Evaluation of Qualitative and Quantitative Imaging: Implications for Diagnostic Imaging Drug Labeling

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Regulatory Review and Regulatory Research

Disclaimers: This presentation reflects the views of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

Outline

- Brief US FDA Regulation
- Diagnostic Imaging Drug Developments for Neurodegenerative Indications
- Diagnostic Assessment – Understood Evaluation Metric
- Qualitative and Quantitative Assessments
- Potential Roles of Quantitative Brain Amyloid PET Imaging

  Staging, Prognosis, Monitoring
- Study Design and Statistical Considerations
- Interim Remarks

Premise of Medical Imaging Drugs

- In May 1999, in response to the requirements of U.S. Food and Drug Administration Modernization Act (FDAMA, 1997), FDA amended the drug and biologic regulations (21 CFR 315 and 601) by adding provisions for the evaluation and approval of in vivo radiopharmaceutical used in the diagnosis or monitoring of disease (64 FR 26657)
- Used solely to **diagnose** or **monitor** diseases or conditions
- Development programs for medical imaging drugs can be tailored to reflect these particular uses

Neurodegenerative Indications Approved Medical Imaging Drugs

An imaging drug that can **bind to** specific pharmacologic target (the hallmark of the disease) that these drugs are aiming at, the distribution and the quantity of the target is generally disease specific, but is intended **to detect or assess the extent of a specific neurological disease** (i.e., **disease or pathology detection or assessment indication**)

- **Ioflupane I-123 (DaTscan)**: striatal dopamine transporter visualization (adult patients with suspected Parkinsonian syndromes or dementia with Lewy bodies) adjunct to other diagnostic evaluations (2011)
- **Fluorodopa F18**: **Visualize dopaminergic nerve terminals in the striatum** (adult patients with suspected Parkinsonian syndromes) adjunct to other diagnostic evaluations (2019)
- **Florbetapir F18 (Amyvid)**: **estimate β-amyloid neuritic plaque density (adult patients with cognitive impairment** who are being evaluated for Alzheimer's disease and other causes of cognitive decline) adjunct to other diagnostic evaluations (2012)
- **Flutemetamol F18 (Vizamyl)**: same as Florbetapir F18 (2013)
- **Florbetaben F18 (Neuraceq)**: same as Florbetapir F18 (2014)
- **Flortaucipir F18 (Tauvid)**: estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) (adult patients with cognitive impairment who are being evaluated for AD) (2020)

Key Characteristics of Approved Brain Amyloid PET Imaging Drugs

- **Truth Standard**: histopathology following autopsy data as a reference (MIDAC 2008)

Neuritic Plaque Counts	CERAD Score	I Image Result
<1	none	Negative
1 - 5	sparse	
6 - 19	moderate	Positive
20+	frequent	

Histopathology derived plaque score based on CERAD (consortium to establish a registry for AD) criteria using neuritic plaque counts

- **Reliability**
  - Repeatability and reproducibility of the scan: intra- and inter-rater read agreement (pre-specified inter-reader kappa agreement thresholds: 0.58, 0.60;
  - Inter-rater: lower bound of 95% CI: Amyvid 0.78, Vizamyl 0.79, Neuraceq 0.77
  - Intra-rater: Amyvid 100% (1), 32/33 (2), 31/33 (1), 30/33 (1)
    Vizamyl 28/29 (2), 27/29 (2)
    Neuraceq 91%-98% for 5 raters
  - Images reproducible when evaluated (semi)quantitatively using an automated assessment of SUV in pre-specified cortical regions of brain

Key Characteristics of Approved Brain Amyloid PET Imaging Drugs (Con't)

- **Diagnostic performance (sensitivity/specificity)**

Example: FDA label reported in 59 autopsied patients

Test Performance		In-Person Training (Study Two)	Electronic Media Training (Study Three)
Sensitivity (%)	Median	92	82
	Range among the 5 readers	(69 – 95)	(69 – 92)
Specificity (%)	Median	95	95
	Range among the 5 readers	(90 – 100)	(90 – 95)

Example: EU label reported 68 end-of-life patients with SoT available

SoT Majority-R
Sensitivity: 86% (72%, 95%)
Specificity: 92% (74%, 99%)

Majority-R by electronic training
Sensitivity: 93% (81%, 99%)
Specificity: 84% (64%, 96%)

Major Points Highlighted in Approved Brain Amyloid PET Imaging Drugs Labeling

- Before image interpretation, all readers underwent special training

  In-person tutorial type of training

  Electronic media-based training

- A positive amyloid scan does not establish a diagnosis of AD or other cognitive disorder (neuritic plaque deposition in grey matter may be present in asymptomatic elderly and some neurodegenerative dementias)
- At the time of approvals, labels from EU and US stated that efficacy for predicting development of AD/dementia/other neurological condition or monitoring response to therapy has not been established

Assessment of Disease Severity or Stage

- **Recent patient population of interest**: early Alzheimer's disease (patients with MCI due to AD or mild AD [mild dementia with stage of disease consistent with stage 3 and stage 4 AD]) – defining the severity of the disease may rely upon pathology stage or staging of disease
- **Approved diagnostic imaging drugs**: *Qualitative (visual read)* diagnostic imaging against SoT as Gold standard; established diagnostic performance
  - Confirmed presence of amyloid pathology in the brain
- **Investigational diagnostic imaging drugs: what should the reference standard be?**
  - What should the role of histopathology/autopsy be as a diagnostic imaging drug?
  - What if all studies subjects are not at the end-stage of their life, would visual read w/o SOT but with some defined clinical-pathology be appropriate/acceptable by the clinical community?
- **Possible roles of quantitative information for image interpretation in clinical trial?**
  - Approved vs investigational?

Assessment of Disease Severity or Stage

- **Recent patient population of interest**: early Alzheimer's disease (patients with MCI due to AD or mild AD [mild dementia with stage of disease consistent with stage 3 and stage 4 AD]) – defining the severity of the disease may rely upon pathology stage or staging of disease
- **Regulatory guidance related to staging of disease**
  - In subjects presenting for diagnostic evaluation of a specific disease or condition in a defined clinical setting

  Common clinical setting:
  - Providing **a diagnosis** in **patients with suspected disease** (in brain amyloid PET imaging, negative scan reduces the likelihood of disease, i.e., rule out disease)
  - **Monitoring and assessing** the extent, rate of progression, or other aspects of the specific disease in **patients previously diagnosed with the disease** (spectrum of disease, e.g., severity or stage)

Assessment of Disease Severity or Stage (Con't)

- **Recent patient population of interest**: early Alzheimer's disease, **defining the severity of the disease may rely upon pathology stage or staging of disease (e.g., association between imaging and functional assessments)**

- **Approved diagnostic imaging drugs***: Qualitative (visual read)* diagnostic imaging against SoT as Gold standard; established diagnostic performance
  - Confirmed presence of amyloid pathology in the brain

- **Investigational diagnostic imaging drugs: what should the reference standard be?**
  - Later stage disease: histopathology/autopsy data (SoT) can be obtained
  - Earlier stage disease: lack of SoT, can clinic-radiographic reference or others be SoR?
- **Possible roles of quantitative information for image interpretation**

Brain Amyloid PET Imaging for Neurodegenerative Disorders

- **Qualitative Assessment/Interpretation**
- ***Negative scan*** – patients with sparse to no neuritic plaques (inconsistent with a neuropathological diagnosis of AD at the time of image acquisition) reduces the likelihood that a patient's cognitive impairment due to AD
- ***Positive scan*** – patients with moderate to frequent amyloid neuritic plaques (neuropathological exam has shown present in patients with AD, may also be present in patients with other types of neurologic conditions and older people with normal cognition) with non-negligible uncertainty in targeting in preclinical population

- **Quantitative Assessment/ Interpretation**
- ***Radioactive signal intensity*** – Use computer (image quantitation) software
  - Require analytical validation
  - Standardization if involving multi-tracers in a diagnostic trial or stratification by tracer
- ***Rheumatoid Arthritis Imaging example –***

  An intra-patient ratio of mean pixel intensity of a joint to mean pixel intensity of the defined reference region: a quantitative measure to assess the degree of RA disease severity
- **Important to assess the level of agreement between qualitative & quantitative results**

Evaluation of Diagnostic Imaging Drugs for Prognosis

- **Prognosis:** identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest
- Possible interest in neurodegenerative disease may be prognosis to predict cognitive decline based on baseline brain amyloid load
- **Some regulatory guidance related to disease prognosis**

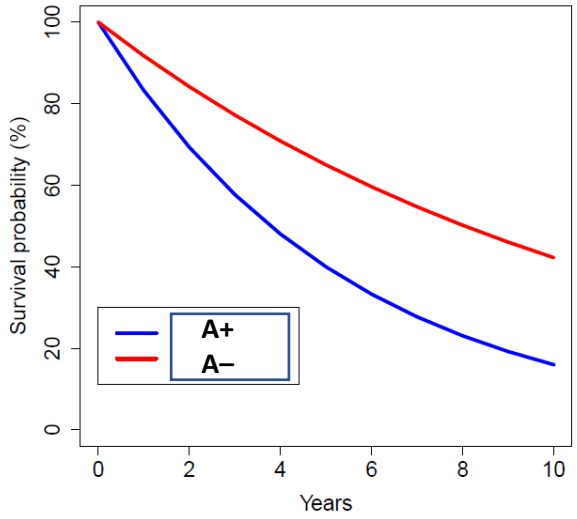
  Compare standard imaging test battery with vs without new imaging drug (added value)

  ➔ Greater sensitivity/specificity

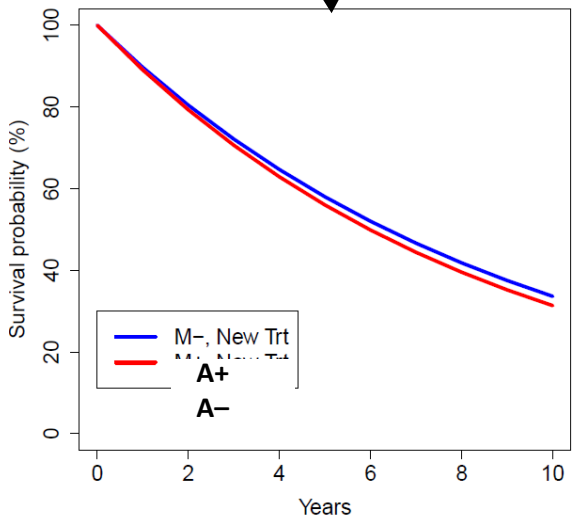
  ➔ New imaging drug improves prognosis

Prognosis to Predict Disease Progression

Prognostic clinical utility



No prognostic clinical utility



A Amyloid status
Positive (+) refers to more severe disease status

A+ : **Amyloid PET +** (Blue curve)
A– : **Amyloid PET –** (Red curve)

A Prognosis Example

Clinical Question: How accurate is the prediction of x-yr mortality based on baseline H/M ratio? Can a diagnostic imaging drug help identify subjects with heart failure who will experience a major adverse cardiac event? Example: Iobenguane I-123

Imaging measurement: baseline H/M ratio (to estimate prognostic performance)

SoT: the pre-specified x-year follow-up mortality status

Evidence: if predicted probability of x-yr mortality can be directly translated from various thresholds of H/M ratio while preserving the association ➔ sensitivity, specificity by threshold

H/M group	Subjects	Death	Survival	1-yr mortality	Sensitivity	specificity
< 1.2	92	12	80	**13.0%**		
≥ 1.2	869	38	831	4.4%	24%	91%
< 1.4	429	33	396	**7.7%**		
≥ 1.4	532	17	515	3.2%	66%	57%
< 1.6	760	48	712	**6.3%**		
≥ 1.6	201	2	199	1.0%	96%	22%

Monitoring Disease Progression or Longitudinal Change

- **Monitoring utility**
  - It is measured repeatedly over time
  - Assessing status of a disease or medical condition (**longitudinal change**)
  - Assessing **disease progression** including occurrence of new disease, worsening of previously existing abnormality, or change in disease severity or specific abnormalities
- **Example of monitor longitudinal change:** baseline assessment compared with periodic testing (longitudinal nature) in natural history studies
- **Example of monitor disease progression**: change in imaging reads/intensity result in change in disease outcome
- Assessment of impact, e.g., increased amyloid burden suggesting disease progressed?

Study Design and Statistical Considerations

- Reliability for qualitative imaging & analytical validation for quantitative imaging: addressing measurement error, systematic bias, variability, repeatability, reproducibility
- Prior to evaluating clinical utility: care should be given on standardization of scan technique, image interpretation, reporting and progression criteria, etc.
- Staging of Disease – clinical validity is less understood with little review experience
- Prognosis
  - Use of quantitative imaging with a focus on patient-level assessment
  - Prognostic performance of baseline imaging is to be demonstrated against a pre-specified threshold with clinical outcome at a landmark time serving as SoT
  - Methodologies for prognostic performance of diagnostic imaging are more than modeling
- Monitoring disease progression or longitudinal change
  - Pattern of change between imaging and disease outcome at patient-level
  - Correlation of amyloid burden and the disease outcome

Interim Remarks

- In neurodegenerative diseases, existing approved diagnostic imaging drugs are based on visual assessment with qualitative read
- For prognostic utility, current experience uses quantitative imaging and directly translates prediction of clinical event from various thresholds of baseline quantitative imaging while preserving the association
- A central issue with diagnostic brain amyloid PET imaging radioactive drug developments is multiple sources of uncertainty in preclinical population
- Possible roles of quantitative information for image interpretation in diagnostic brain amyloid PET imaging drugs: approved vs investigational?
- What could be acceptable standard of reference for staging of disease in preclinical population such as early Alzheimer's disease, given autopsy / histopathology data are too distant to obtain?

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- Sperling RA, Donohue MC, Raman R, et al. Association of factors with elevated amyloid burden in clinically normal older individuals. JAMA Neurology 2020

Thank you

Quantitative Amyloid Imaging in Clinical Trials: Mayo Clinic Aging Research

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Mayo Clinic College of Medicine

Rochester, MN, USA

FDA Quantitative Amyloid PET Workshop 11/2022

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Potential Conflict of interests

Research Funding from:

- GE Health Care
- AVID Radiopharmaceuticals
- Siemens Molecular Imaging
- State of Minnesota
- NIA, NIH, NCI

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TOPICS

1. *Discuss quantitative amyloid imaging in cognitively unimpaired, research study participants, at the Mayo Clinic.*

2. *Review findings of quantitative amyloid imaging and comparisons with other pathology detection methods in early AD.*

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Details of the Mayo Clinic Study of Aging (MCSA)

- Random population-based sample in Olmsted County (Rochester, MN area)
- About 8000 nondemented subjects ages 30 and older recruited since 2004.
- Around 3000 current enrollment with 130 participants active for 15+ years.
- 5000 amyloid PET scans, 2000 tau PET scans, 8000 MRIs, 26,000 blood samples (1.6 million tubes).

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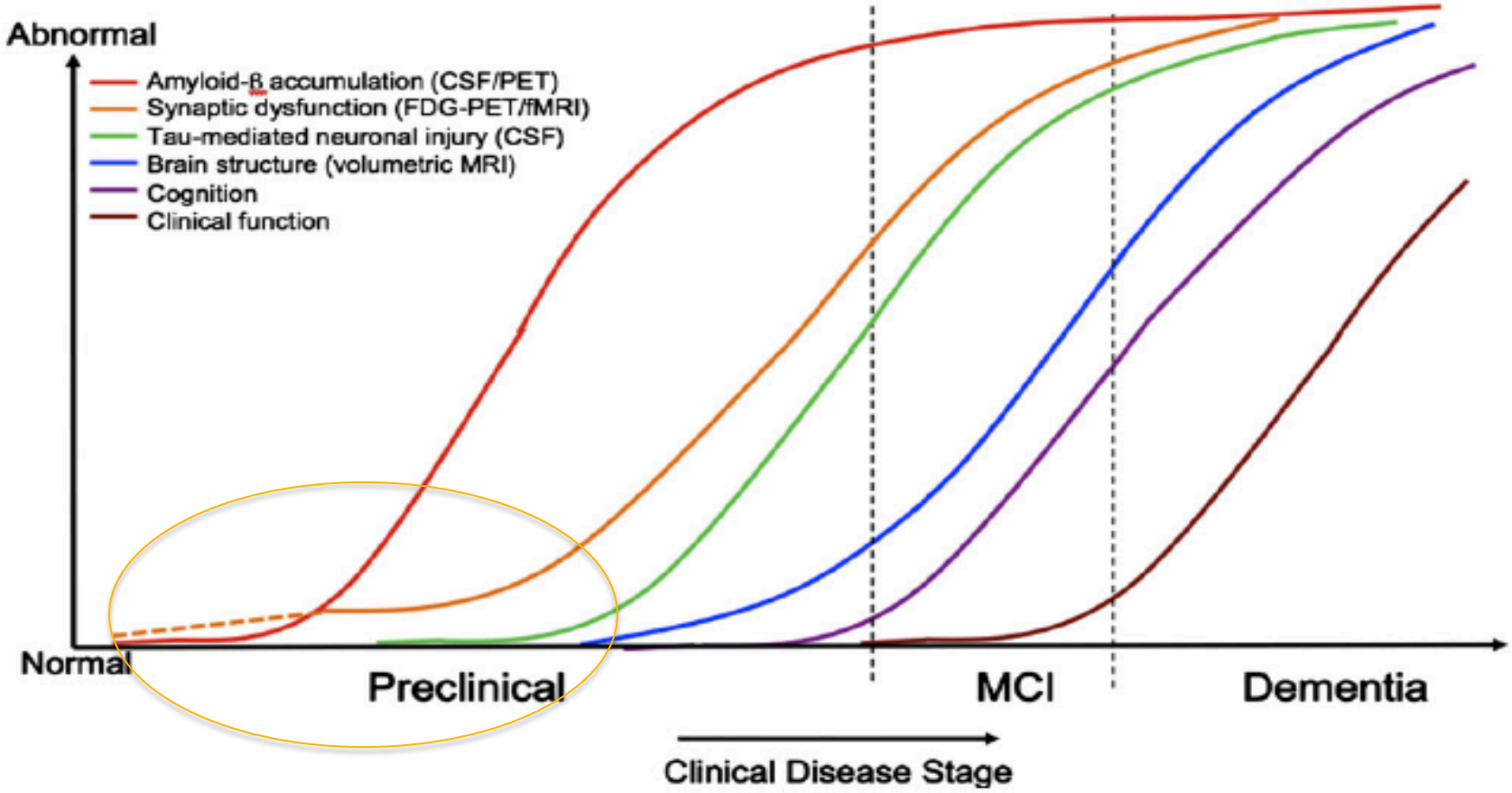
Aim to detect the pathology of early Alzheimer's Disease



Sperling RA, et al. *Alzheimers Dement*. 2011.

What do we want to predict from pre-AD disease imaging?

