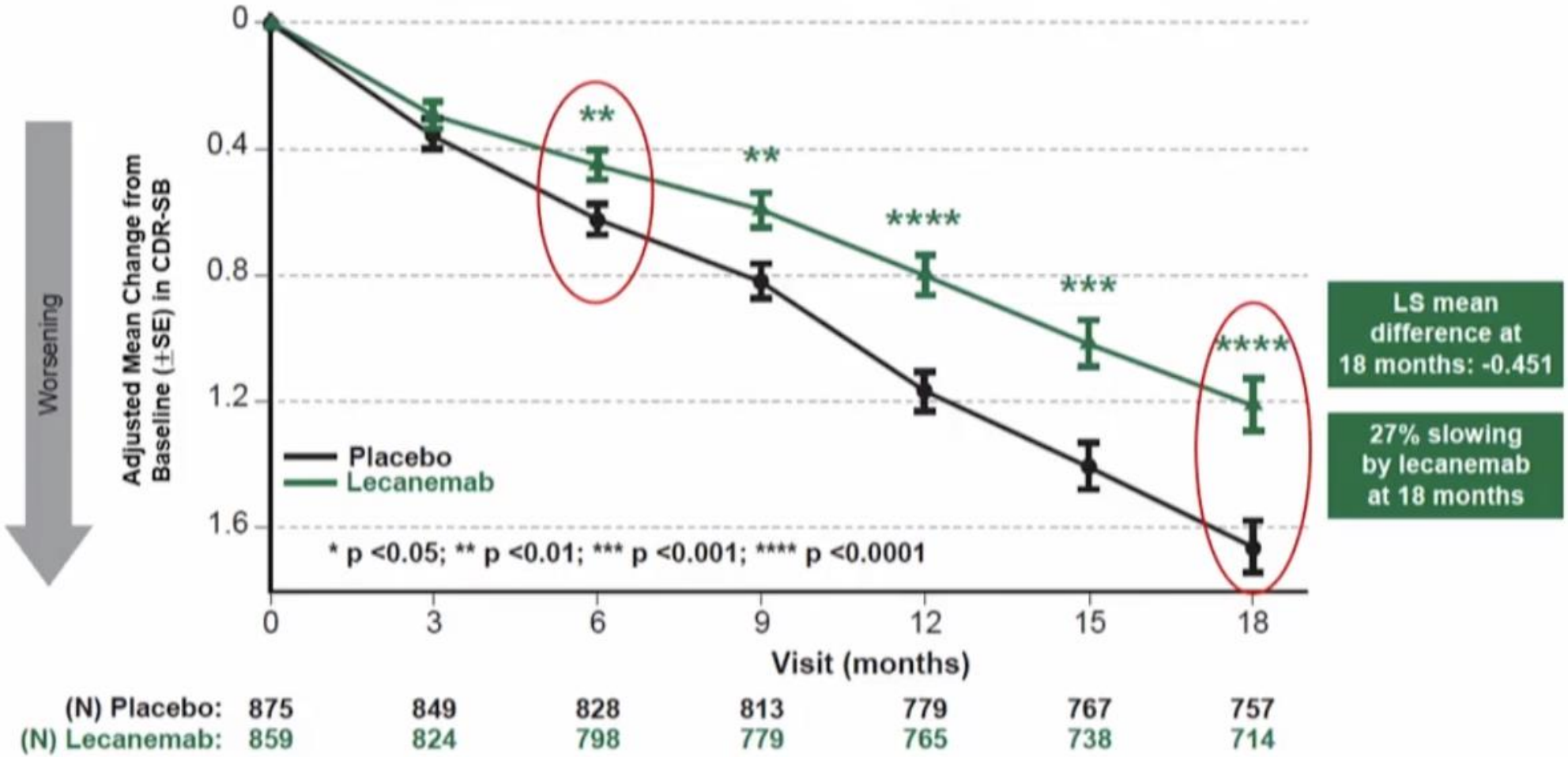


Lecanemab



Clarity AD Primary Endpoint: CDR-SB

Lecanemab Significantly Slowed Disease Progression on CDR-SB by 27% at 18 Months and at All Time Points Beginning at 6 Months