- **What fraction of people with "pathology" on preclinical imaging go on to develop dementia?**
- **Will intervention in "positive amyloid" people reduce their progression to dementia?**
- **Are there patterns from multimodality imaging or other testing that will inform us about disease progression ?**

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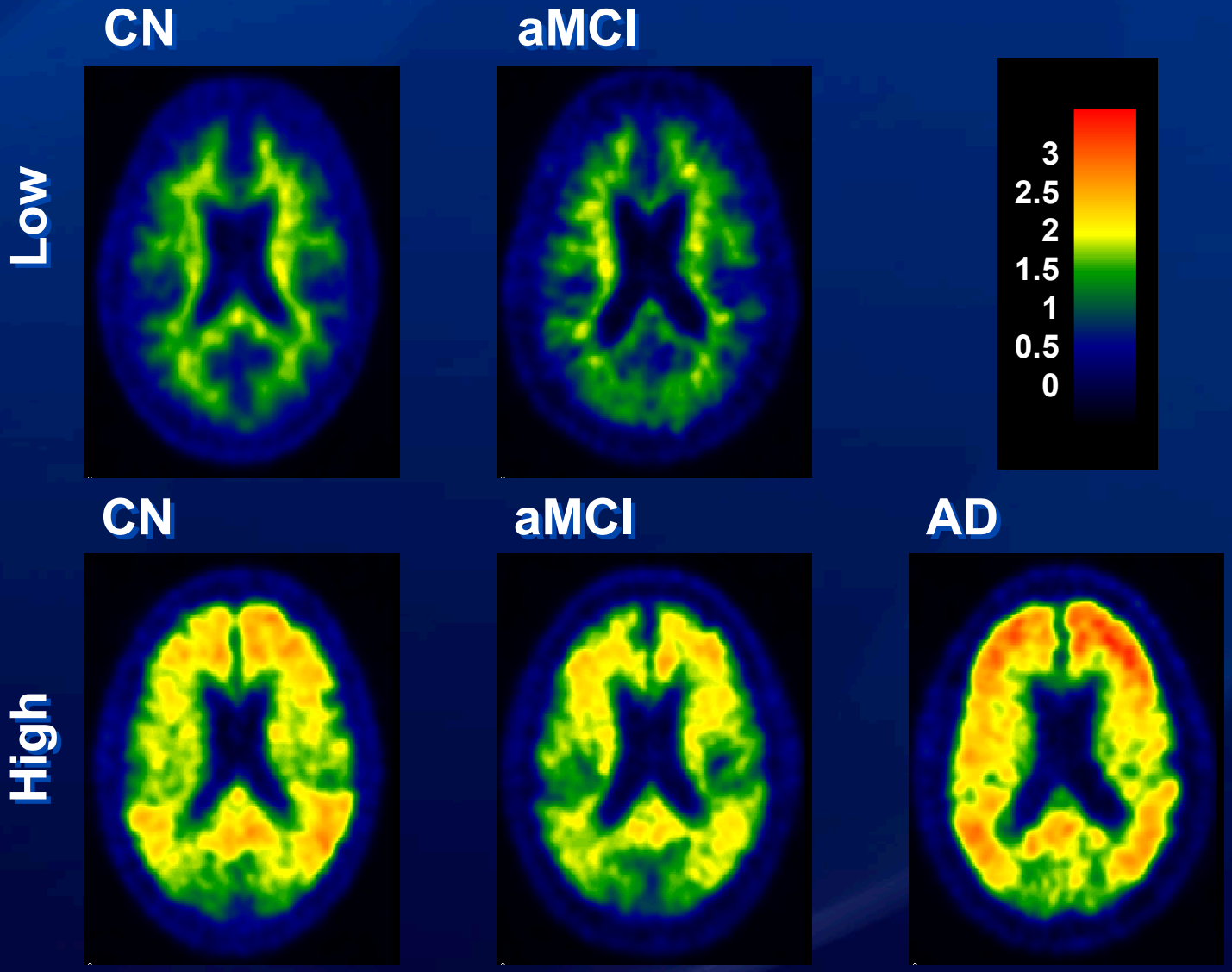
Important to have quantitative Amyloid PET with a full spectrum of disease.



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A/T/N Classifications

Descriptive nomenclature: Profile staging determined by imaging

		Cognitive stage		
		Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
Test Profile	$A^- T^- (N)^-$	normal AD testing. cognitively unimpaired	normal AD testing with MCI	normal AD testing with dementia
	$A^+ T (N)$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ (N)^+$			
	$A^+ T (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^- T^+ (N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	$A^- T^- (N)^+$			
	$A^- T^+ (N)^+$			

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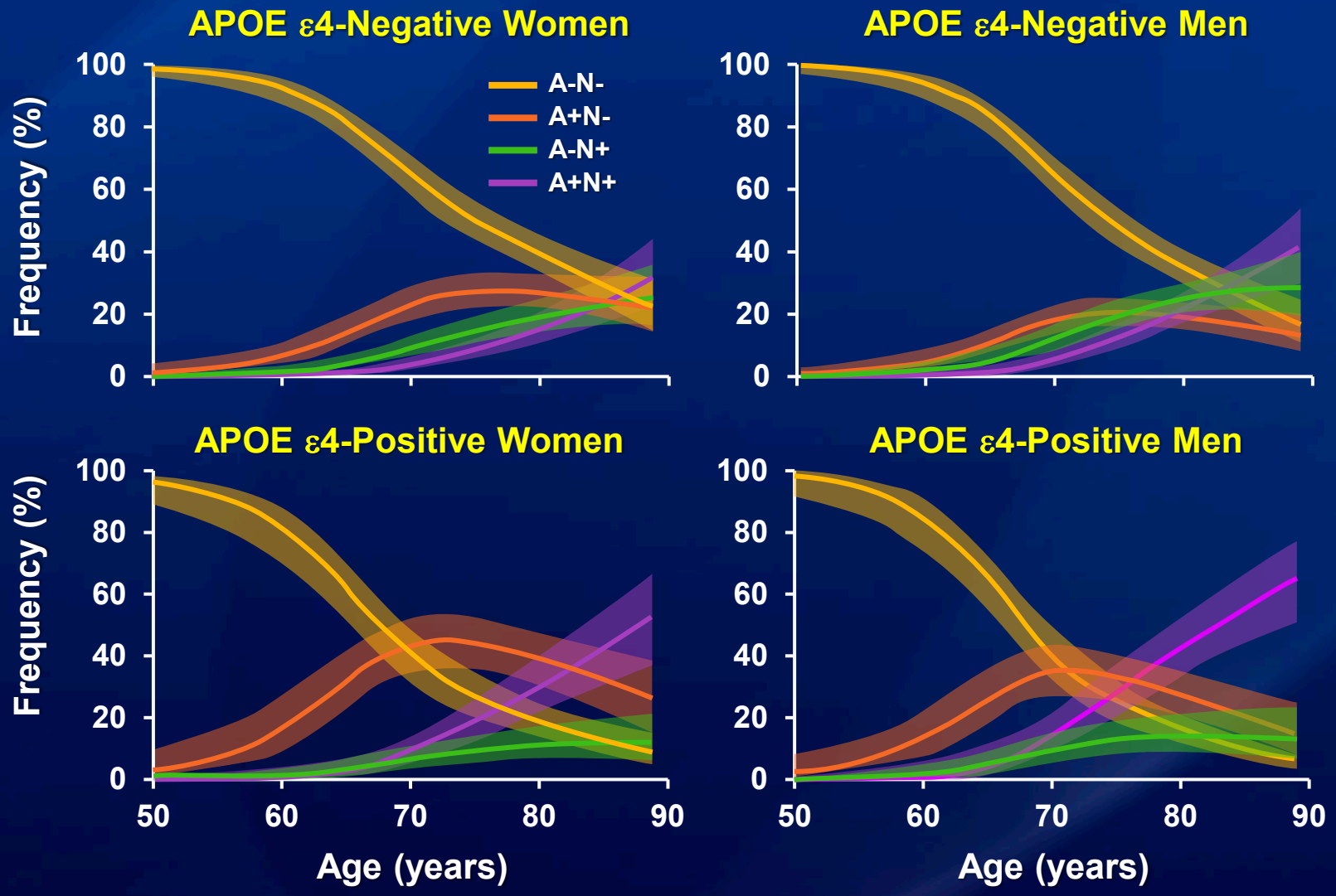
Jack et al: Alzheimers Dement. 2018 Apr;14(4):535-562.

Population Frequencies of Amyloid and Neurodegeneration by Age, Sex and ApoE4 Status



Jack et al: Lancet Neurol 13:997, 2014

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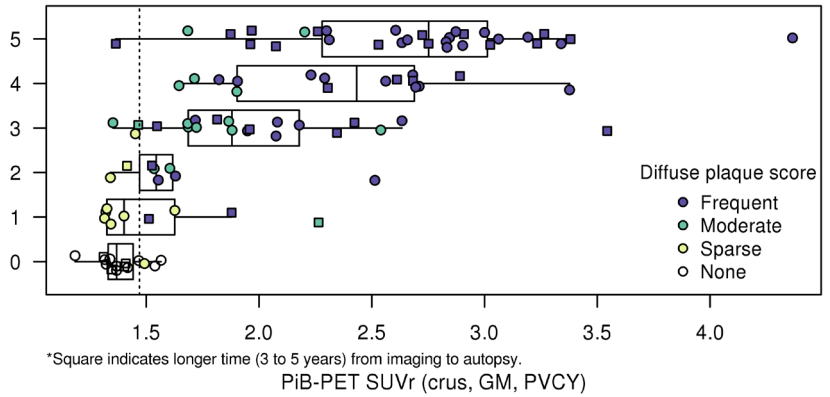
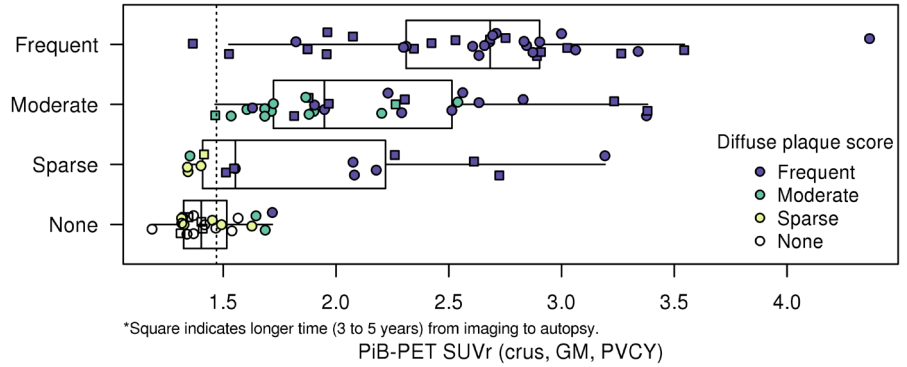
Quantitative amyloid PET correlates with different neuropathologic scoring methods.

Lowe, et al, Alzheimers Dement. 2019 Jul; 15(7): 927–939.

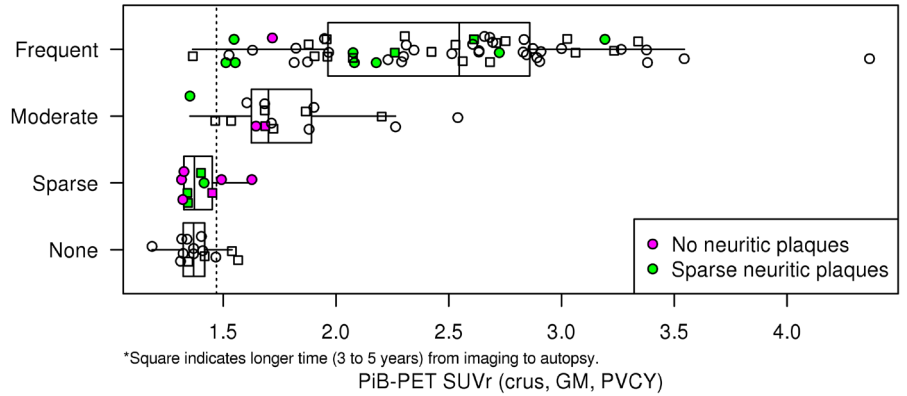
A. Thal amyloid phase



B. Neuritic plaque score



C. Diffuse plaque score



D. Spearman rank correlation (p-value)

Method	Thal	Neuritic plaques	Diffuse plaques
PIB crus, GM, PVCN	0.75 (p<0.001)	0.69 (p<0.001)	0.78 (p<0.001)
PIB crus, GM, PVCY	0.77 (p<0.001)	0.71 (p<0.001)	0.77 (p<0.001)
PIB crus, GM+WM, PVCN	0.73 (p<0.001)	0.68 (p<0.001)	0.77 (p<0.001)
PIB crus, GM+WM, PVCY	0.76 (p<0.001)	0.71 (p<0.001)	0.77 (p<0.001)

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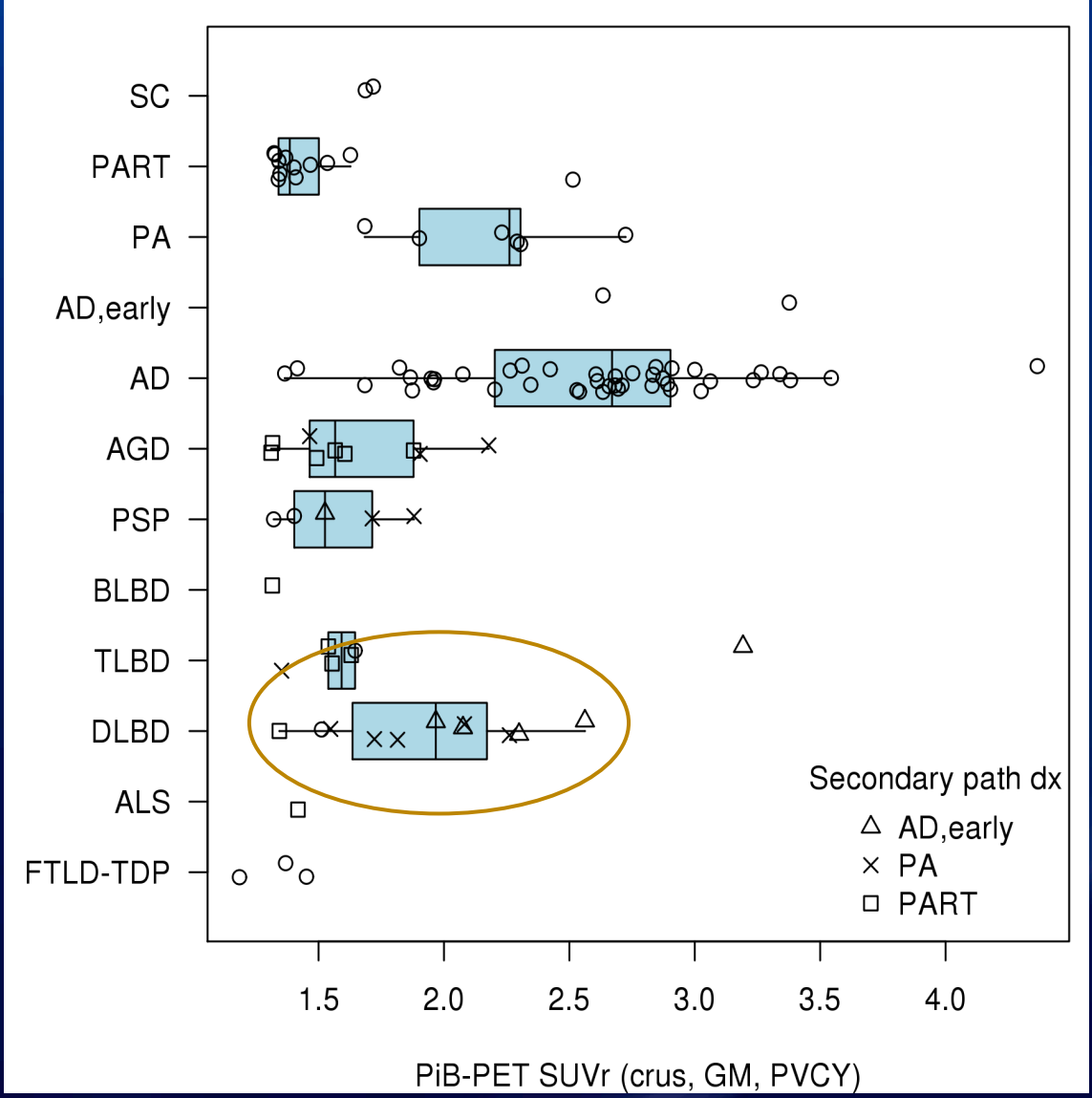
Quantitative amyloid PET aids in mixed pathology as seen in different neuropathologic diagnoses



Lowe, et al, Alzheimers Dement. 2019 Jul; 15(7): 927–939.

Questions for Quantitative Correlative Imaging Methods

- Is one dementia imaging method sufficient for disease characterization?
- Can imaging with many modalities inform us about the direction and sequence of disease development?
- How do different preclinical AD tests perform on cost-benefit analysis?

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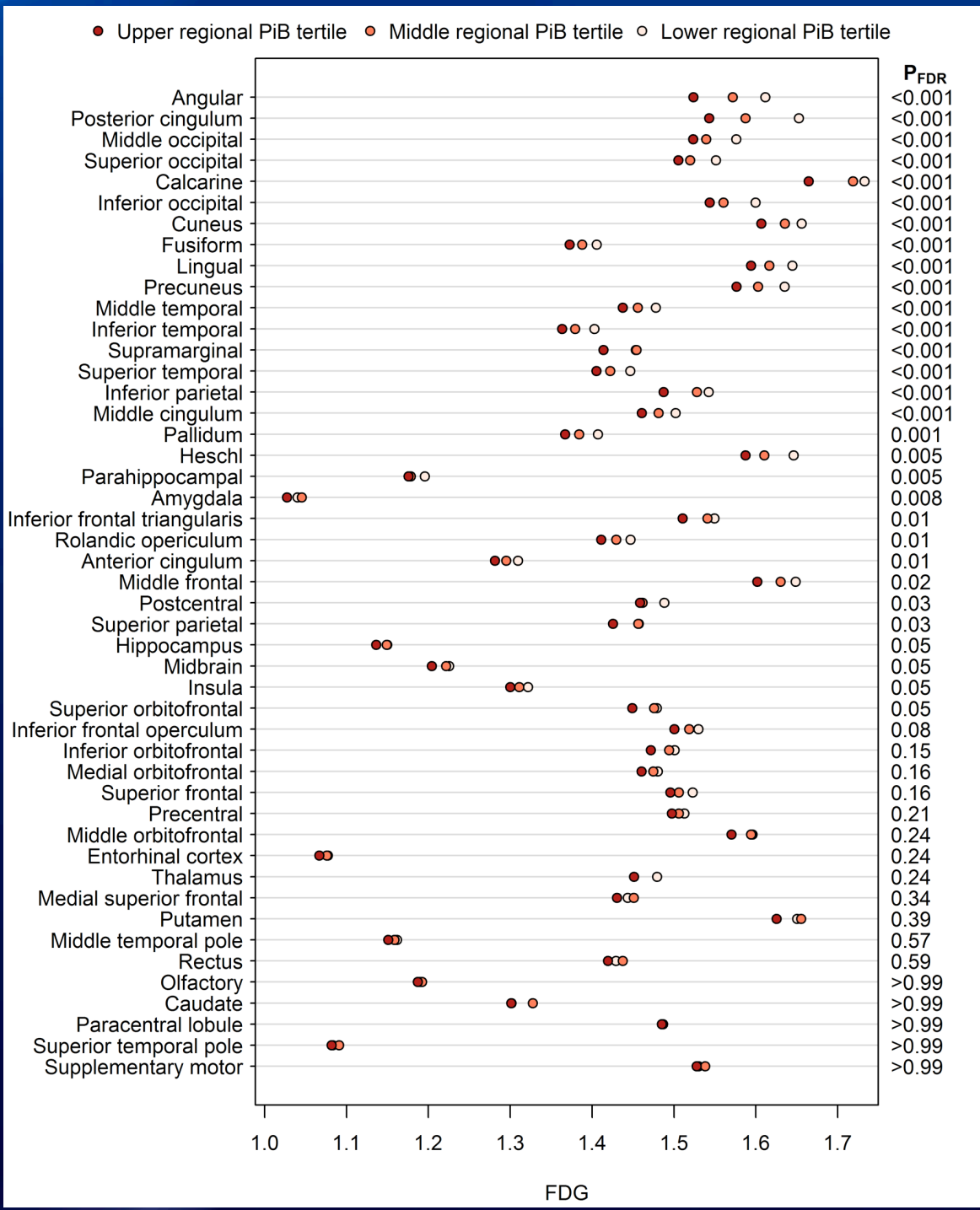
In Cognitively Unimpaired, *Regional Hypometabolism is Associated with Regional Amyloid*



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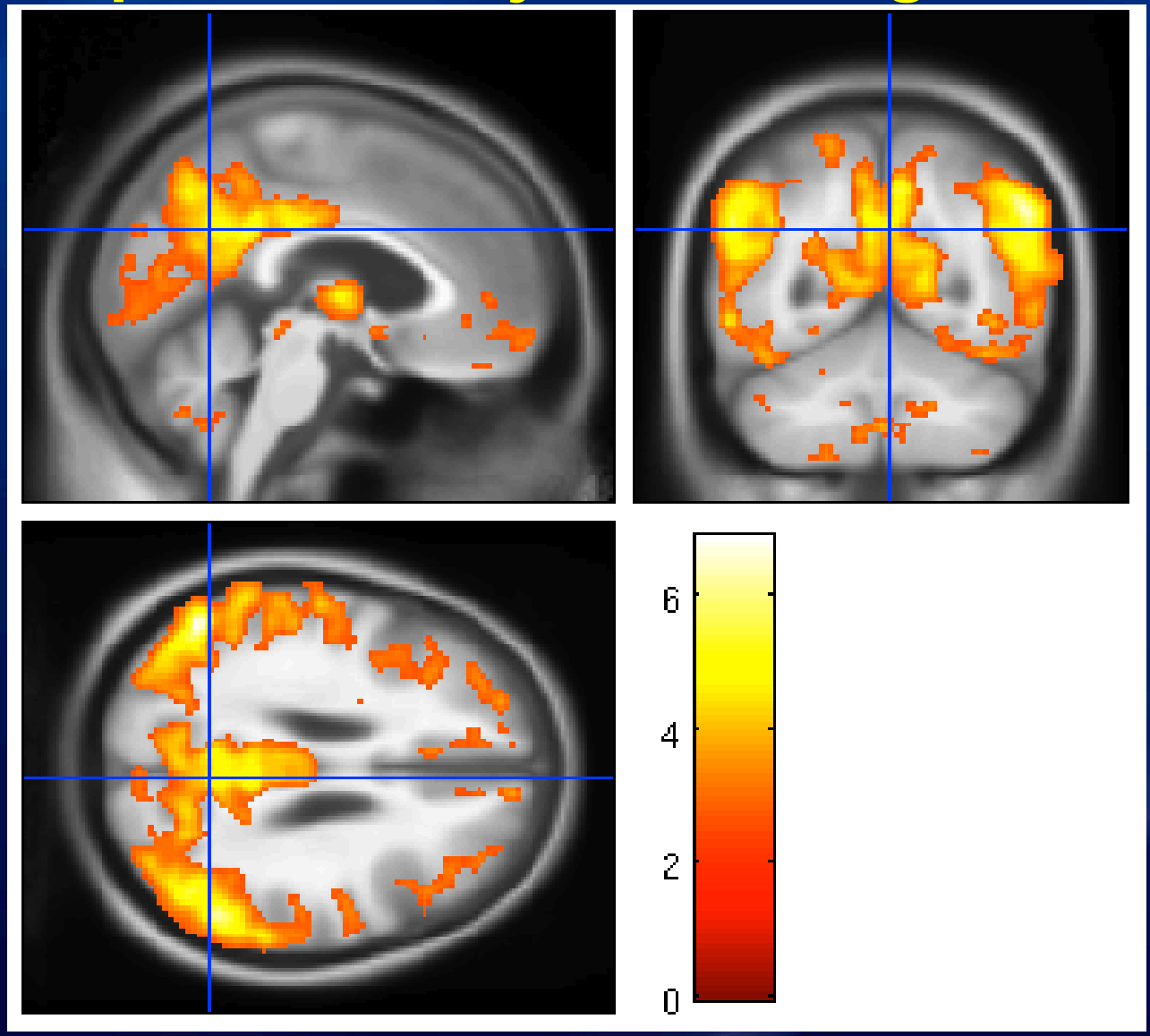
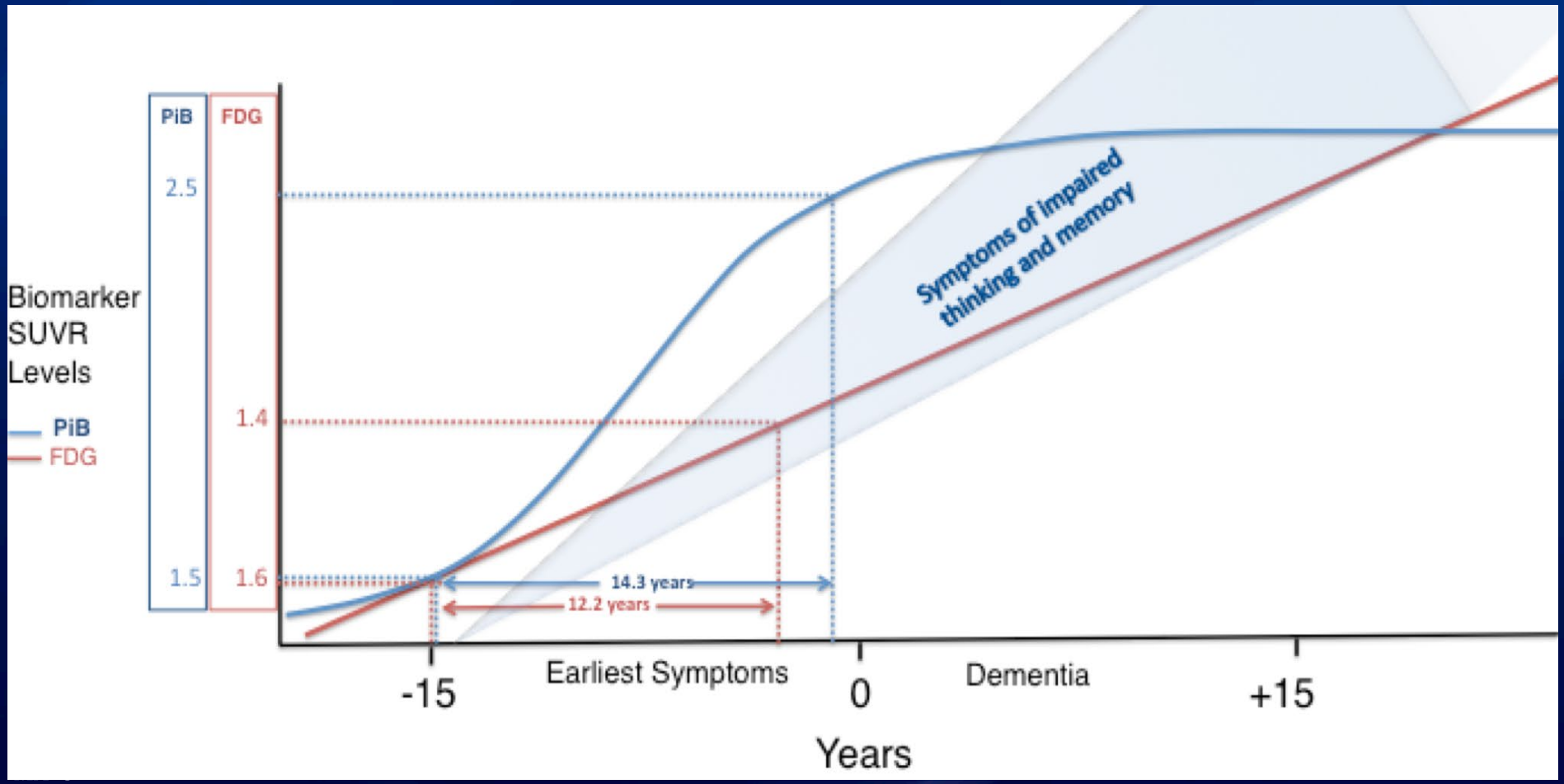
Lowe VJ, et al. Neurology 2014

Pattern of hypometabolism seen in unimpaired amyloid positive subjects vs. negative subjects



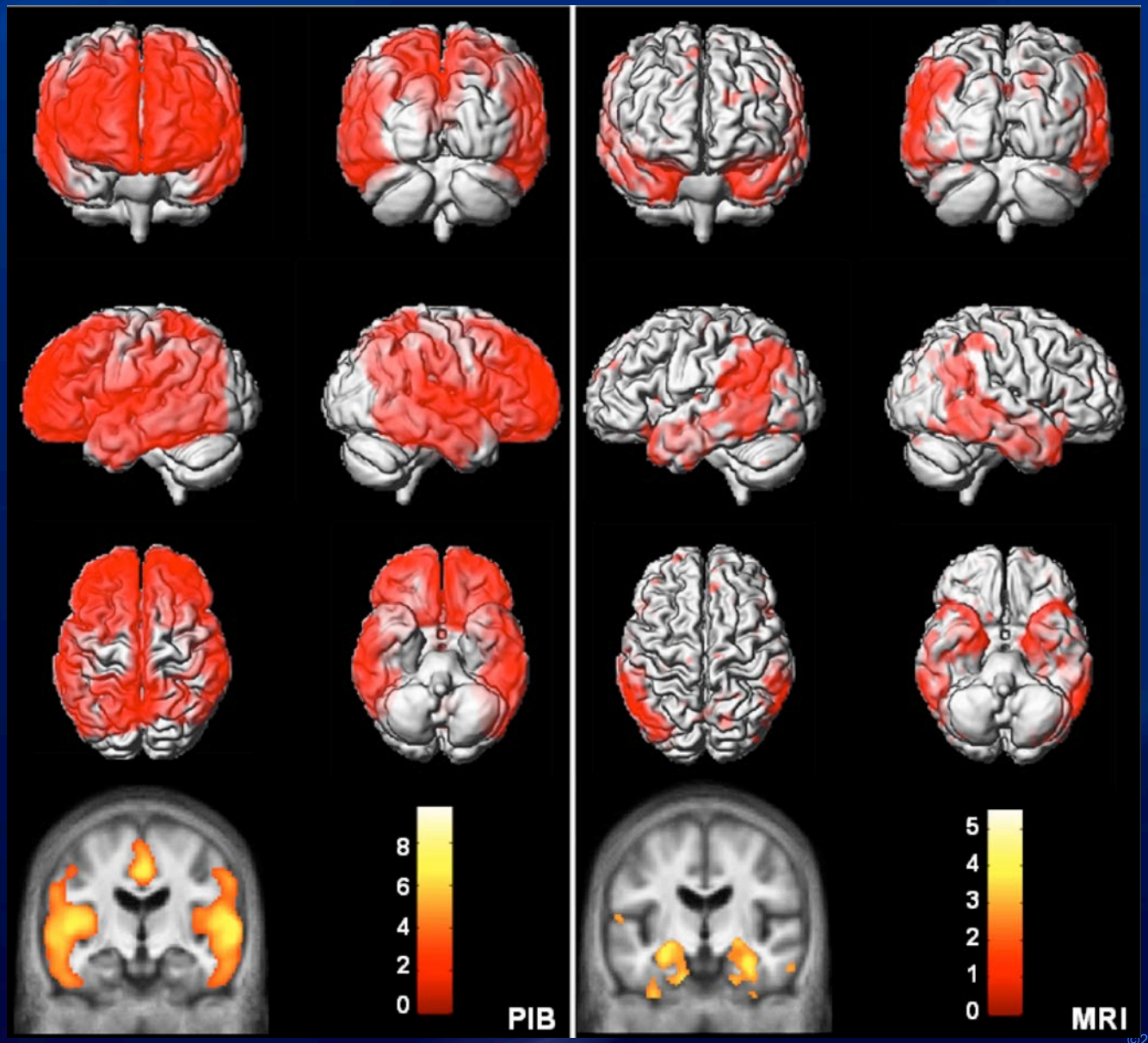
Lowe VJ, et al. Neurology 2014

Data Driven Models of Alzheimer's Disease Pathology can be developed.



Lowe VJ, et al. Neurology 2014, 82:1959-67

PET amyloid and MRI atrophy separate early AD and CN, but with different sensitivities



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Amyloid and Tau PET Associations

- Tau PET change occurs with amyloid and without amyloid positive scans in cognitively unimpaired.
- The regions of tau PET signal match Braak predictions imperfectly.
- There may be more diffuse brain deposition in early disease development than previously thought.

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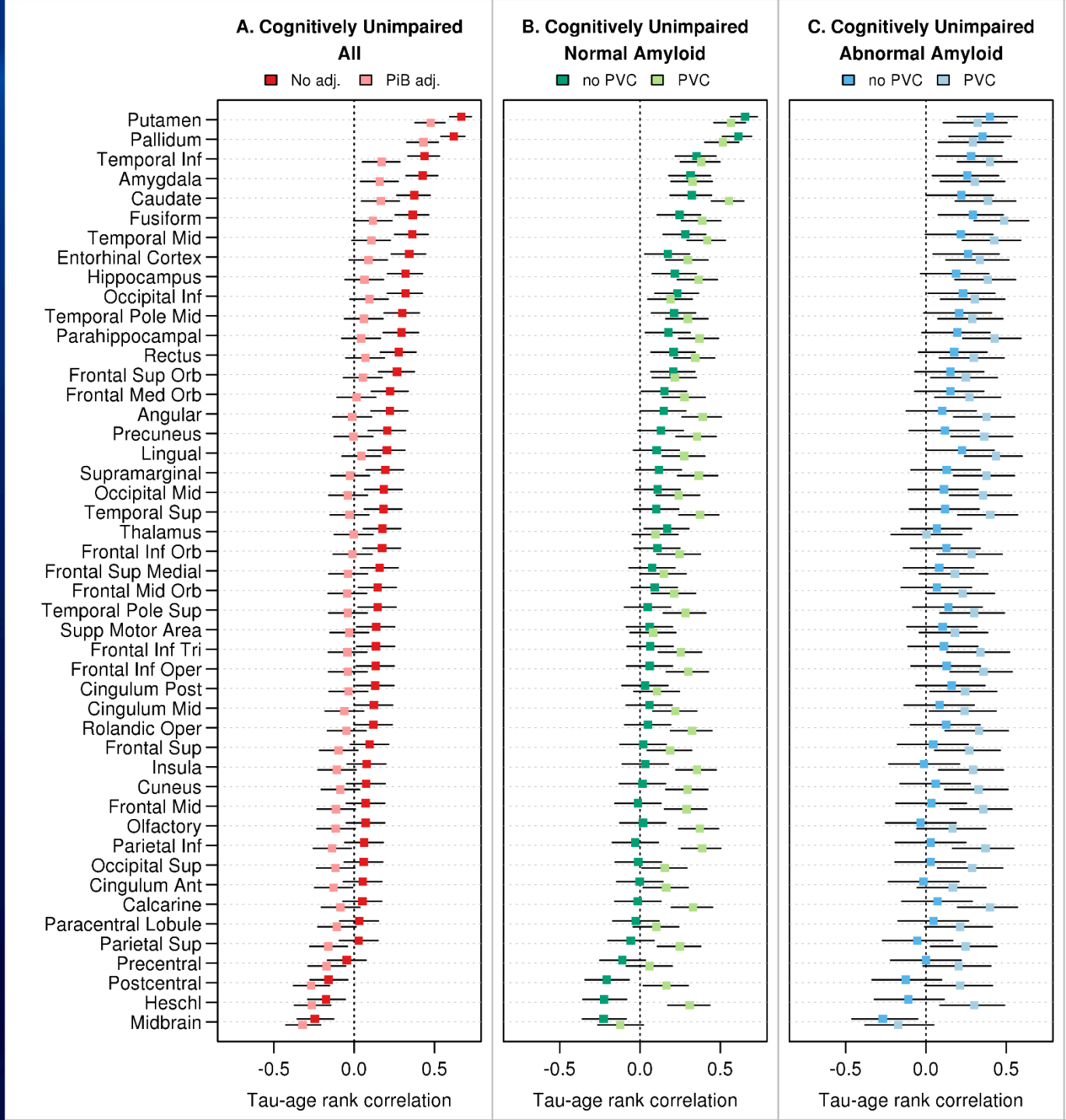
Widespread Tau in the brain even without amyloid



Lowe VJ, Brain 2018;141:271-287

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Important to assess these preclinical findings in-light of the Alzheimer's Disease new Conceptualization

- **Alzheimer's Disease** refers to the underlying presence of plaques (amyloid) and neurofibrillary tangles (tau).
- **Clinical spectrum** is parallel but separate from "Alzheimer's Disease"
  - Cognitively normal-MCI-dementia
- Alzheimer's disease is no longer a clinical-pathological entity but becomes **defined by the existing pathology as seen in clinical tests like imaging.**

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Future Directions

- Further characterize Alzheimer's disease as a pathological entity using quantitative amyloid imaging and other tests.
- Describe clinical syndromes associated with contributing etiologies as seen in preclinical stages.
- Help develop interventions based on imaging and biomarker-defined, pathological profiles.

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Mayo Clinic AD Research

Rochester

Ronald Petersen
Brad Boeve
Dave Knopman
Cliff Jack
Mary Machulda
Michelle Mielke
Rosebud Roberts
Walter Rocca
Walter Kremers
Keith Josephs
Jenny Whitwell
Kejal Kantarci
Joe Parisi
Eric Tangalos

Jacksonville

Neill Graff-Radford
Steve Younkin
Dennis Dickson
John Lucas
Tanis Ferman
Rosa Rademakers
Nilufer Taner-Ertekin
Len Petrucelli
Guojun Bu

Scottsdale

Rick Caselli
Bryan Woodruff
Yonas Geda
Janina Krell-Roesch

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Thank You

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Session IV: Quantitative Imaging in Staging of Disease, Prognosis and Monitoring Disease Progression: Implications for Diagnostic Imaging Drug Labelling

Industry Perspectives

Value of quantitation in diagnostic imaging of amyloid; Experience from European Labelling Activities

Gill Farrar, Global Medical Leader, GE Healthcare, UK

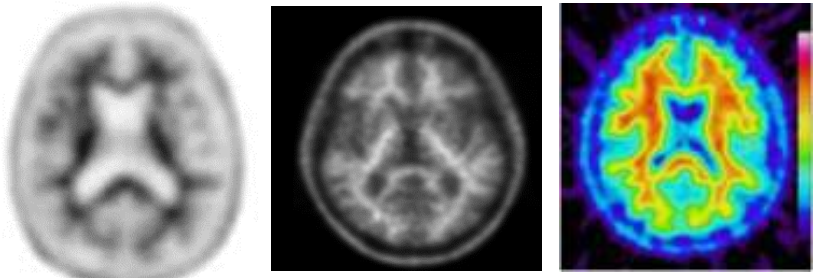
Disclosure: GF is a full-time employee of GEHC

Current Approved Methods of Interpretation of AMYLOID PET in the USA

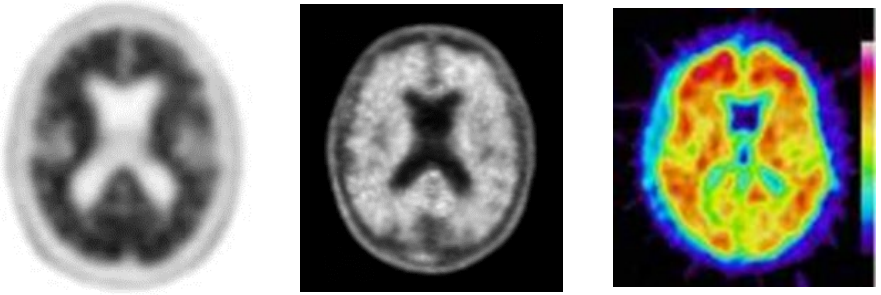
AMYViD® Florbetapir F 18 Injection

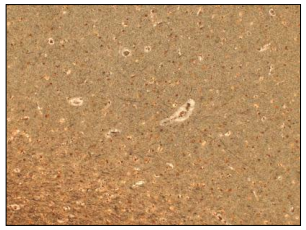
NeuraCeq™ florbetaben F18 injection

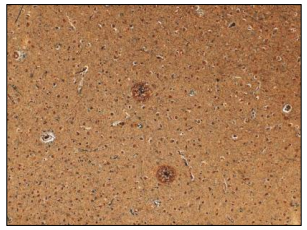
VIZAMYL™ Flutemetamol F18 Injection



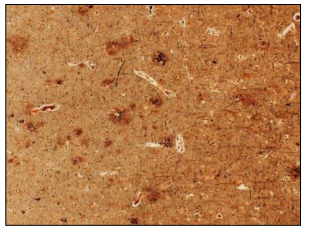
VISUAL INSPECTION

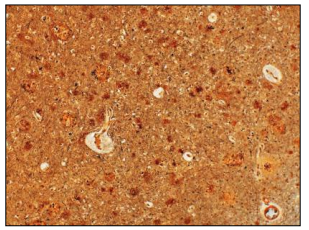






vs CERAD pathology as SOT





None Sparse

Moderate Frequent

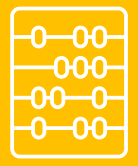
Negative

Positive

Value of quantitation in diagnostic imaging of amyloid

A diagnostic scan for the presence of amyloid could support the initiation of anti-amyloid therapy