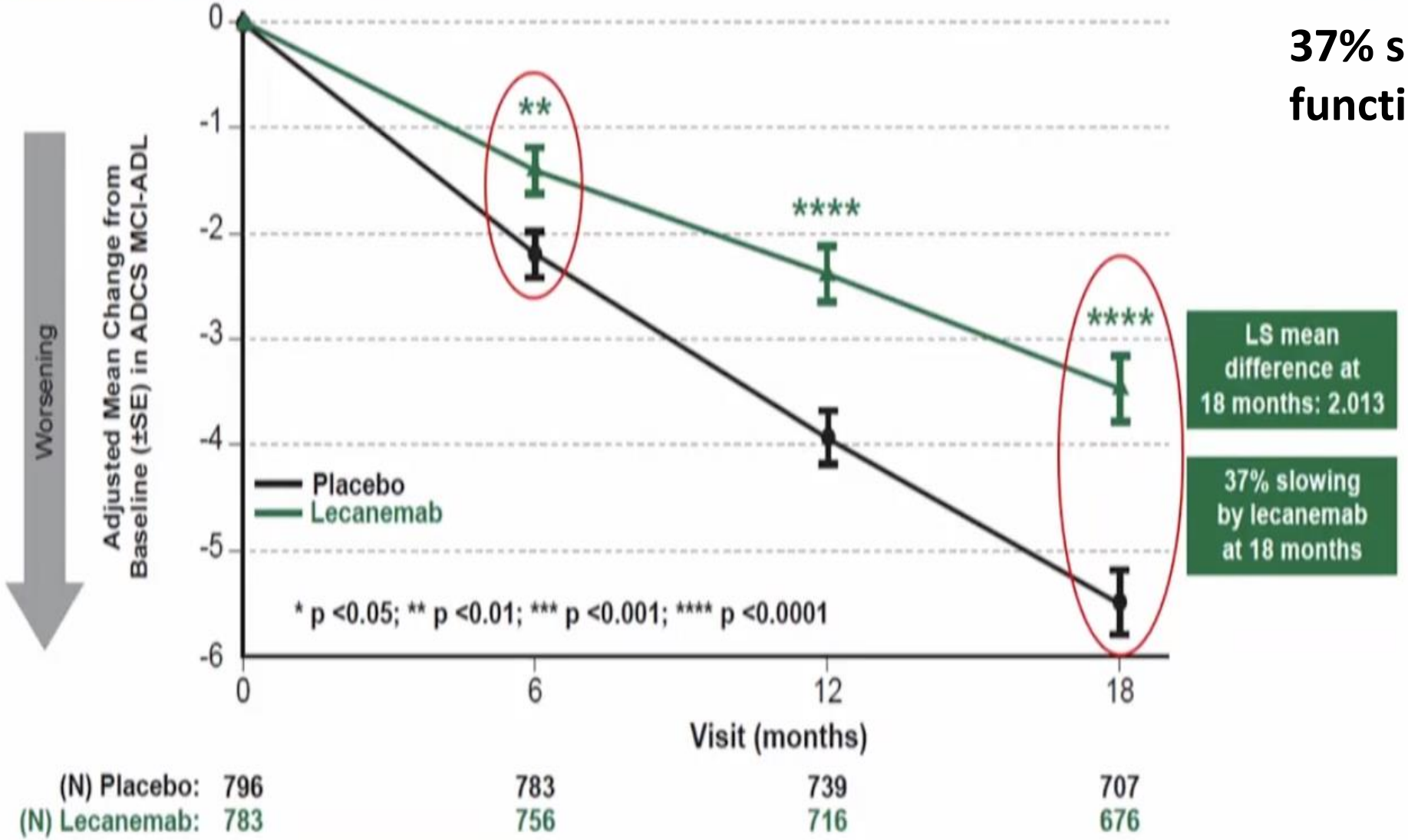


(N) Placebo:	875	849	828	813	779	767	757
(N) Lecanemab:	859	824	798	779	765	738	714

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
CDR-SB, Clinical Dementia Rating, sum of boxes; LS, least squares; SE, standard error.

ADCS MCI-ADL:

Lecanemab Significantly Slowed Disease Progression on ADCS MCI-ADL by 37% at 18 Months and at All Time Points Beginning at 6 Months

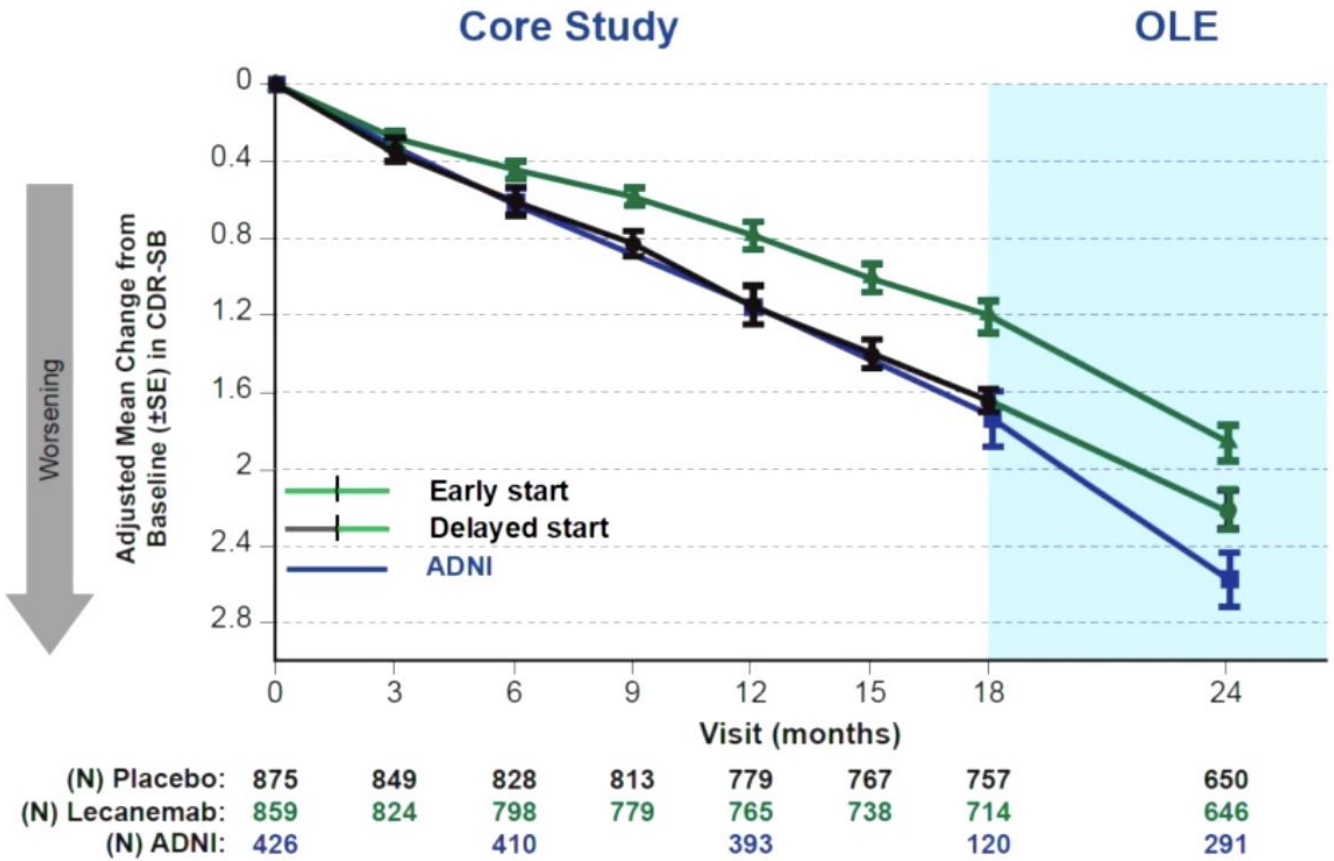


37% slowing of functional decline

Lecanemab Benefit

Clarity AD CDR-SB: OLE in Context of Observational Cohort

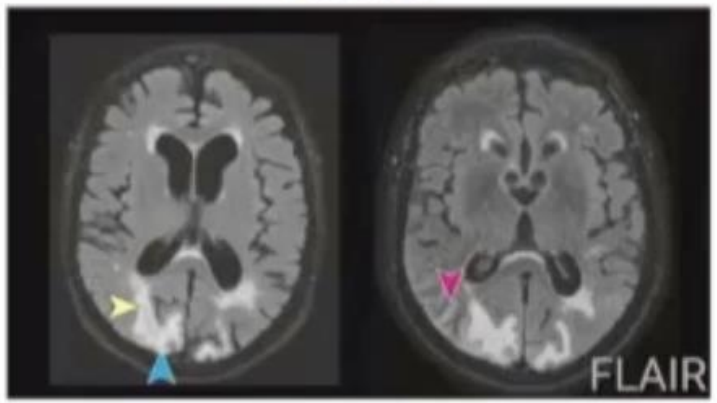
Lecanemab-Treated Participants Continued to Benefit Through 24 Months



- These ADNI participants selected to match with Clarity AD population
  - Baseline demographics and clinical characteristics including randomization strata
- Matched ADNI participants show similar degree of decline to placebo group out to 18 months
- Caveats
  - ADNI is an observational cohort;
  - Delayed start is Open-label; all participants know they are receiving lecanemab

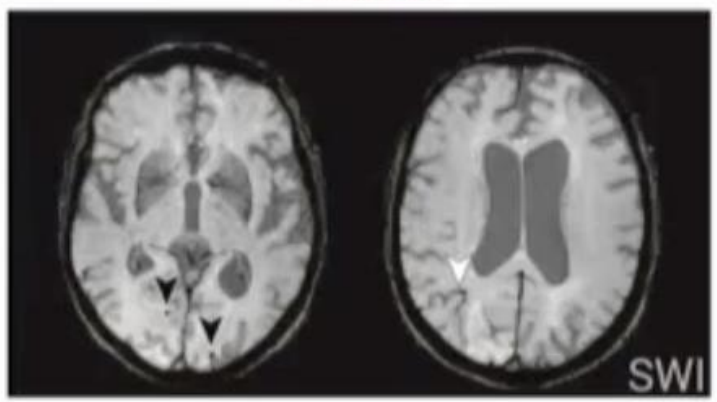
Adverse Reactions

ARIA-E



possible continuum

ARIA-H



ARIA-E
- **MRI:** parenchymal edema, sulcal effusion, gyral swelling
- **Incidence**: 11-35% at early stages of treatment, transient
- **Risk factors:** dosage, ApoEε4, microhemorrhages

ARIA-H
- **MRI:** microhemorrhages, superficial siderosis
- **Incidence:** 17-21% at early stages of treatment
- **Risk factors**: ARIA-E, APOEε4, microhemorrhages,

Symptomatic ARIA-E or H
- **Symptomatic:** 2.8-8.4% of treated patients
- **Common symptoms**: headache, confusion, dizziness, visual disturbance, nausea
- **Serious symptoms or macrohemorrhages:** 0.3-0.7% of treated patients
- **Management:** MRI monitoring, down-dosing, anti-inflammatory

Immune reactions
- **Infusion reactions:** <0.01% - 26.4%
- **Anti-drug antibodies:** 0% - 90%

Images: Filippi *et al., JAMA Neurol.* 2022; Salloway *et al., JAMA Neurol* . 2021; FDA prescribing information, Ref ID: 4822820; Swanson *et al., Alzheimer's Res. Ther.* 2021; Mintun *et al., NEJM* 2021; Landry *et al.*, AAIC 2022; Van Dyck *et al., NEJM 2022* ,

ARIA-E

Lecanemab

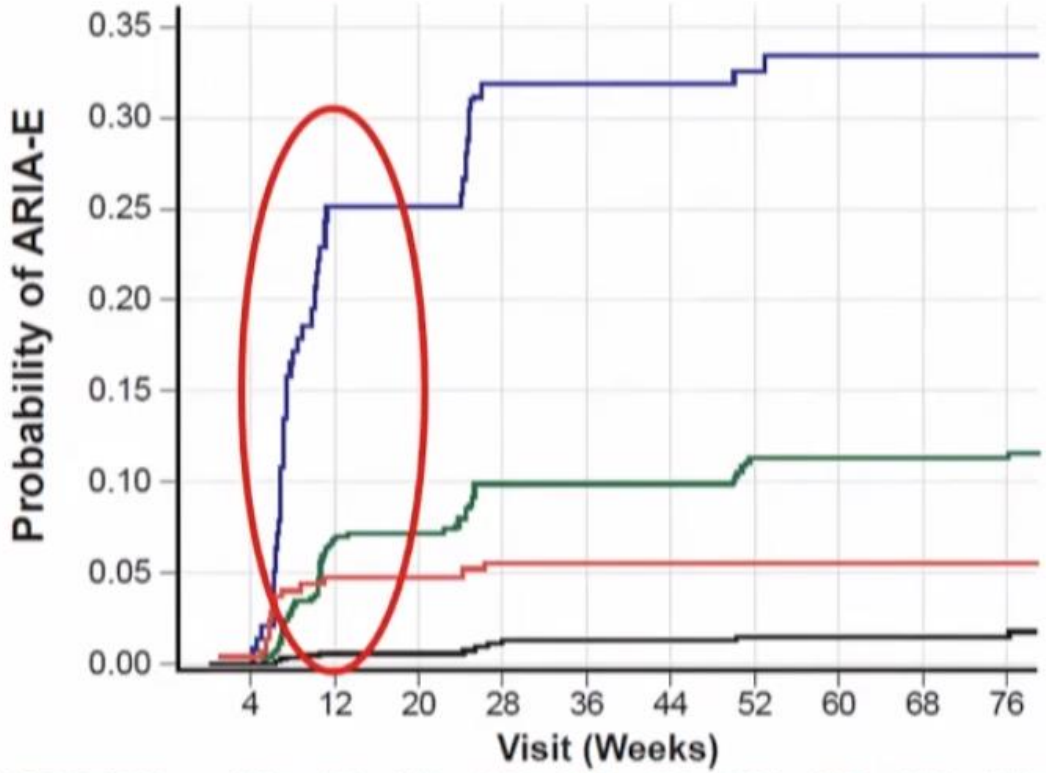
	Placebo (N=897) n/N (%)	Lecanemab (N=898) n/N (%)
ARIA-E	15/897 (1.7)	113/898 (12.6)
ARIA-E by ApoE4 genotype		
ApoE4 noncarrier	1/286 (0.3)	15/278 (5.4)
ApoE4 carrier	14/611 (2.3)	98/620 (15.8)
ApoE4 heterozygote	9/478 (1.9)	52/479 (10.9)
ApoE4 homozygote	5/133 (3.8)	46/141 (32.6)
Symptomatic ARIA-E*	0	25/898 (2.8)
ApoE4 noncarrier	0	4/278 (1.4)
ApoE4 carrier	0	21/620 (3.4)
ApoE4 heterozygote	0	8/479 (1.7)
ApoE4 homozygote	0	13/141 (9.2)