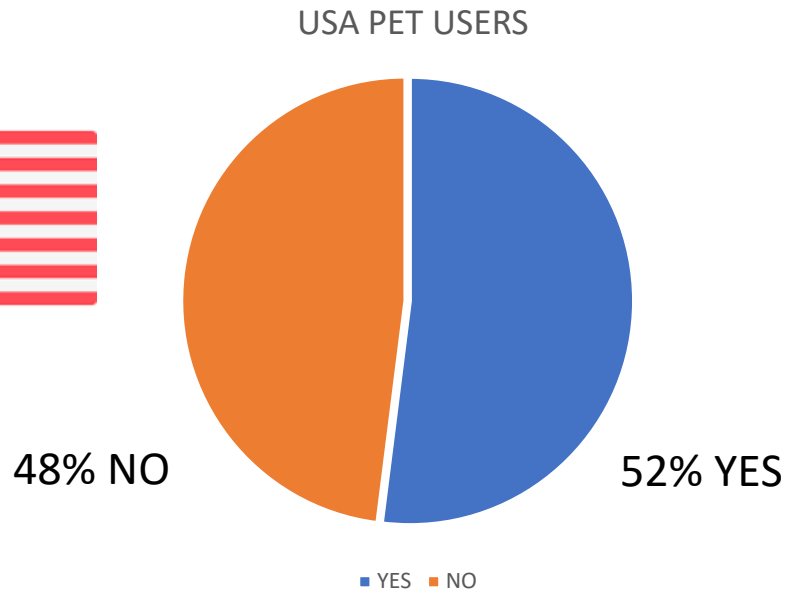
Quantitative information from this initial scan could be used as a baseline for subsequent monitoring purposes



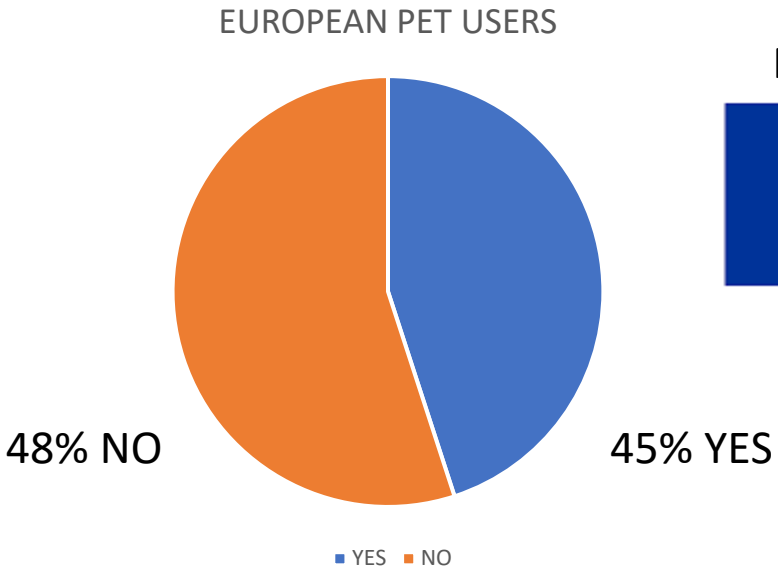
Quantitation allows for a continuous measure beyond the dichotomous yes/no that visual inspection provides

A proportion of US and European clinical users are using software tools for amyloid quantification in 2020/2021

N=176



Data c/o Bonnie Clarke SNMMI



N=113

Data c/o GE Healthcare Survey 2021
Manuscript submitted

Vizamyl Analysis to Support the Addition of Quantitation to EU Label

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05311-5

ORIGINAL ARTICLE

A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [^{18}F]flutemetamol amyloid PET images

Marco Bucci[1] · Irina Savitcheva[2] · Gill Farrar[3] · Gemma Salvadó[4,5] · Lyduine Collij[6] · Vincent Doré[7,8] · Juan Domingo Gispert[4,5,9,10] · Roger Gunn[11,12] · Bernard Hanseeuw[13,14] · Oskar Hansson[15] · Mahnaz Shekari[4,5,9] · Renaud Lhommel[13] · José Luis Molinuevo[4,5,9,16] · Christopher Rowe[7,17] · Cyrille Sur[18] · Alex Whittington[11] · Christopher Buckley[3] · Agneta Nordberg[1,19]

EMA

4.4: Quantitative assessment of cortical radioactive signal intensity using validated, and CE marked computer software <u>may be used</u> to assist in the visual estimate of radioactive signal distribution

5.1: Clinical studies x2; (n=379) using CE marked tools. 98% agreement

2770 Vizamyl images

3 clinical studies

6 research cohorts

Used CE marked/510(k) cleared + research tools

Assessed visual read +/- vs SUVr pons (threshold 0.59-0.62)

Mean concordance between visual and quant was 94%

Amyvid Analysis to Support/Augment the Addition of Quantitation to EU Label

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-016-3601-4

ORIGINAL ARTICLE

Quantitation of PET signal as an adjunct to visual interpretation of florbetapir imaging

Michael J. Pontecorvo[1] · Anupa K. Arora[1] · Marybeth Devine[1] · Ming Lu[1] · Nick Galante[1] · Andrew Siderowf[1] · Catherine Devadanam[1] · Abhinay D. Joshi[1] · Stephen L. Heun[1] · Brian F. Teske[1] · Stephen P. Truocchio[1] · Michael Krautkramer[1] · Michael D. Devous Sr.[1] · Mark A. Mintun[1]

EMA

4.4: Adjunctive use of amyloid PET quantitative information only used by readers trained…including selection of CE-marked software….
….Adjunct to visual inspection and may improve reader accuracy….
5.1: Studies x2, n=96 images (46 autopsy verified) significant increase from baseline accuracy with quantitation

96 Amyvid images (46 with autopsy SOT)

1) Visual read first as baseline (80 readers)

2) Read with access to quant (x 3 CE marked software)

3) With quant 93.1% vs 90.1% read accuracy at baseline for autopsy verified scans

Neuraceq Analysis to Support the Addition of Quantitation to EU Label

Validation of quantitative assessment of florbetaben (18F) PET scans as an adjunct to visual assessment *(manuscript in preparation)*

Methods:

FBB PET scans from 589 subjects quantified with three analytical methods:

- MiMneuro (CE / 510(k))
- Hermes Brass (CE/ 510(k))
- Neurocloud (CE)
- NMF

Results:

Across all pipelines:

- Sensitivity: **95.8**±1.8%
- Specificity: **98.1**±1.4%

(compared to histopathology)

Mean percentage of agreement between binary quantitative assessment and visual majority assessment: **91.2**±1.7%

Conclusions:

Quantification can complement the visual assessment of FBB PET images.

EMA

4.4: *Quantitative information generated by CE-marked image quantitation software for the quantification of amyloid-beta PET scans can be used as an adjunct to visual interpretation. Users of the CE-marked software should be trained by the manufacturer and perform quantification according to the manufacturer's instructions, including quality checks of the quantitative process.*

5.1: x 2 Components *(i) the diagnostic performance (i.e., sensitivity and specificity) of quantitative assessment of florbetaben PET scans vs histopathological confirmation … (ii) concordance of visual majority read of five independent blinded readers to quantitative assessment of florbetaben PET scans (n=386).*

General Considerations for the Use of Quantitation in Clinical Routine in Europe

Adjunctive use of quantitative information for image interpretation may improve reader accuracy

Software tools only used by readers trained in the application of quantitative information to aid visual image interpretation.

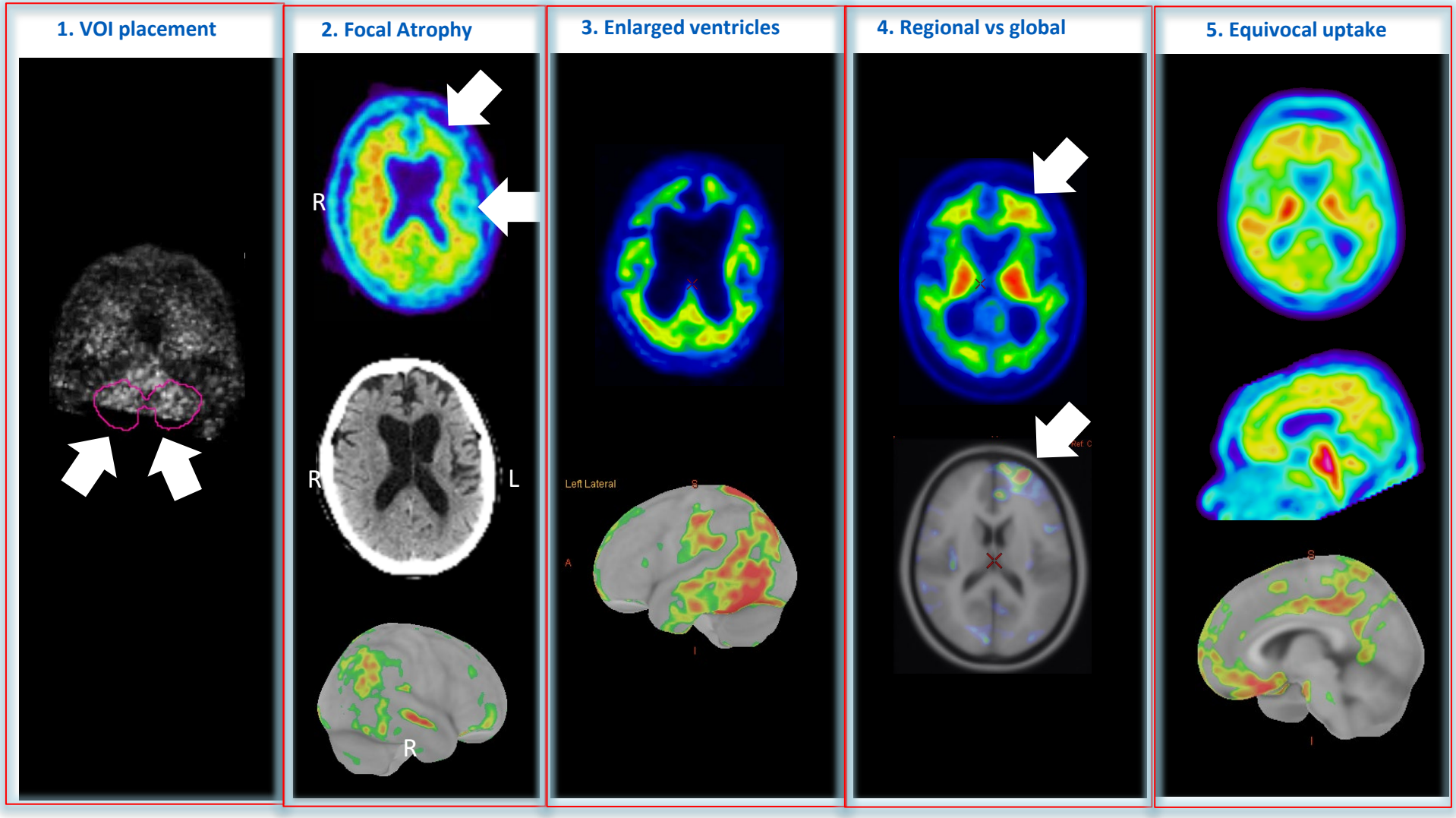
Selection of appropriate CE-marked software tools

Readers should visually interpret the scan first, then perform quantitation according to manufacturer's instructions

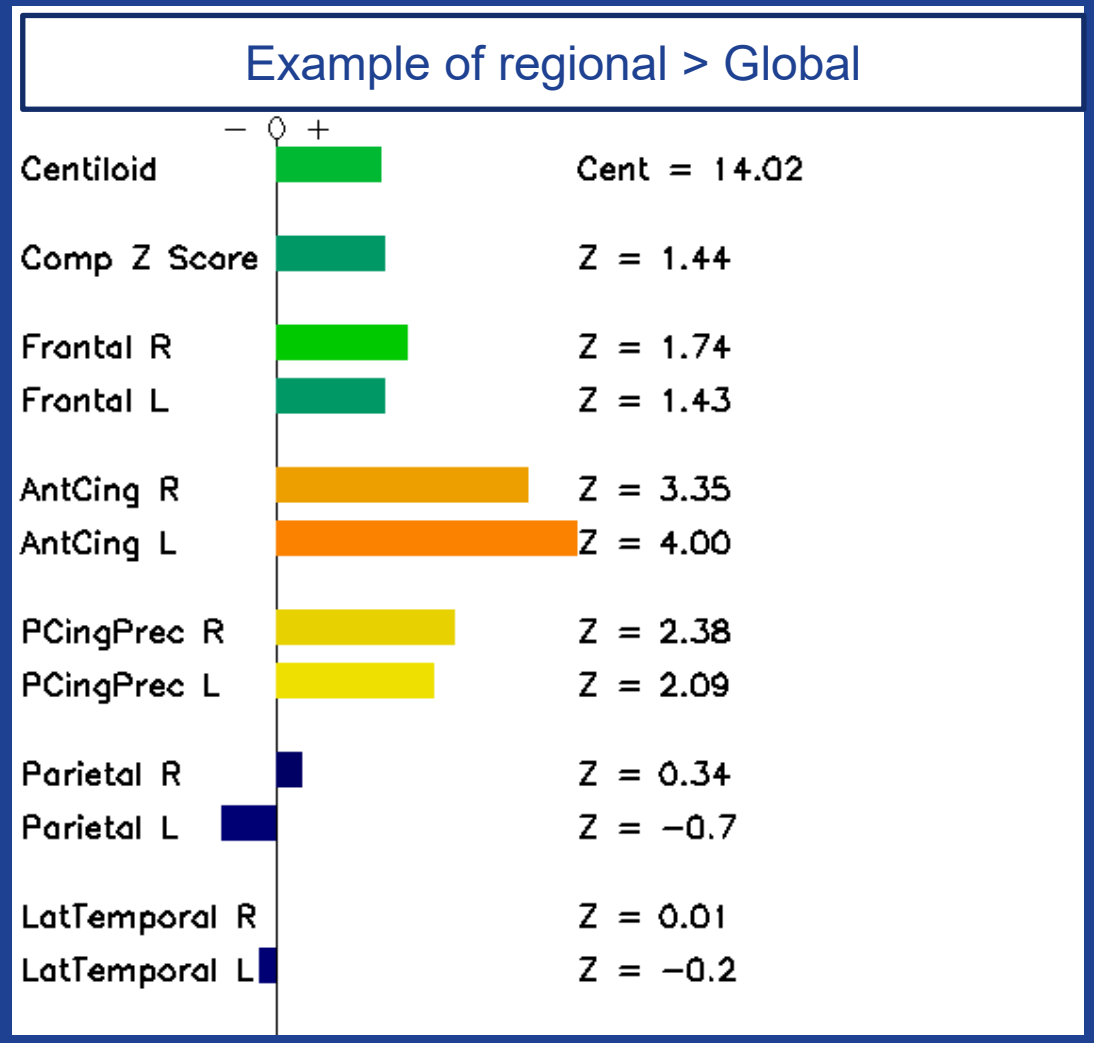
Quality checks of the quantitative process are required

If the quantitation result is inconsistent with the initial visual interpretation carefully inspect the placement of cortical and reference regions eg to assess for atrophy

Training and Education is valuable:
Flutemetamol (18F) Image Interpretation Guidance for Visual Inspection and Adjunctive Use of Quantitation



In routine image assessment where a dichotomous +/- is required: A composite cortical measure is not always sufficient



Clinical case example from AMYPAD DPMS

Regional z-score could help with overall assessment where levels are close to threshold

Software Quantitation Compatibility Study

- *BRASS* - Hermes Medical Solutions

- *CortexID* - GE Healthcare

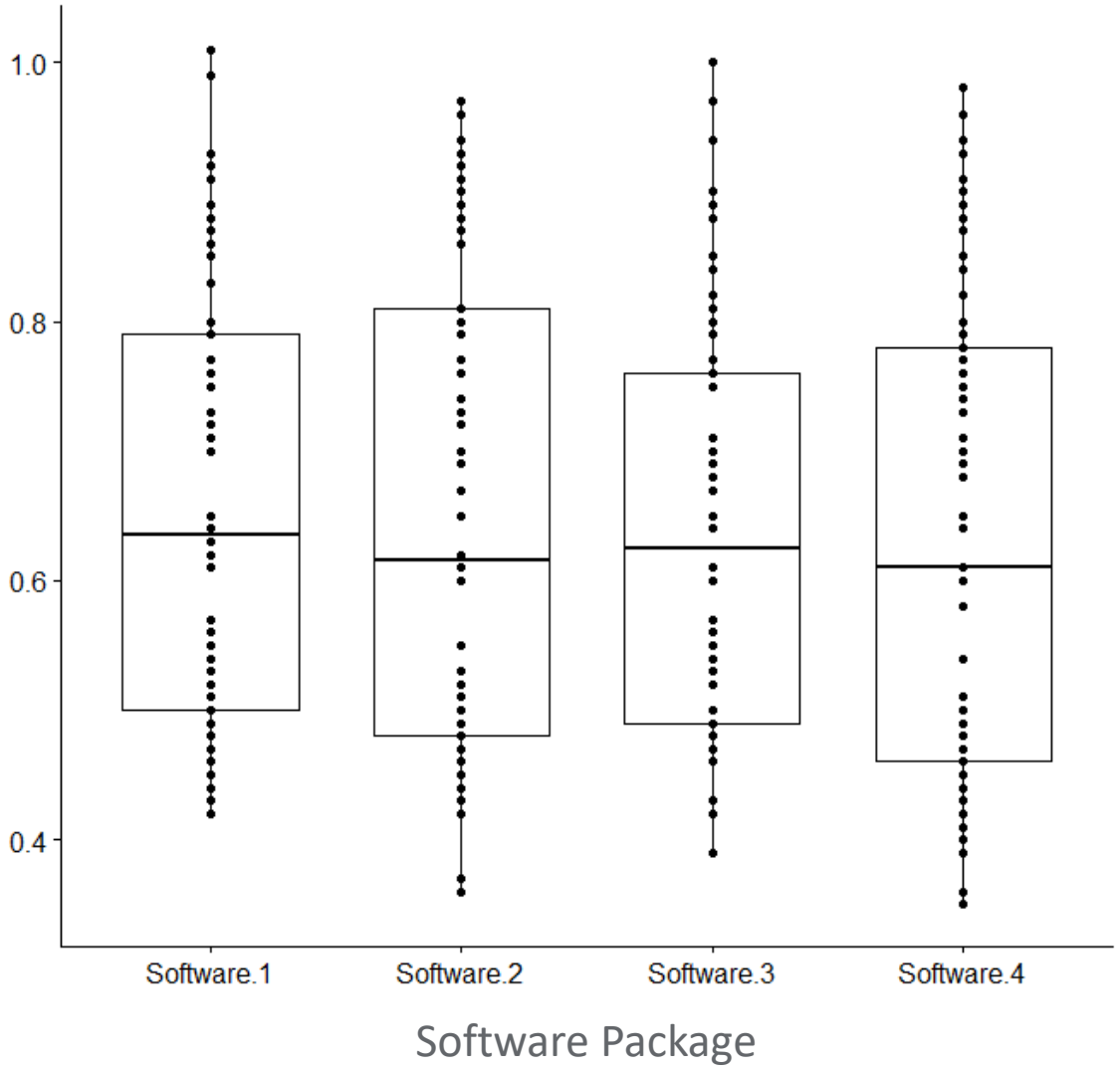
- *MIMneuro* - MIM Software

- *NeuroQ* - Syntermed

- Vizamyl Images (AD, CU) x 12
- Assessed initial SUVr (pons) measure from 4 software tools
- Applied optimized cortical mask
- Repeat SUVr measure for x 80aMCI Vizamyl scans
- Assess reliability between tools