*Symptomatic concurrent ARIA-E and ARIA-H were included under ARIA-E.

- ARIA-E events were largely mild-to-moderate radiographically (91%) and asymptomatic (78%)
- In the 2.8% of subjects with symptomatic ARIA-E, commonly reported symptoms were headache, visual disturbance, and confusion
- Recurrent ARIA-E
  - Placebo: 1 (0.1%)
  - Lecanemab: 28 (3.1%)

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits

Time to ARIA-E Events



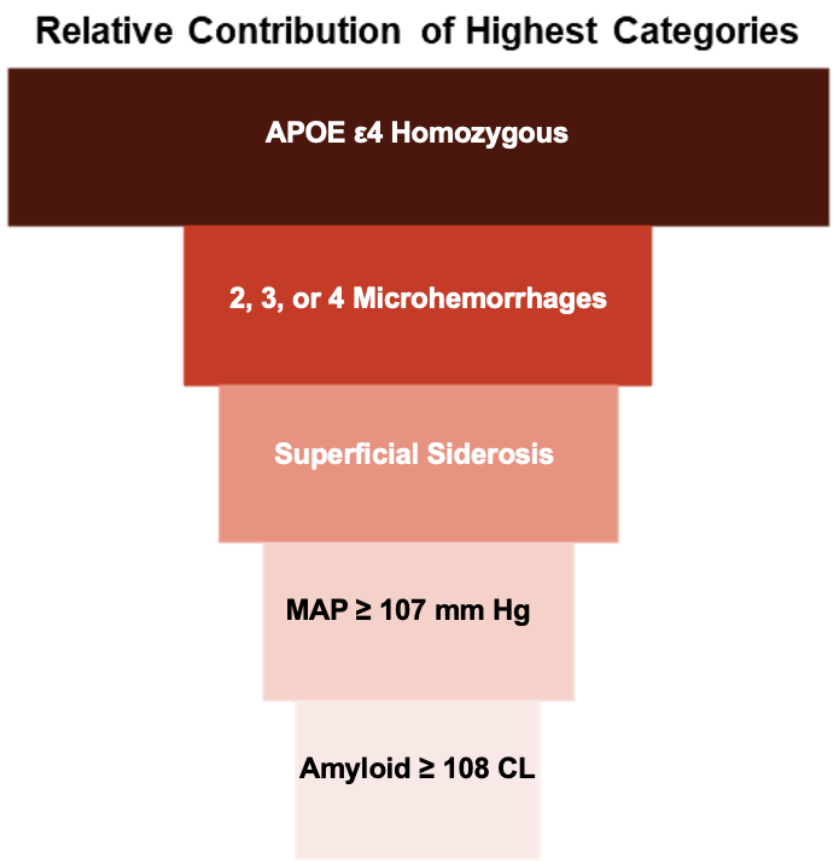
Heterozygous for LEC10-BW	479	423	410	395	387	381	374	367	362	343
Homozygous for LEC10-BW	141	101	100	91	89	89	88	86	85	83
Noncarrier for LEC10-BW	277	255	247	239	231	221	216	211	205	204
Overall Placebo	897	879	863	850	822	800	792	777	762	731

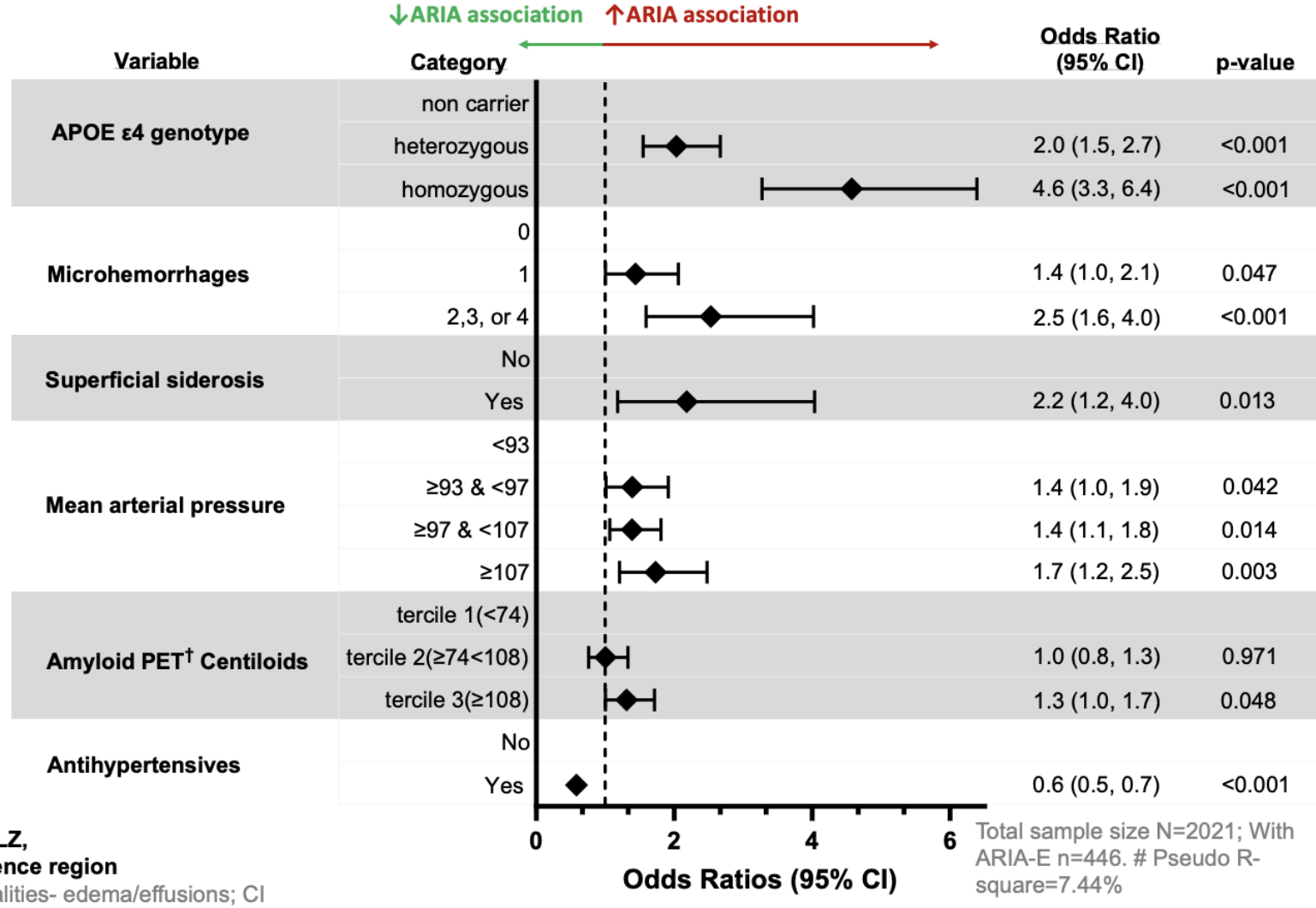
- ARIA-E with lecanemab generally occurred within the first 3 months of treatment (71%) and by 6 months (92%)
- ARIA-E resolved within 4 months of detection (81%), regardless of ApoE4 carrier status
  - 60/111 (54%) resolved by 90 days
  - 90/111 (81%) resolved by 120 days

ApoE4, apolipoprotein E4. ARIA-E, amyloid related imaging abnormalities - edema; LEC10-BW, lecanemab 10 mg/kg biweekly.

Can we increase benefit and reduce risk by better patient selection?

APOE ε4 genotype and baseline MRI are the greatest contributing factors to ARIA-E*





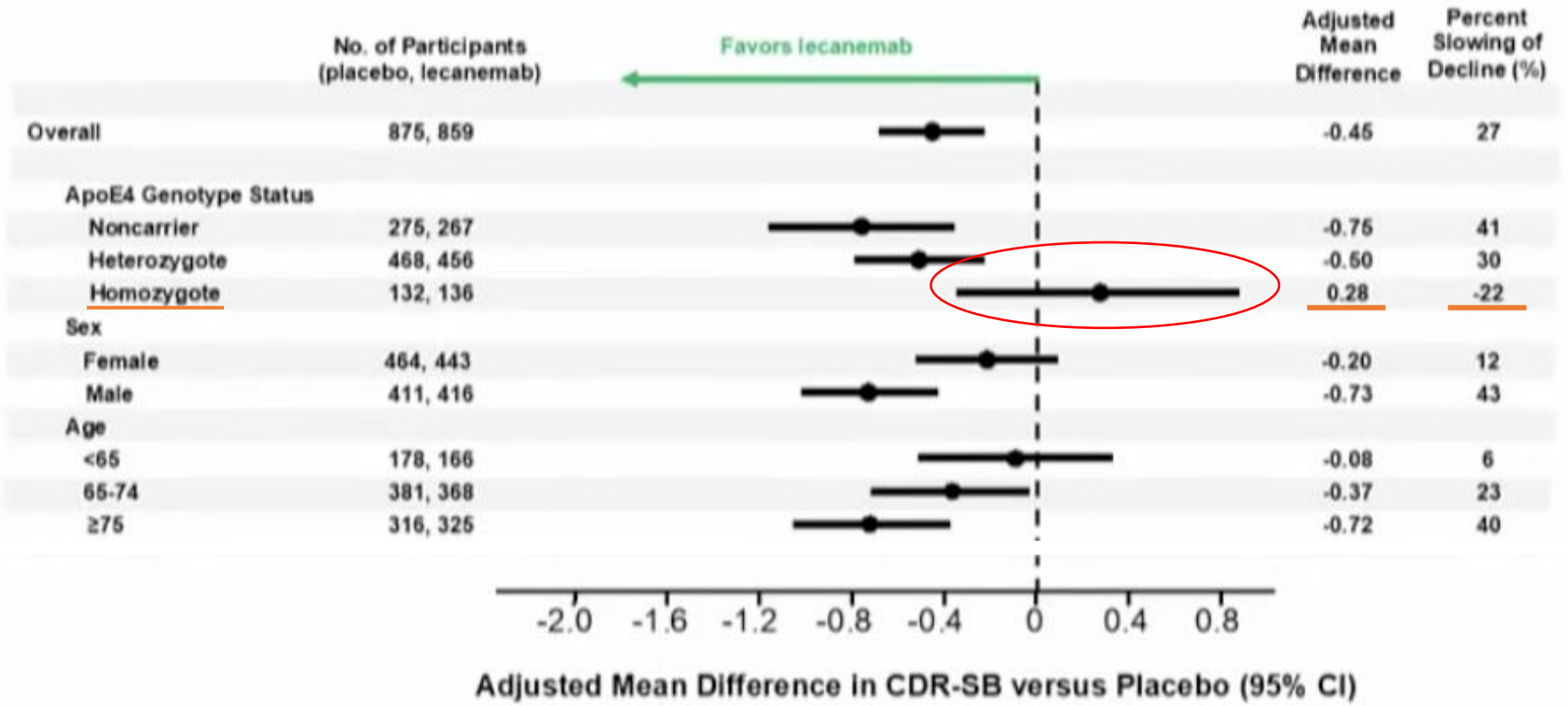
Total sample size N=2021; With ARIA-E n=446. # Pseudo R-square=7.44%