Ref: data presented by GEHC at SNMMI 2022 and now submitted for publication

Results: Composite SUVr highly correlated across the software packages



Excellent reliability between composite SUVr for all 4 software packages

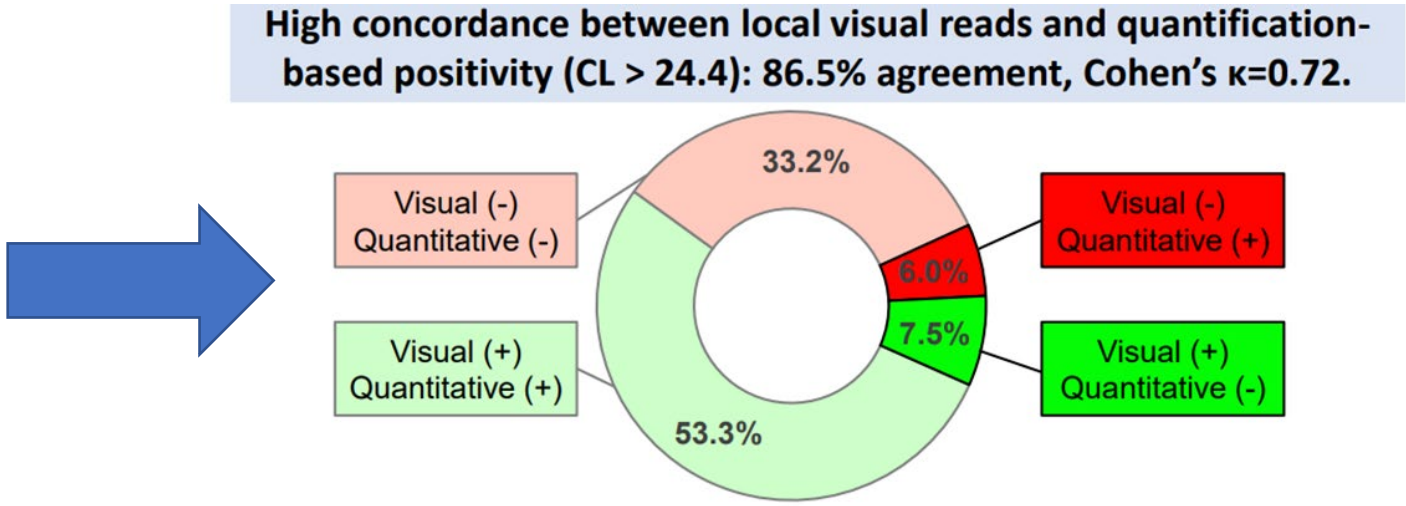
The average measure Intraclass Correlation Coefficient was 0.97

95% confidence interval from 0.957 to 0.979

Ref: data presented by GEHC at SNMMI 2022 and now submitted for publication

Value of Quantitation: could bridge the gap between local and expert readers?

Study	Tracer	Agreement V/Q
Pontecorvo 2018	FBP	93.1%
ABIDE (2017)	FBB	93.1%
Bucci multicentre (2021)	Flute	94%



Expert Readers 3 major studies: 93-94% agreement

IDEAS (n=6150) Local readers vs Quant: 86.5% agreement

Ref: IDEAS presentation at AAIC 2022

Summary:

1) Visual read and quantitation of routine clinical images is generally very concordant

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3) Addition of quantitation on the European label has allowed active discussions with routine users as they move forward to using software tools

Summary:

1) Visual read and quantitation of routine clinical images is generally very concordant
2) Education/training is valuable for the optimal use of quantitation/software tools
3) Addition of quantitation on the European labels has allowed active discussions with routine users as they move forward to using software tools
4) Quantitation and visual inspection methodology are complementary; both add value to overall image interpretation

Thank-you

Backup slides

Amyloid PET labelling in Europe has been updated since initial approvals

Amyvid Labelling Language

Adjunctive use of quantitative information for image interpretation:
Adjunctive use of amyloid PET quantitative information should only be used by readers trained in the application of quantitative information to aid visual image interpretation, including recommendations for selection of appropriate software to support the methods. Incorporation of quantitative information generated by CE-marked image quantitation software as an adjunct to the visual interpretation method may improve readers' accuracy. Readers should visually interpret the scan, then perform quantitation according to manufacturer's instructions, including quality checks of the quantitative process, and 6 compare quantitation of scan with typical ranges for negative and positive scans. If the quantitation result is inconsistent with the initial visual interpretation

Vizamyl Labelling Language

Quantitative assessment of cortical radioactive signal intensity using validated and CE marked computer software may be used to assist in the visual estimate of radioactive signal distribution. Such software provides a calculation of brain amyloid load by dividing the mean image intensity in the cortical regions associated with amyloid deposition (raised in AD subjects) with the mean image intensity in a reference region such as the pons. The measure is referred to as Standard Uptake Value ratio or SUVR. Dichotomous visual reads for flutemetamol (18F) scans were validated against the boundary between sparse and moderate neuritic plaque densities. An SUVR threshold value of 0.59 to 0.61 derived from CE marked software using the pons as a reference has been determined to give very high concordance with visual reads (see section 5.1) and may be used as an adjunct to visual reading

Amyloid PET labelling in Europe has been updated since initial approvals

Neuraceq Labelling Language

Quantitative information generated by CE-marked image quantitation software for the quantification of amyloid-beta PET scans can be used as an adjunct to visual interpretation (see section 5.1). Users of the CE-marked software should be trained by the manufacturer and perform quantification according to the manufacturer's instructions, including quality checks of the quantitative process. Readers should visually interpret the scan and then compare the quantitation result with typical ranges for negative and positive scans. If the quantitation values are inconsistent with the visual assessment, the reader should review the following aspects:

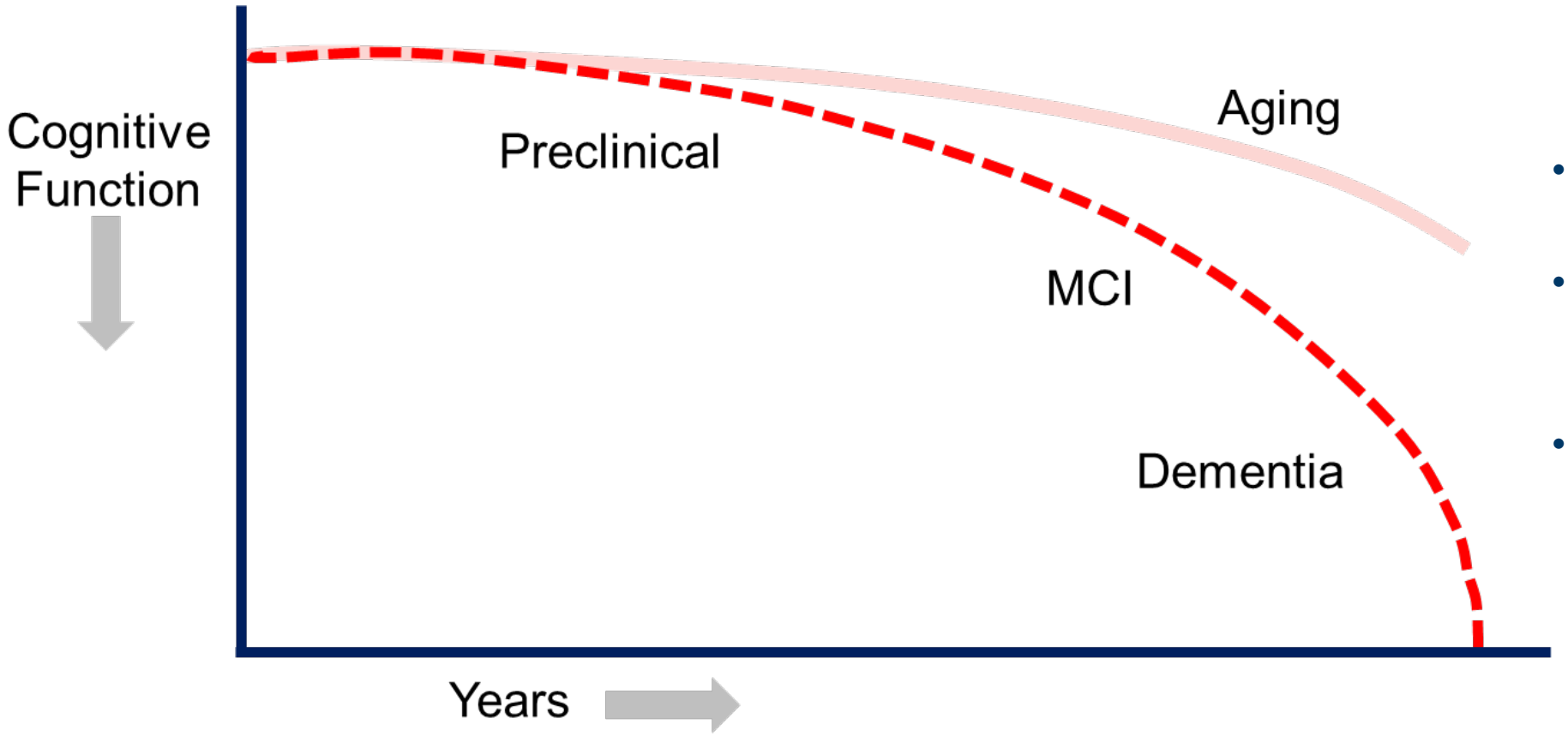
Topic: Amyloid early detection/prognostic issues and how the Centiloid metric can help

Andrew Stephens

Disclosure

- Andrew Stephens is a full-time employee of Life Molecular Imaging
- Neuraceq® (florbetaben F18) is approved for routine clinical use by FDA and EMA
- PI-2620 is a research compound that has not been approved in any jurisdiction

AD is disease continuum with a long asymptomatic period, followed by cognitive decline and eventual dementia



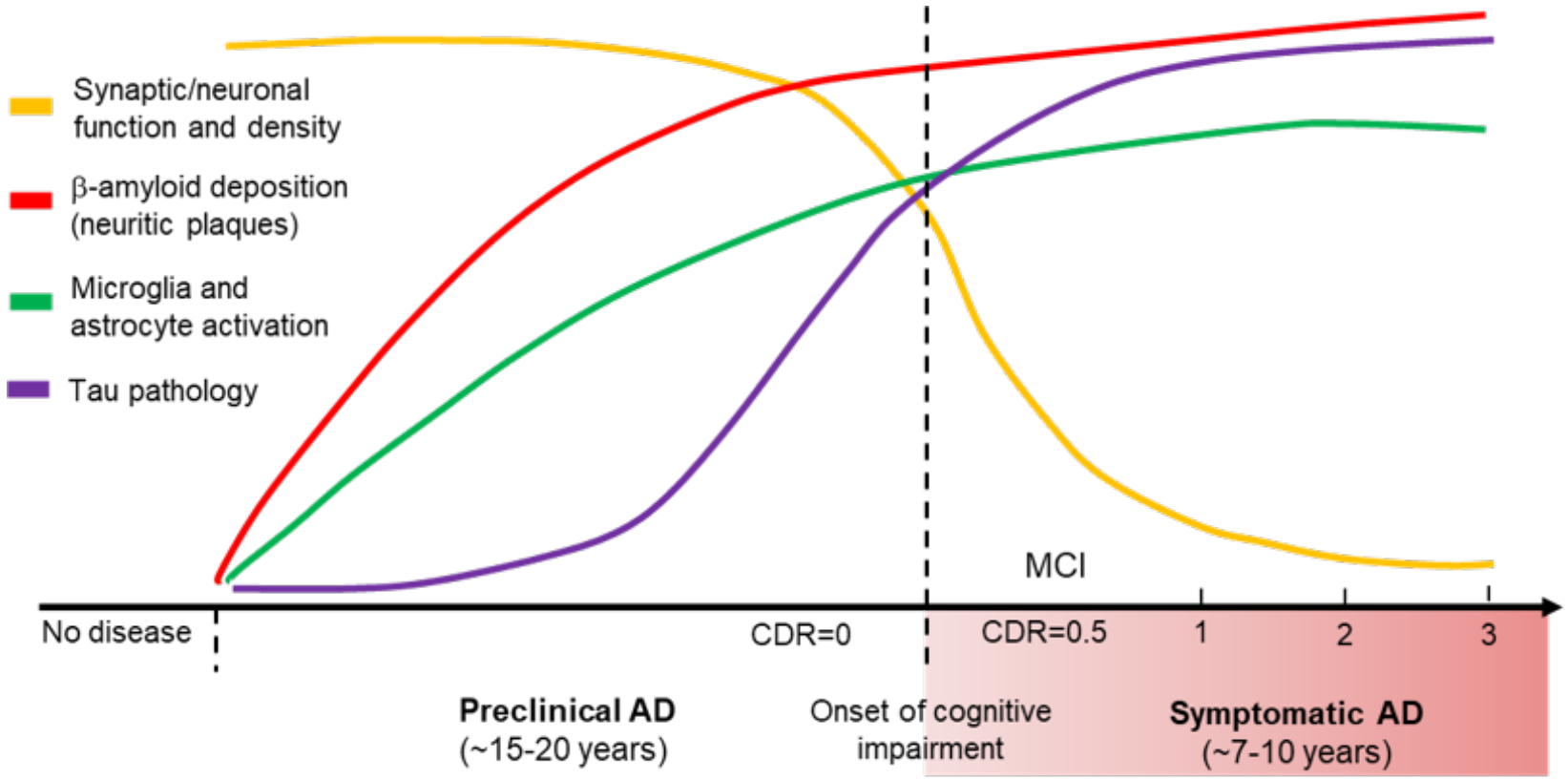
- Long process lasting 15-20 years
- Results confounded by normal ageing process
- 12-18 month trials may show limited changes of any intervention

Adapted from Sperling RA, et al. *Alzheimers Dement*. 2011;7(3):280-292.

AD pathology is characterized by sequential trajectories of amyloid plaques, neuroinflammation and tau

Sequential interplay of 3 key pathologies:

- Beta-amyloid deposition is the first abnormal biomarker in the AD continuum
- Activated microglia and astrocytes follow and cause an inflammatory reaction
- Emerging tau pathology is closely linked to loss of neuronal function and cognitive decline

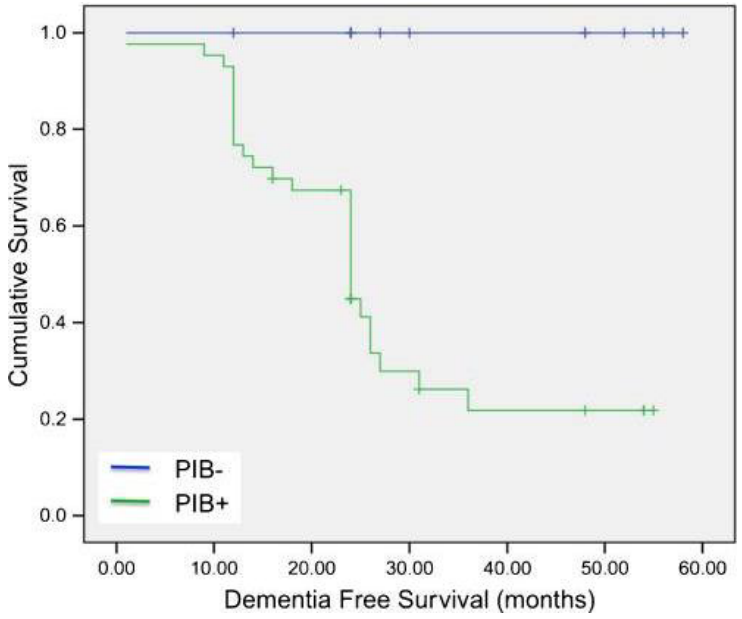


Long JM, Holtzman DM. *Cell*. 2019

Prior clinical studies showed link between Amyloid-positivity in MCI subjects and possible future onset of AD dementia

- MCI subjects previously stratified only for amyloid positive/negative
  - Amyloid-neg MCI did not show progression to AD dementia over time, whereas many Amyloid-pos MCI did
  - AD dementia onset and rate of cognitive decline in amyloid-PET positive MCI subjects determined by complex interplay with other pathologies and risk factors

^{11}C-PIB-PET in 64 MCI subjects
β-amyloid status: 43 pos/21 neg



Nordberg et al. EJNMMI 2013

Florbetaben-PET in 45 MCI subjects
β-amyloid status: 24 pos/21 neg

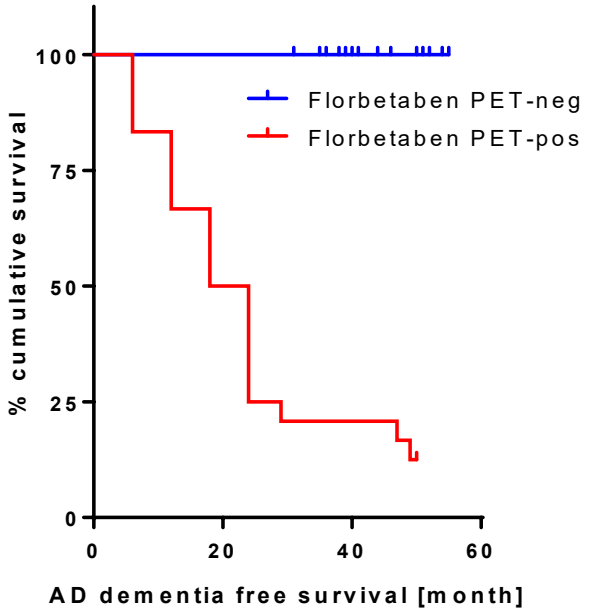
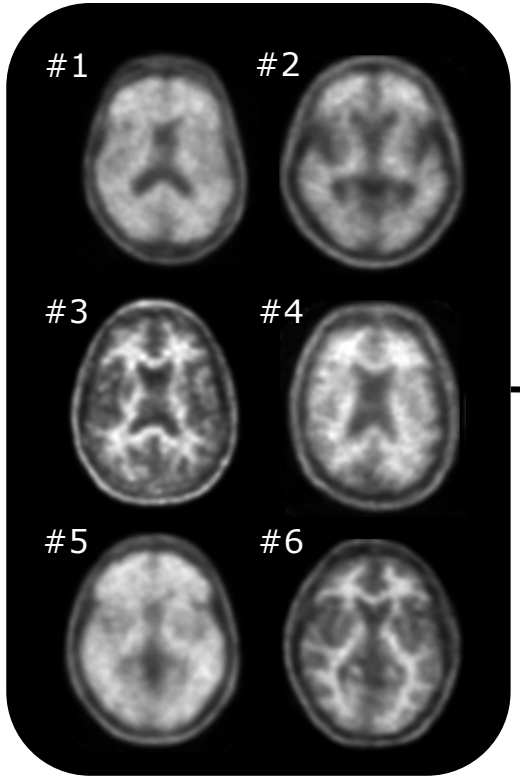


Figure created using data from Ong et al. JNNP 2015

PET quantification for Neuraceq® incorporated in EU SmPC after retrospective analysis using 15 analytical pipelines



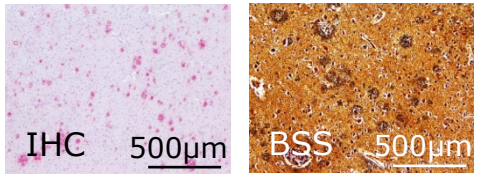
673 florbetaben PET scans from previous clinical trials

Software	Metric
CapAIBL	Centiloid
Centiloid	Centiloid
MIMneuro*#	Centiloid
Neurology toolkit	Centiloid
NMF	Centiloid
SPM (WC, PET only)	Centiloid
Amyloid^{IQ} (PET only)	Amyloid load
Amyloid^{IQ} (MR)	Amyloid load
Neurology toolkit	Amyloid index
Hermes BRASS*#	SUVR
Neurocloud*	SUVR
PMOD Neuro	SUVR
SPM (WC)	SUVR
SPM (WC2)	SUVR
SPM (CGM)	SUVR

*CE-marked, #510(k)

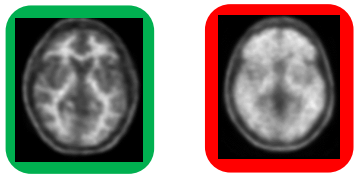
Analysis with 15 different pipelines (~11,000 PET assessments)

High diagnostic efficacy



Histopathology

High concordance with visual assessment



Robust performance across all quantitative pipelines

Sensitivity / Specificity

- CE pipelines 95.8% / 98.1%
- All pipelines 96.1% / 96.9%

Inter-software reliability

- kappa 0.90 (95% CI: 0.88, 0.93)
- Average correlation coefficients between pipelines: 0.95±0.03

Intra-software reliability

- R^2 ranging between 0.98 and 1.00

Concordance visual majority read and quantification

- CE-marked pipelines: 91.2%
- All 15 pipelines: 92.4%

Manuscript in preparation

Dichotomous visual read is the primary assessment method of Amyloid PET, quantification can provide further insights

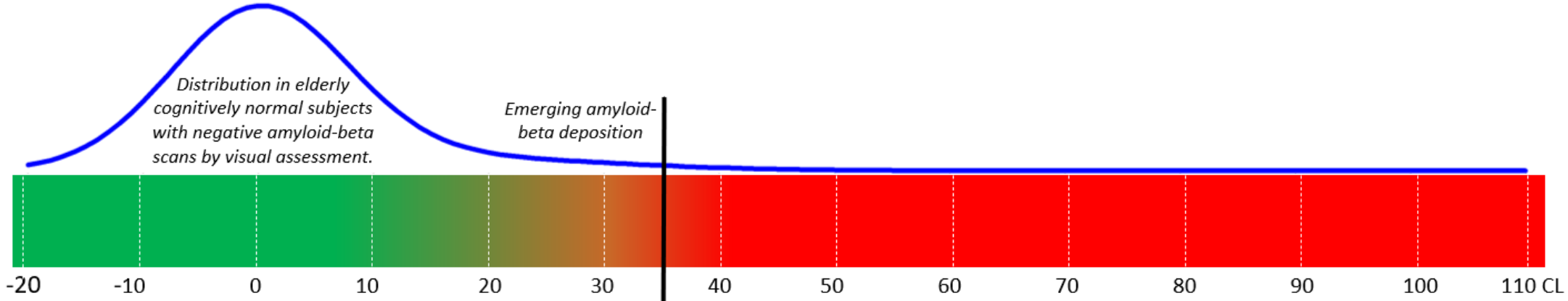
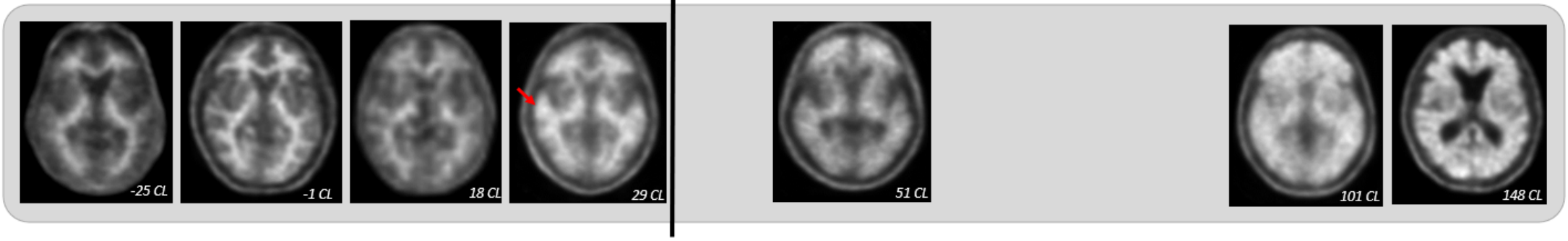
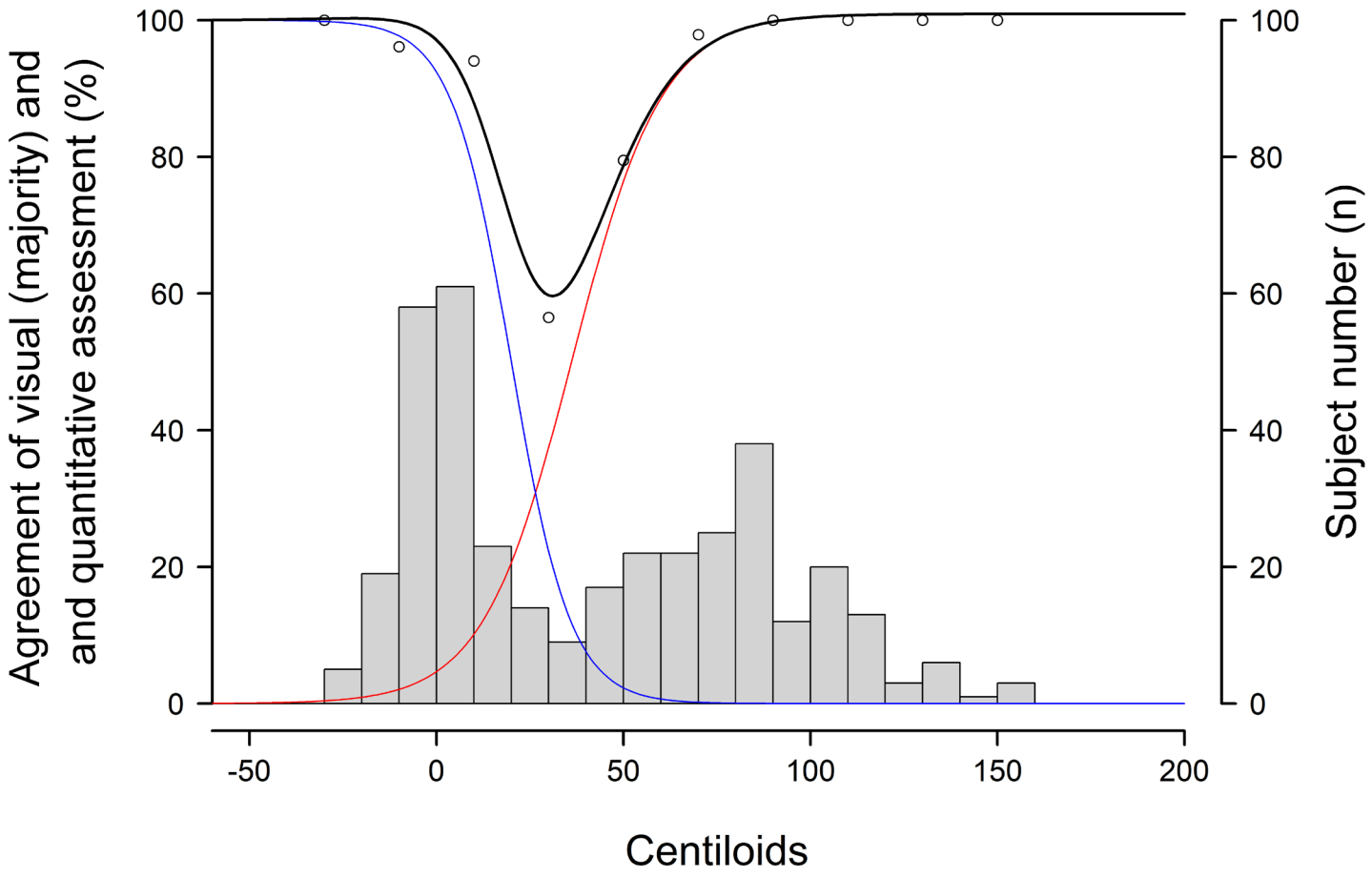


Illustration for representative Neuraceq scans:



LMI unpublished data

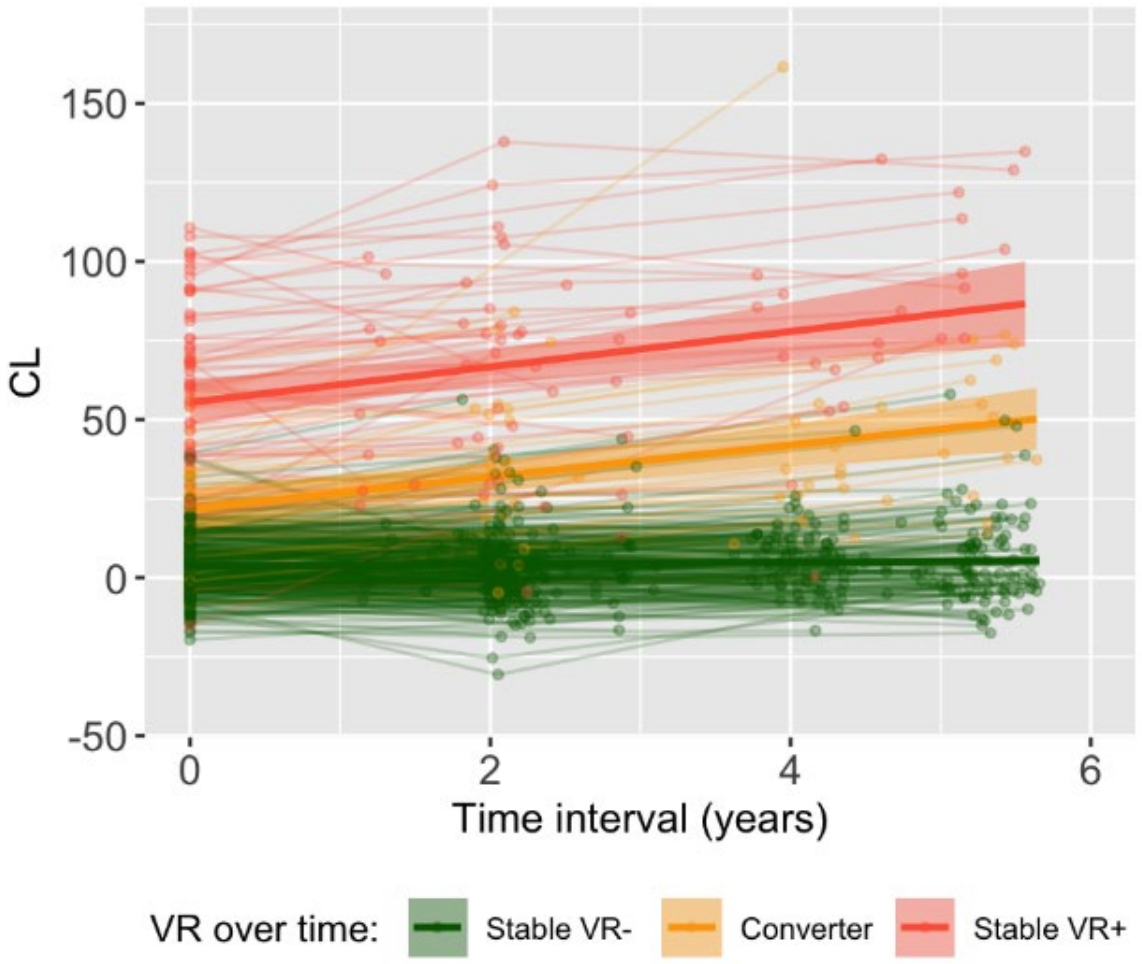
Discordance between visual reads and quantification around the grey zone



- Retrospective analysis of florbetaben image read study 16034 (n=461)
- Blue line is a sigmoidal curve modeling agreement in Amyloid negative subjects
- Red line is a sigmoidal curve modeling agreement in Amyloid positive patients
- Black line is the sum of the two sigmoidal curves

LMI unpublished data

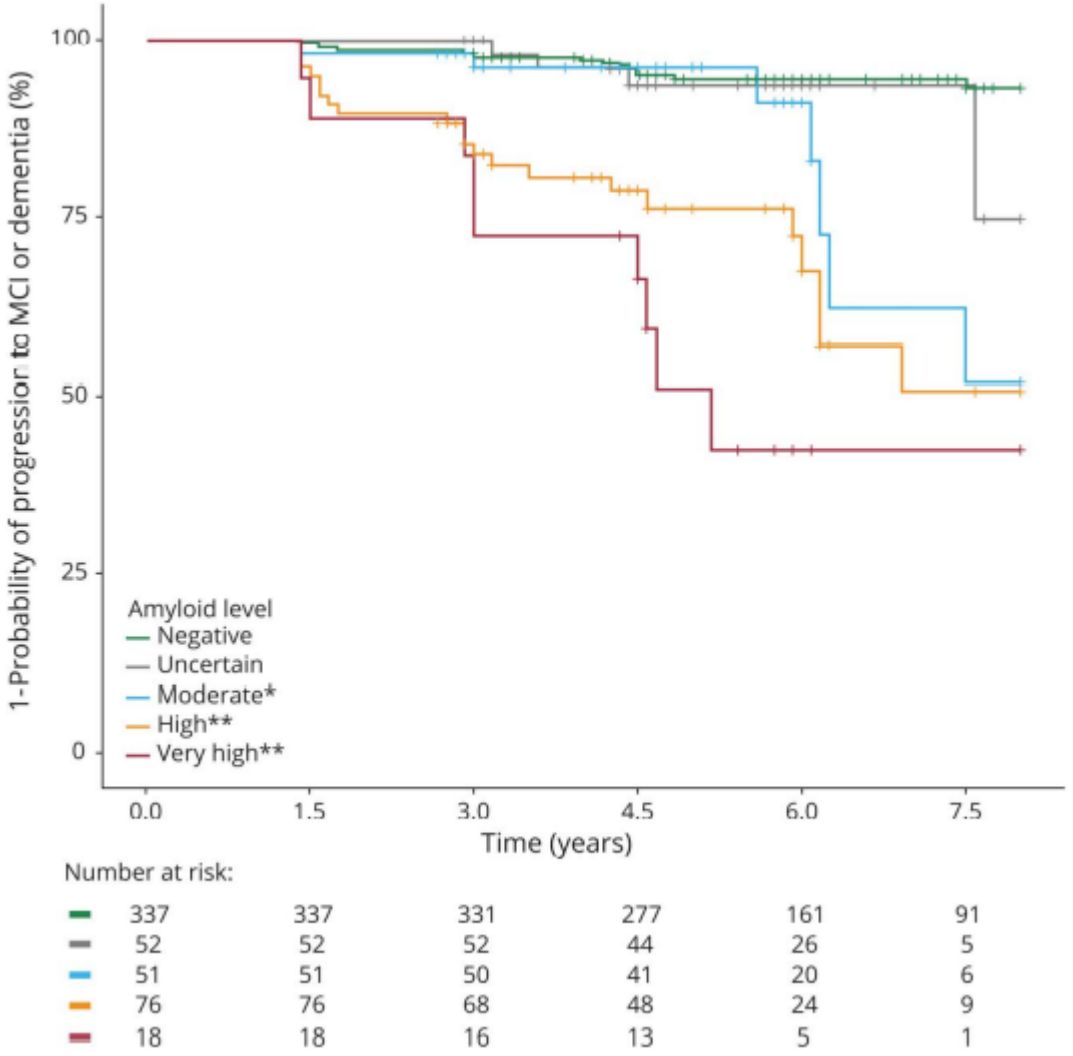
Centiloid window to help predict amyloid accumulation

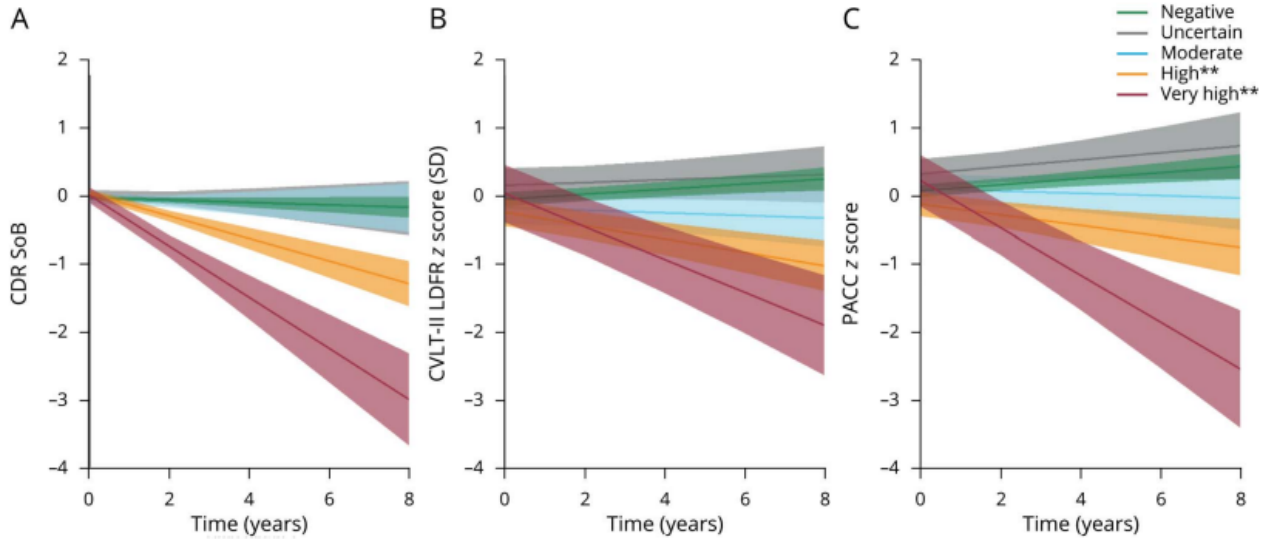


- Longitudinal trajectories of amyloid accumulation based on visual assessment
- Projected stable groups show <5 CL increase per year
- Annual increase in CL above 5 CL can be considered amyloid accumulation
- Centiloid window of approx. 12-50 CL units is predictive of those subjects where a significant rise in amyloid load might be expected

Unpublished data, Amypad Consortium

Association of β-Amyloid Level, Clinical Progression and Cognitive Change in Normal Older Individuals in AIBL, n=534





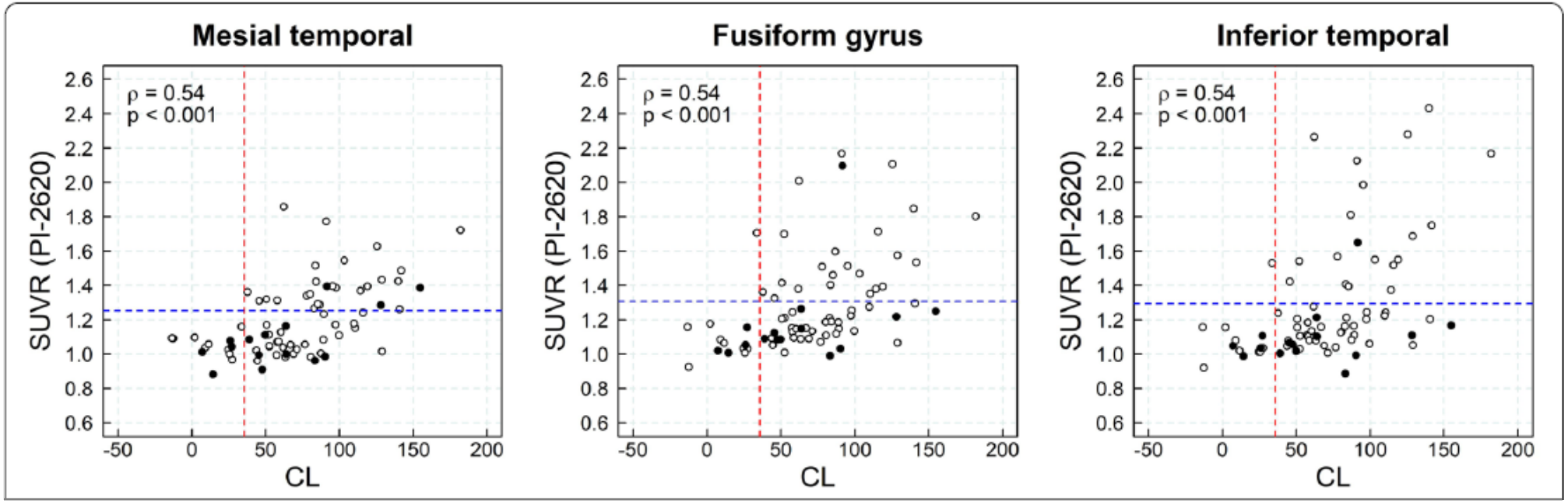
Cognitive trajectory measured by (A) Clinical Dementia Rating Sum of Boxes (CDR SoB), (B) California Verbal Learning Test II Long Delay Free Recall (CVLT-II LDFR), and (C) Preclinical AD Cognitive Composite (PACC). Shaded regions are 95% confidence interval. *$p < 0.05$ and ***$p < 0.001$ significantly different slope from the "negative" reference category. Decline is against baseline for each category.