***Analyses completed with multiple logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. †Cerebellum used as reference region**

Abbreviations: *APOE* = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities- edema/effusions; CI = confidence interval; MAP = Mean arterial pressure; PET= positron emission tomography.

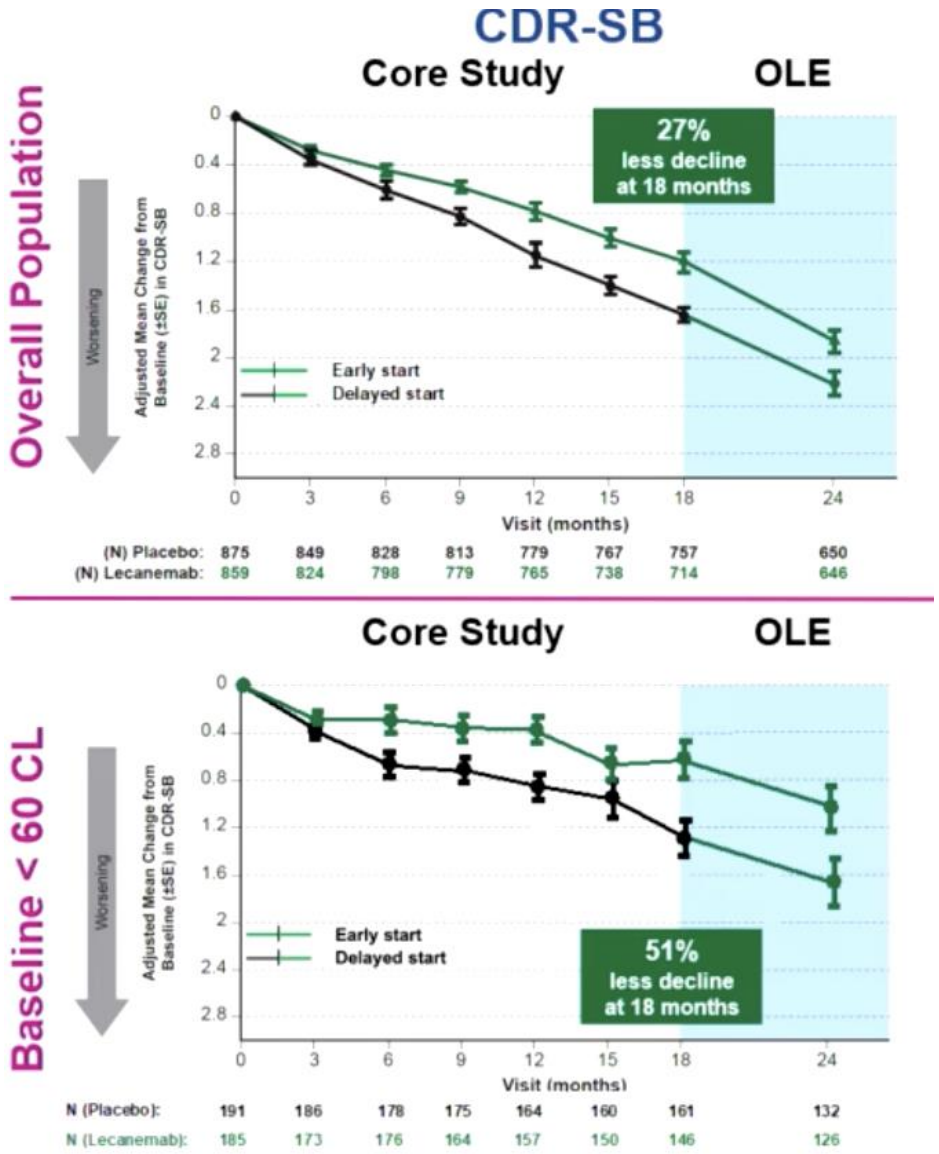
Clarity AD Subgroup Analyses: CDR-SB

Consistent Results Across Other Subgroups of Interest