Classification	Centiloid	HR (95% Int)	Signif.
Negative	<15		
Uncertain	15-25	1.6 (0.5-4.7)	
Moderate	26-50	3.2 (1.3-7.6)	p<0.05
High	51-100	7.0 (3.7-13.3)	p<0.001
Very High	>100	11.4 (5.1-25.8)	p<0.001

Van der Kall *et al,* Neurology 2021

High amyloid load is correlated with high Tau load

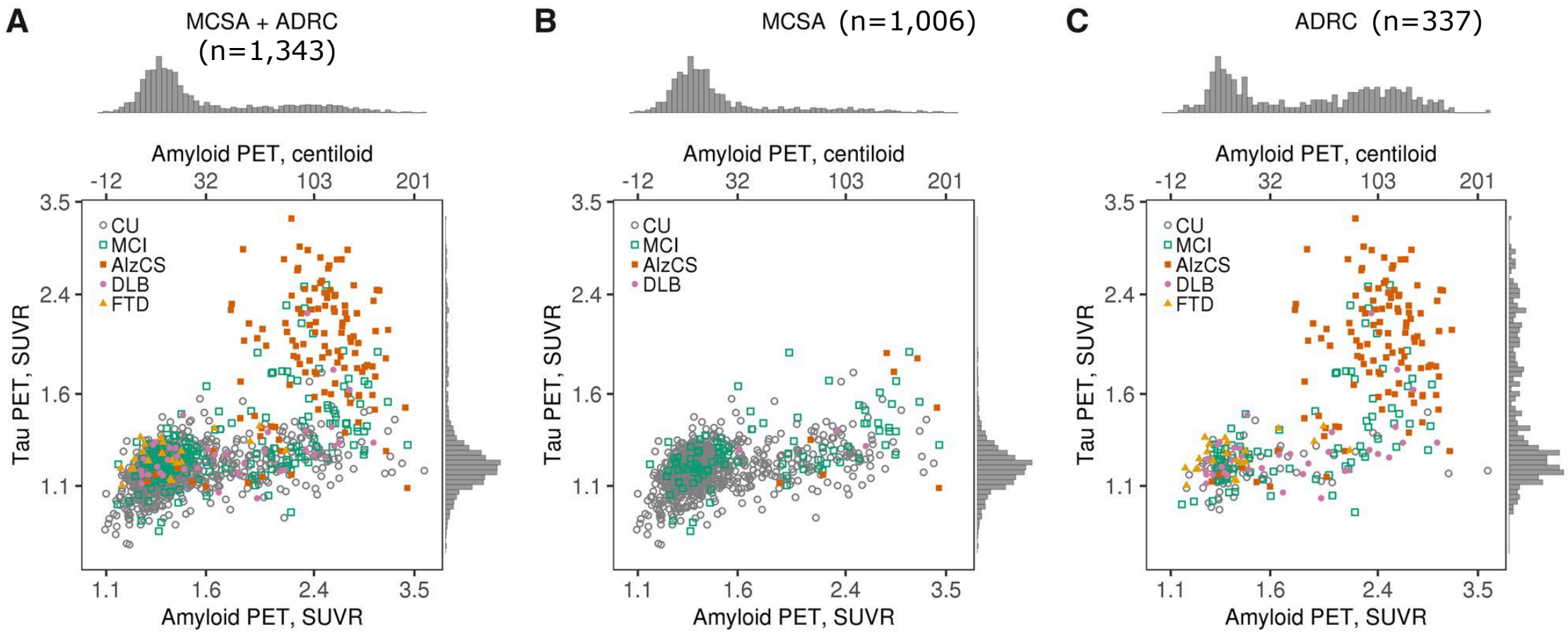
- Tau deposition is low in subjects with minor amyloid-beta deposits (CL<36)
- N= 78; 76 y/o; MMSE = 27; CDR-SB = 2.34; 97% MCI due to AD



- MissionAD study sponsored by Eisai. Amyloid-PET performed with Neuraceq, Tau-PET with PI-2620 at baseline
- Subjects with MCI due to AD or mild AD dementia including
  - MMSE $\geq$ 24; CDR global score of 0.5, CDR Memory Box score $\geq$ 0.5, and
  - impaired episodic memory confirmed by a list learning task

Bullich *et al. Alzheimer's Research & Therapy (2022) 14:105*

High amyloid load is correlated with high Tau load in a larger populational study (Mayo)

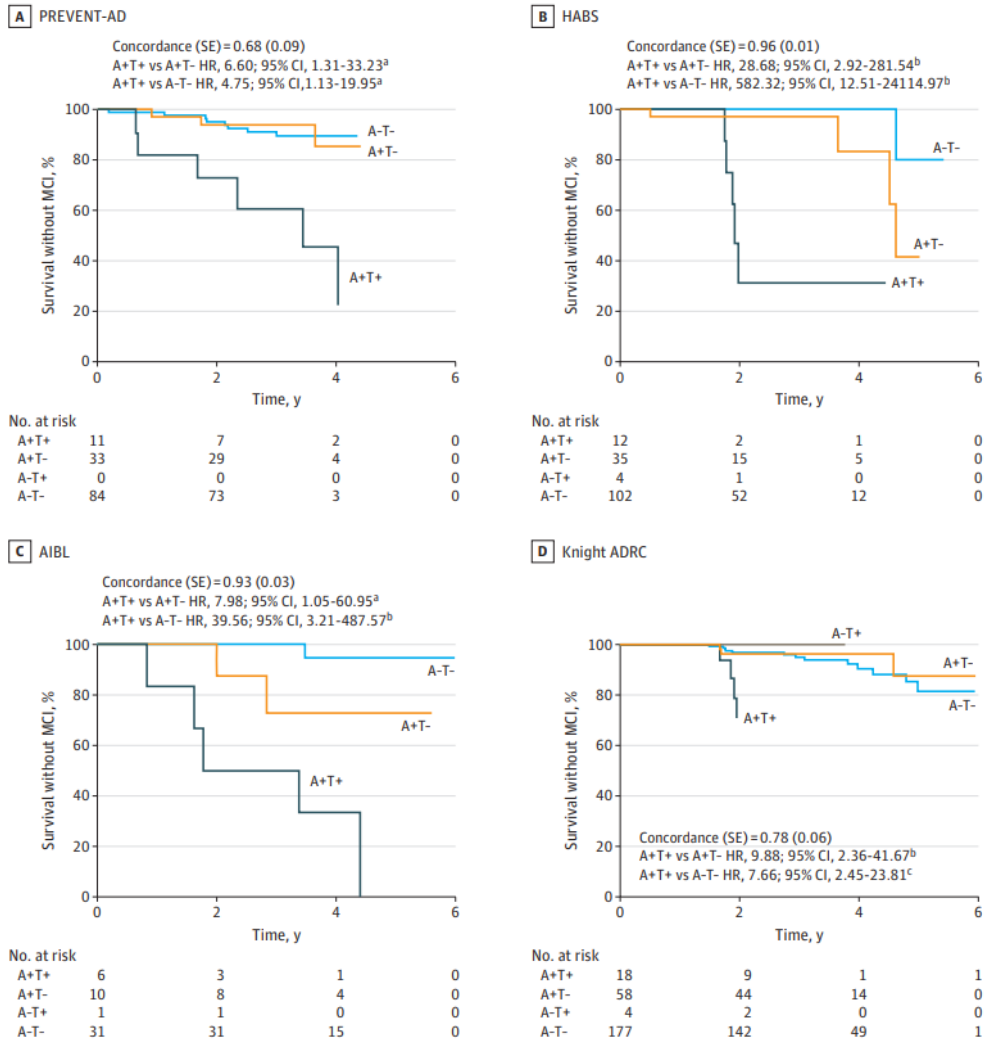


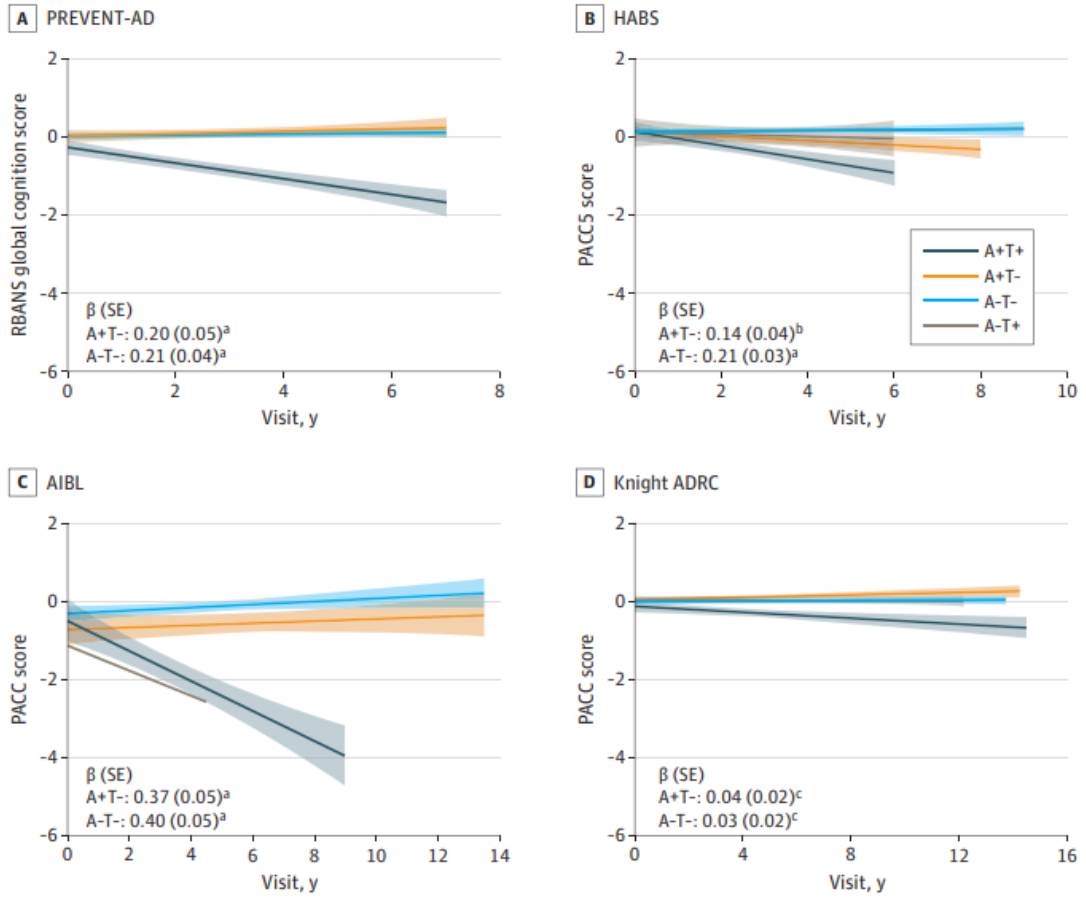
Amyloid-PET: ^{11}C-PiB
Tau-PET: flortaucipir

Jack et al. Brain 2019: 142; 3230–3242

Mayo Clinic Study of Aging (MCSA)
Mayo Alzheimer Disease Research Center (ADRC)

Amyloid and Tau positivity drives cognitive decline





Strikwerda-Brown, JAMA Neurol 2022

Summary

- Amyloid accumulation is a continuous process, extending over many years and is not a part of normal aging
- Dichotomous visual read of Amyloid-PET scans clearly identifies subjects either with no or substantial amyloid load
- Intermediate amyloid accumulation is not accurately assessed by visual reads
- Intermediate amyloid accumulation can be differentiated from normal by quantification and represents the earliest point on the Alzheimer Disease continuum
- The natural history and prognosis for patient changes depending on the amount of amyloid
- Identification and possible interventions at an earlier amyloid load are possible and important

Quantitative Amyloid & Tau PET Imaging in Clinical Trial Research

Mark Mintun, M.D.

Sr Vice President of Neuroscience Research and Development
President of Avid Radiopharmaceuticals

PRESENTER DISCLOSURE
Mark Mintun, MD

Employee: Avid Radiopharmaceuticals / Eli Lilly and Company
Stock/Shareholder: Eli Lilly and Company

Importance of Amyloid PET Quantitative Imaging for Assessment of Disease

Quantitation slightly outperformed readers in autopsy study

- Original autopsy study of amyloid plaques showed quantitation had slightly better accuracy than trained readers (Clark et al., 2012):

Visual Read (5 readers, 59 cases)	
Sensitivity median, mean	92%, 87%
Specificity median, mean	95%, 95%
Semiautomated SUVr (prespecified cutoff= 1.10)	
Sensitivity (N, CI)	97% (38 of 39, 85-100)
Specificity (N, CI)	100% (20 of 20, 80-100)
Accuracy (N, CI)	98% (58 of 59, 90-100)

Readers appear to perform better with access to quantitation

- Increased accuracy in visual readers vs autopsy when given access to quantitation (Pontecorvo et al., 2017)
  - Overall readers improved accuracy from 90.1% to 93.1% - a 30% reduction in errors
  - Quantitative information did not lower accuracy of high performing readers

Visual read inter-rater disagreement

- Studies report between-rater visual read disagreements for 18F amyloid PET: **9%** (22/252) (Paghera et al., 2020)

Preclinical population are particularly difficult to evaluate

- Only **50.1%** (663/1323) of preclinical Aβ+ participants (SUVr mean 1.33 (0.18)) were visually read as positive (Sperling et al., 2020).

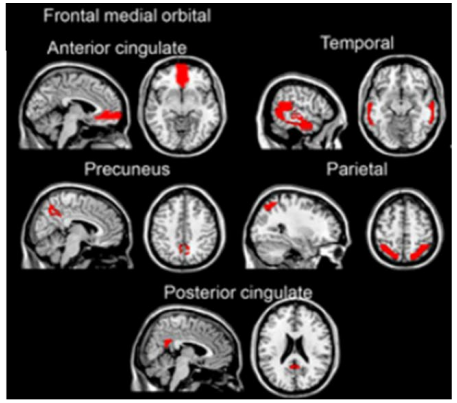
Quantitation of Amyloid Imaging

- The 100-point **Centiloid (CL) scale** (Klunk et al., 2015) allows standardization across different amyloid PET tracers standardized uptake value ratio (SUVr) (i.e. [^{18}]Flutemetamol, [^{18}]Florbetapir, [^{18}]Florbetaben, NAV4694, Pittsburgh Compound B).

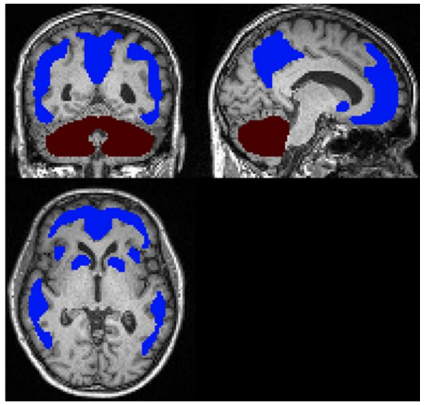
$$Centiloid = 100 * \frac{SUVr - Avg.YCN\ SUVr}{Avg.AD\ SUVr - Avg.YCN\ SUVr}$$

- Standardization method is supported by the Global Alzheimer's Association Interactive Network (GAAIN).