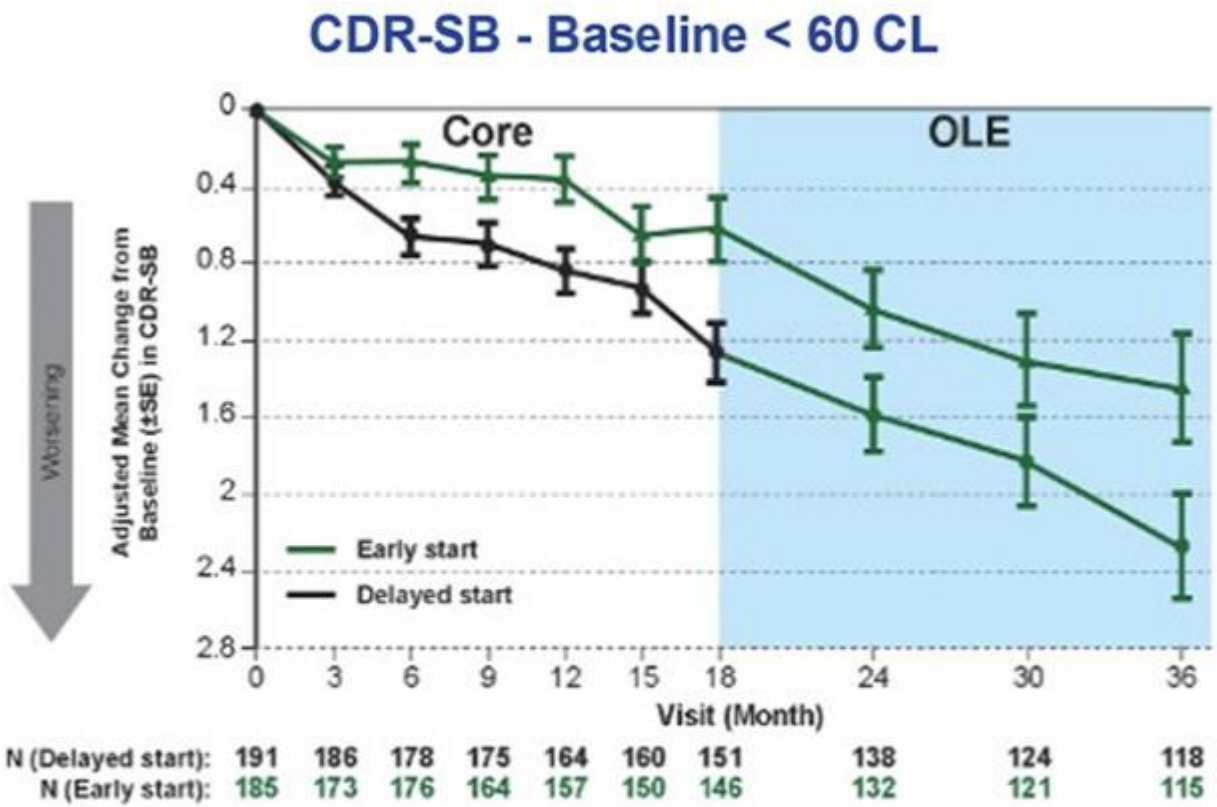


Lecanemab (Eisai)

Outcomes Through 24 Months (Overall and Baseline <60 CL)



Three year treatment



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.]*

Can we increase benefit and reduce risk by better patient selection?

YES

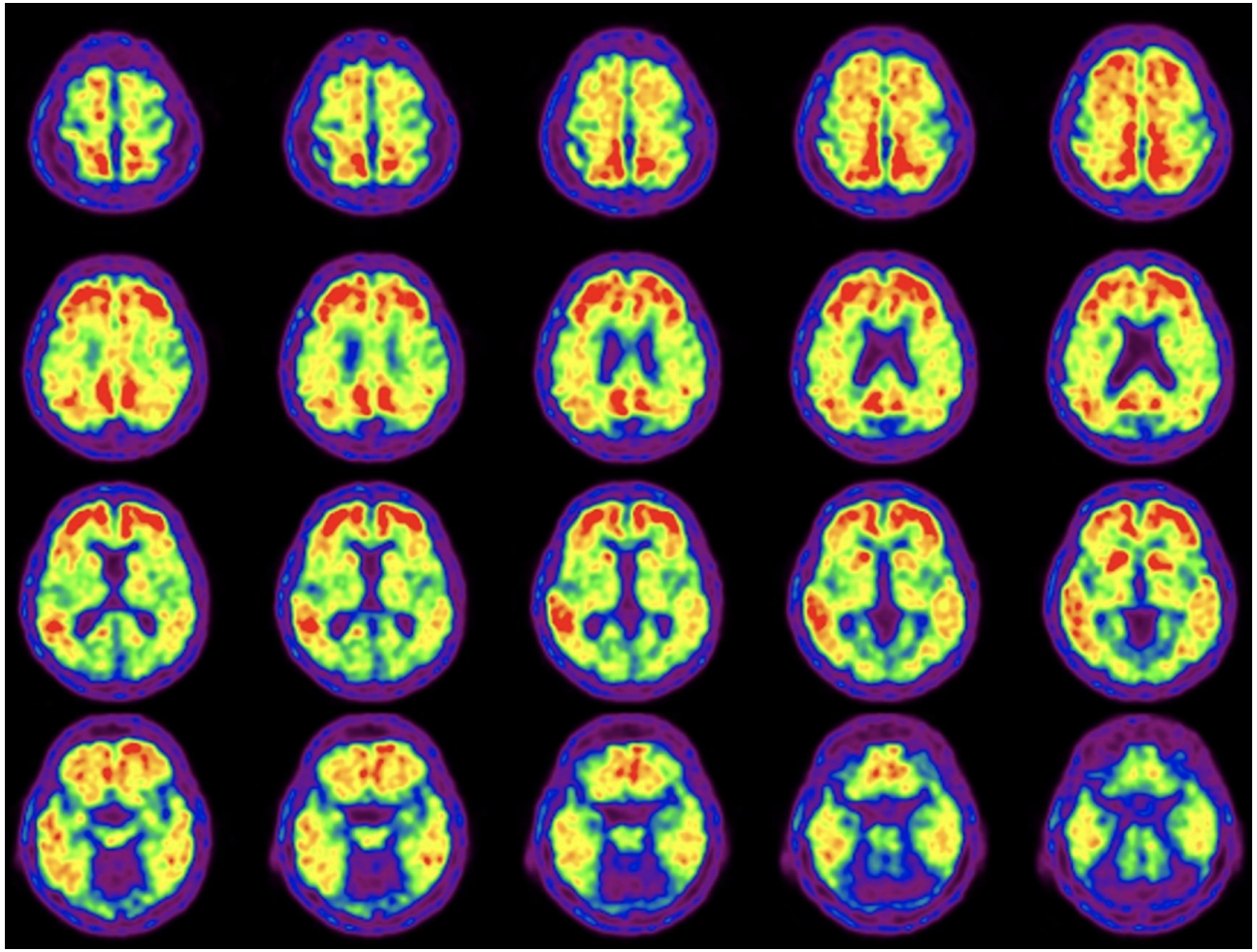
Excluding ApoE-e4 homozygote carriers:
- reduces symptomatic ARIA risk to 1.5%
- improves slowing of decline in Clinical Dementia Rating from 27% to 35%.