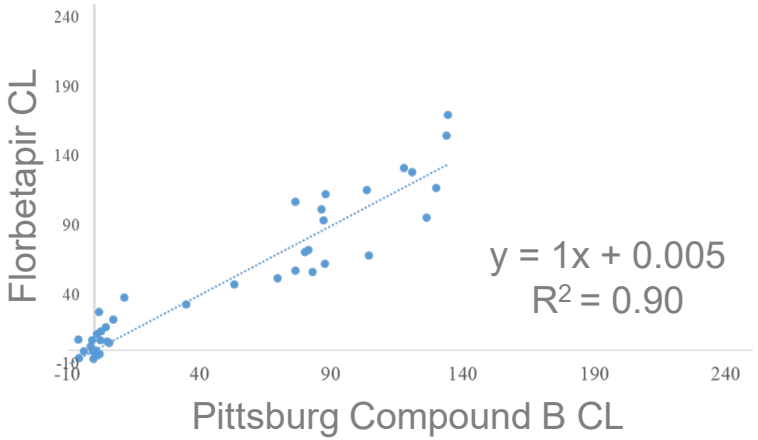
Florbetapir ROIs



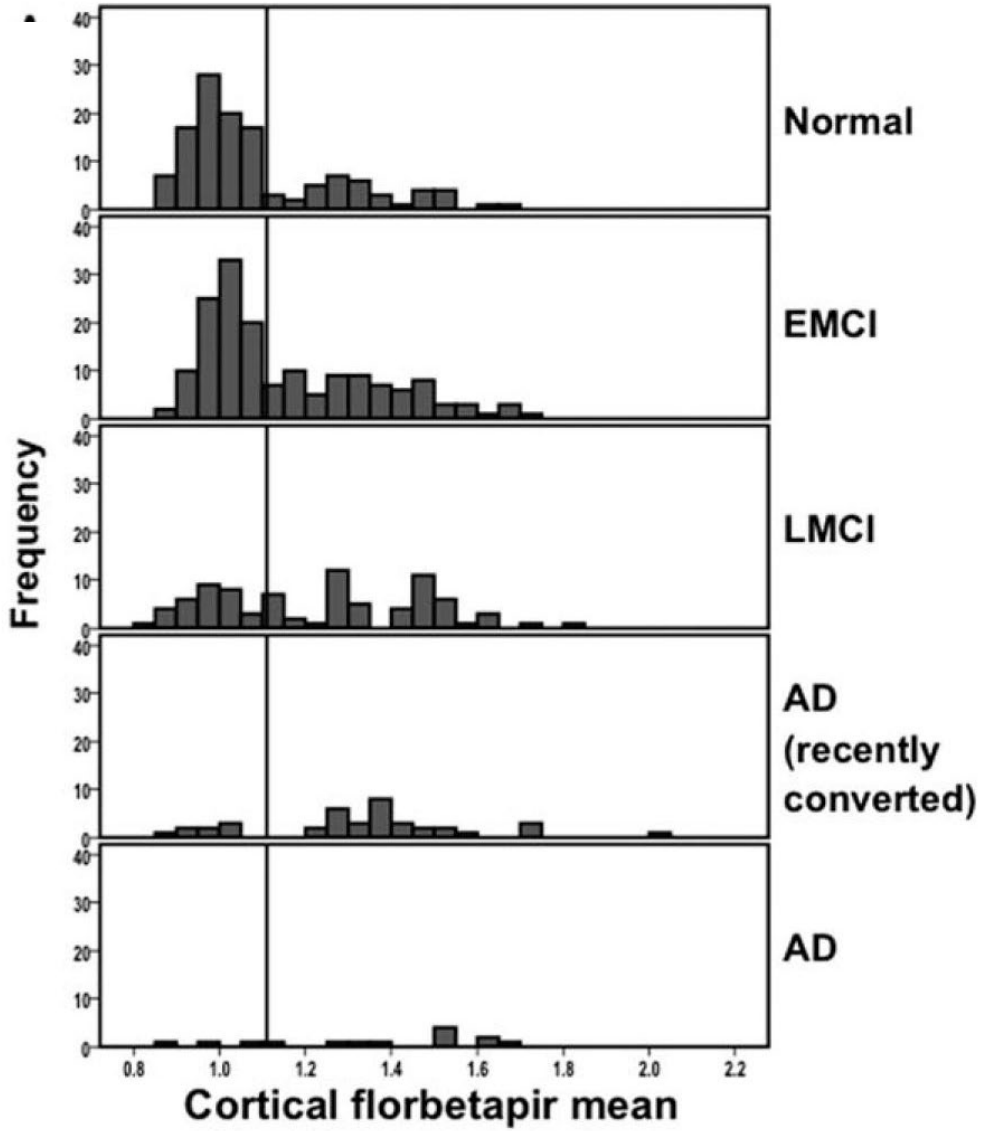
Pittsburg Compound B ROIs



Adapted from Navitsky et al., AAIC 2016

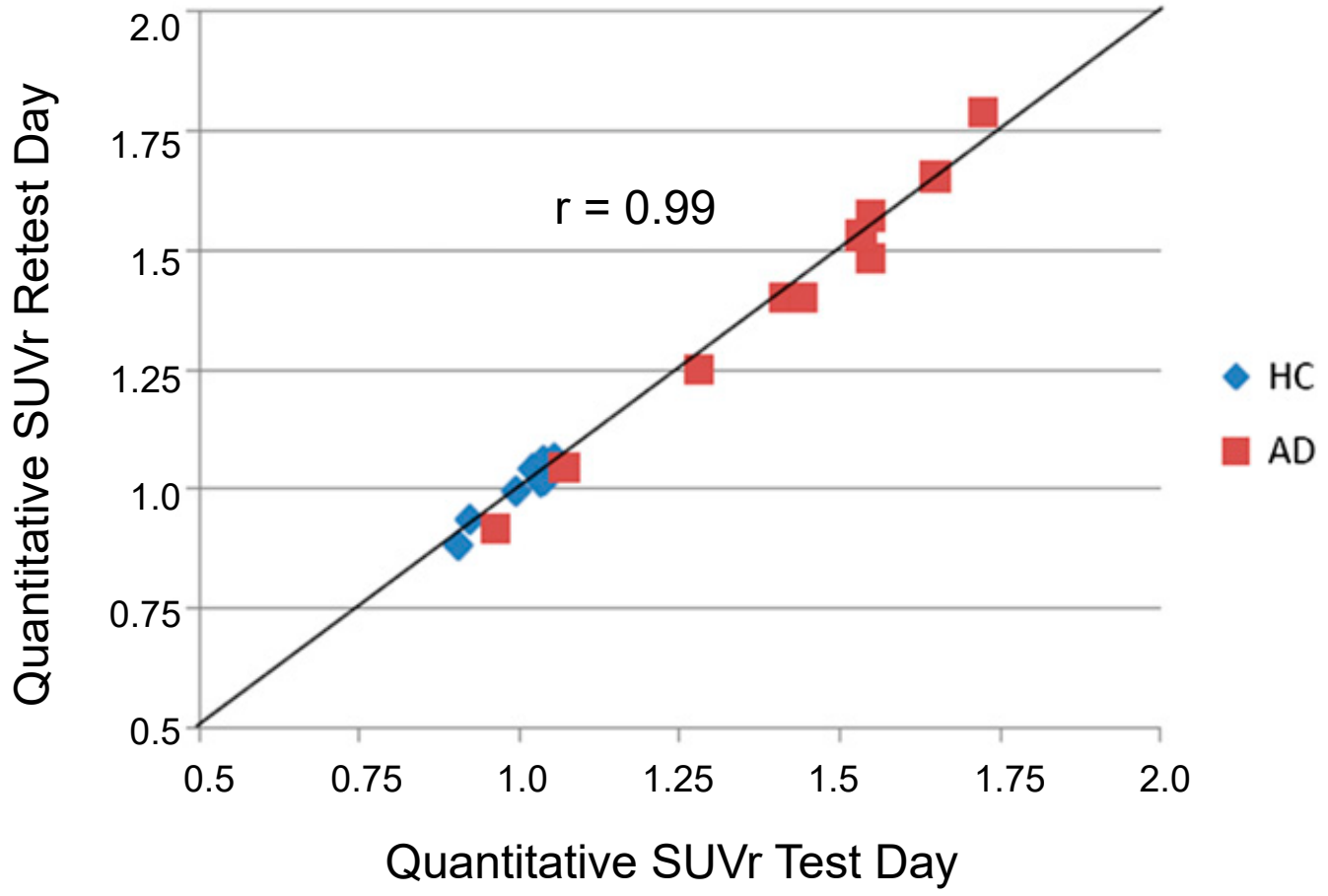


Distribution of Quantitative Amyloid PET Values in Various Populations



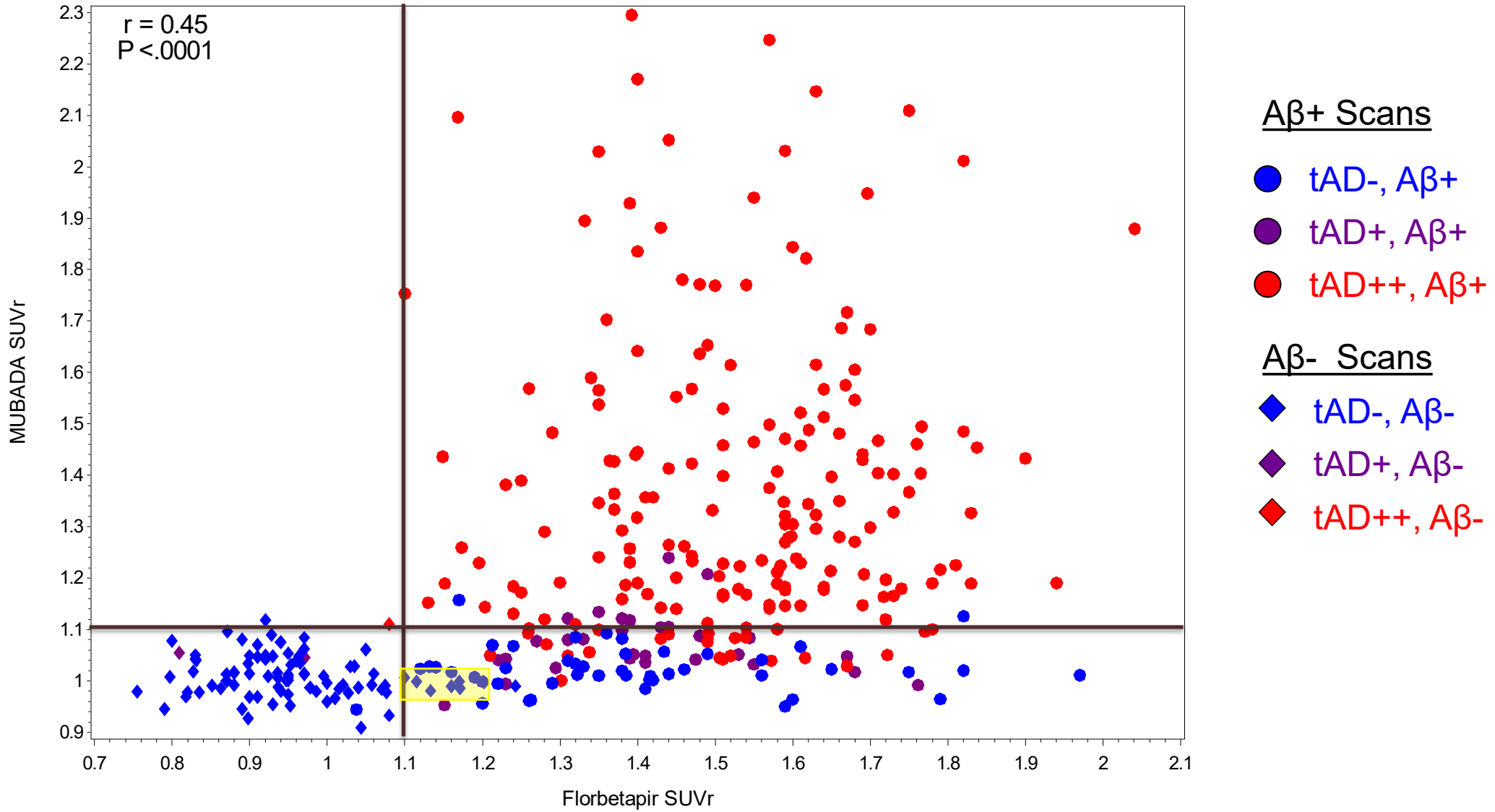
Adapted from Landau et al., 2012
EMCI=Early Mild Cognitive Impairment; LMCI=Late Mild Cognitive Impairment; AD= Alzheimer's Disease

Amyloid PET Imaging Reliability



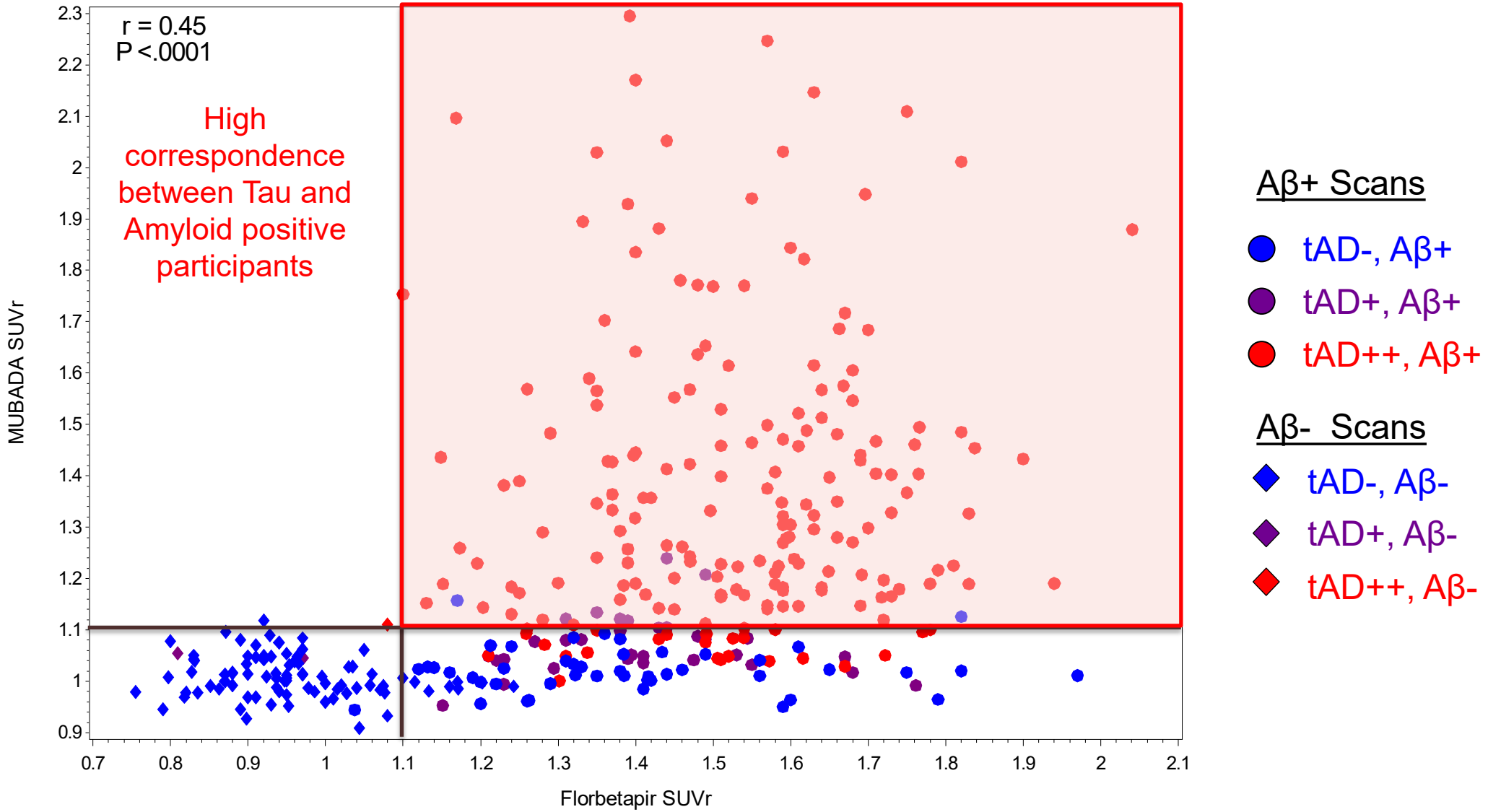
Data adapted from Joshi et al., 2012

Distribution of Florbetapir and Flortaucipir reads with respect to Florbetapir and Flortaucipir SUVr



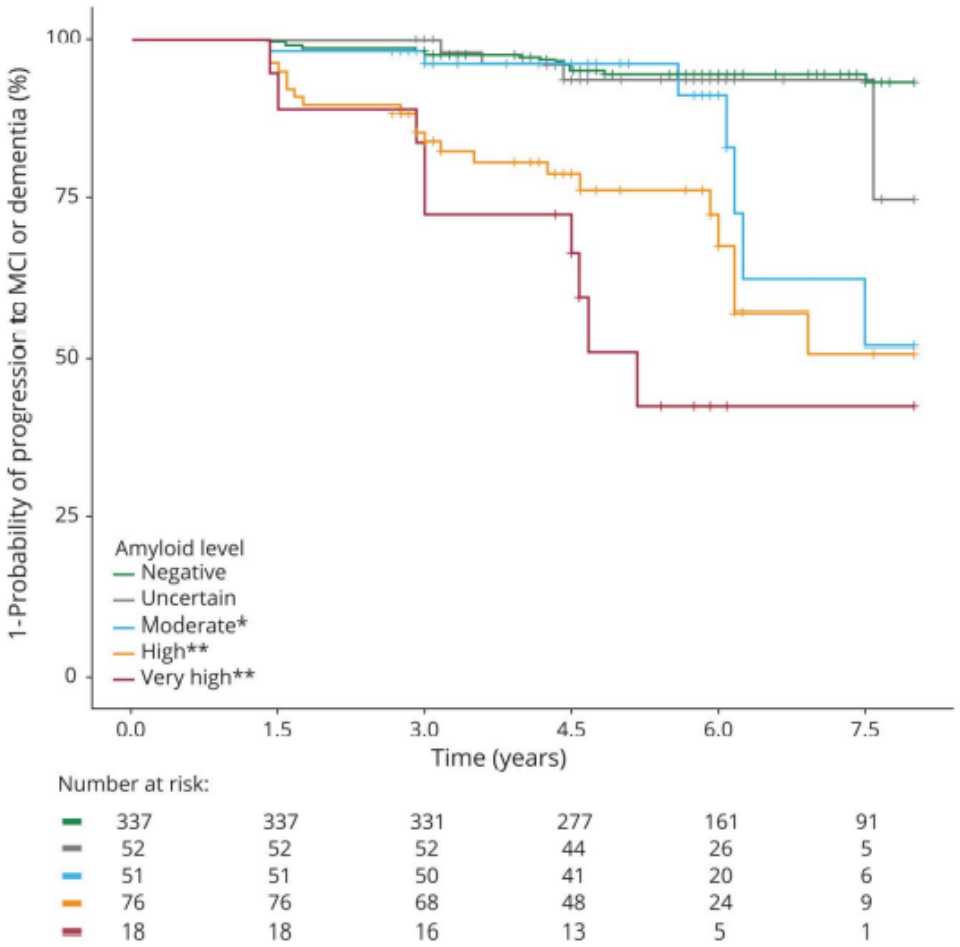
Data adapted from Pontecorvo, Winter Conference on Neuroplasticity, 2020
Cases from Pontecorvo et al., Brain 2017 and Lu et al., JAMA Neurol 2021

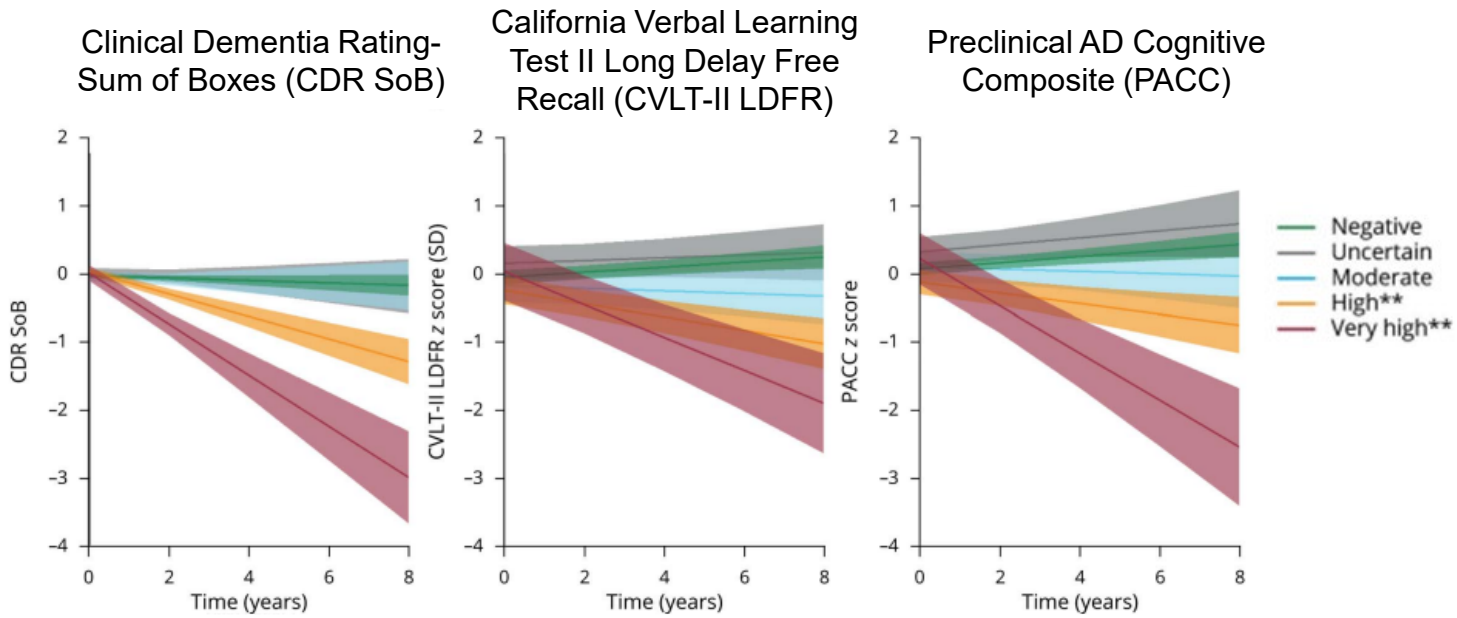
Distribution of Florbetapir and Flortaucipir reads with respect to Florbetapir and Flortaucipir SUVr



Data adapted from Pontecorvo, Winter Conference on Neuroplasticity, 2020
Cases from Pontecorvo et al., Brain 2017 and Lu et al., JAMA Neurol 2021

Association of β-Amyloid Level, Clinical Progression and Cognitive Change in Normal Older Individuals in AIBL, n=534