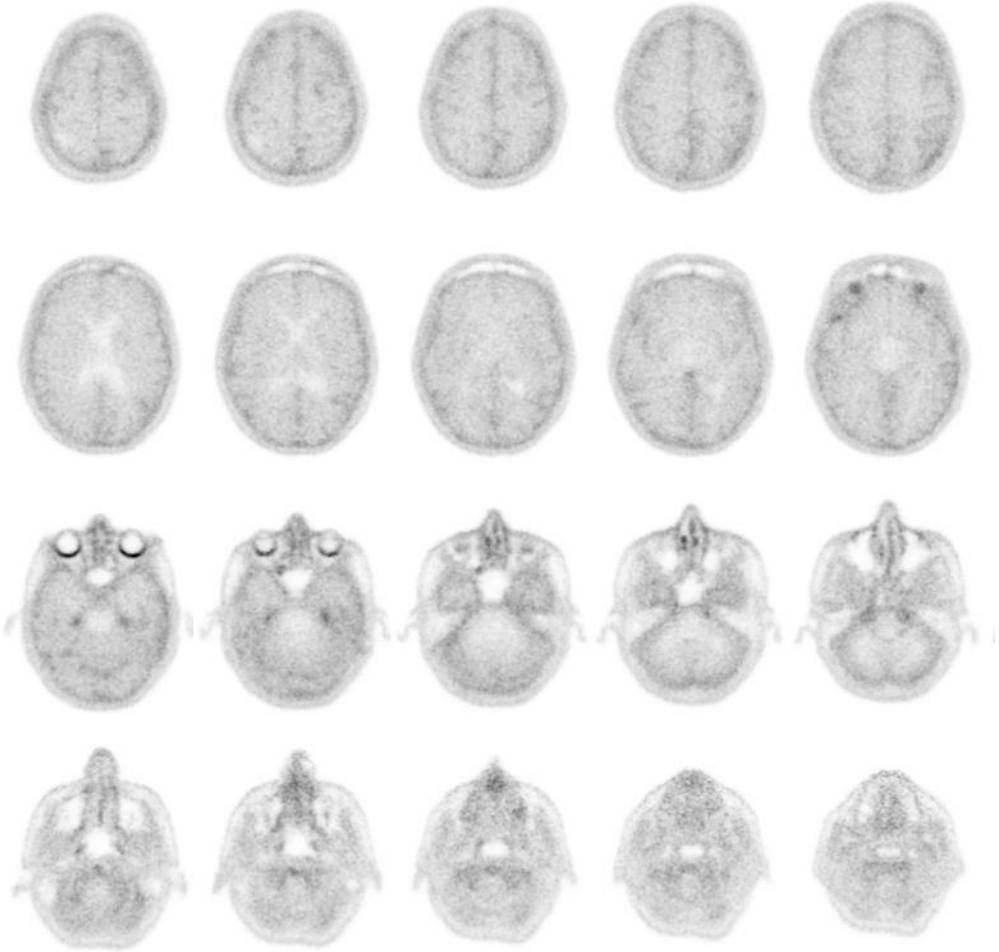
Exclusion of any microbleed or superficial siderosis may further reduce ARIA.

Treating persons with lower levels of AD pathology slows decline in CDR >50%.

Amyloid and Tau PET

Ideal patient for amyloid mAb therapy: A+/T_{MTL}





Are we ready for amyloid monoclonal antibody therapy ?

- Inclusion/exclusion criteria limits eligibility to <10% of patients typically presenting to a memory clinic.
- Safety monitoring registry required – Ready.
- Early and accurate diagnosis of AD – needs work in primary care.
- Access to Memory Disorders Specialists – Biggest problem. Current wait times average 3 months but in regional areas may be over a year.
- Access to amyloid PET – most PET cameras are at full capacity with oncology. Tracer production capacity also a concern. Cost uncertain.
- CSF – two analysis labs in Australia (Florey Melbourne, Concord Hospital, Sydney).
- Safety MRI for ARIA – baseline then 3 more in first 6 months plus at 12 months.

Lots of critical questions remain:

- Does the slowing of decline persist?
- Will the safety profile change in “real world” practice?
- At $35,000 per year for the drug alone, what is the cost-benefit to society?
- Optimal duration of dosing is unclear. Lilly stops drug when amyloid PET becomes negative but Eisai continues indefinitely.
- What other factors influence risk vs benefit in an individual?
- Will faster clearance increase risk of ARIA?
- Are the benefits clinically meaningful to patients and carers?

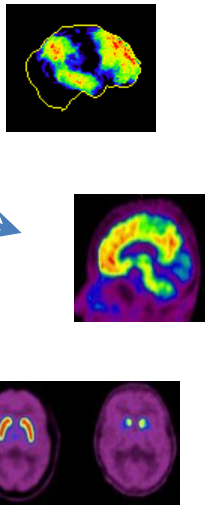
Future Diagnostic Practice

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

Austin HEALTH

The Florey

THE UNIVERSITY OF MELBOURNE

Thank you for your attention

Australian Dementia Network

REGISTRY. CLINICS. TRIALS.

aibl

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing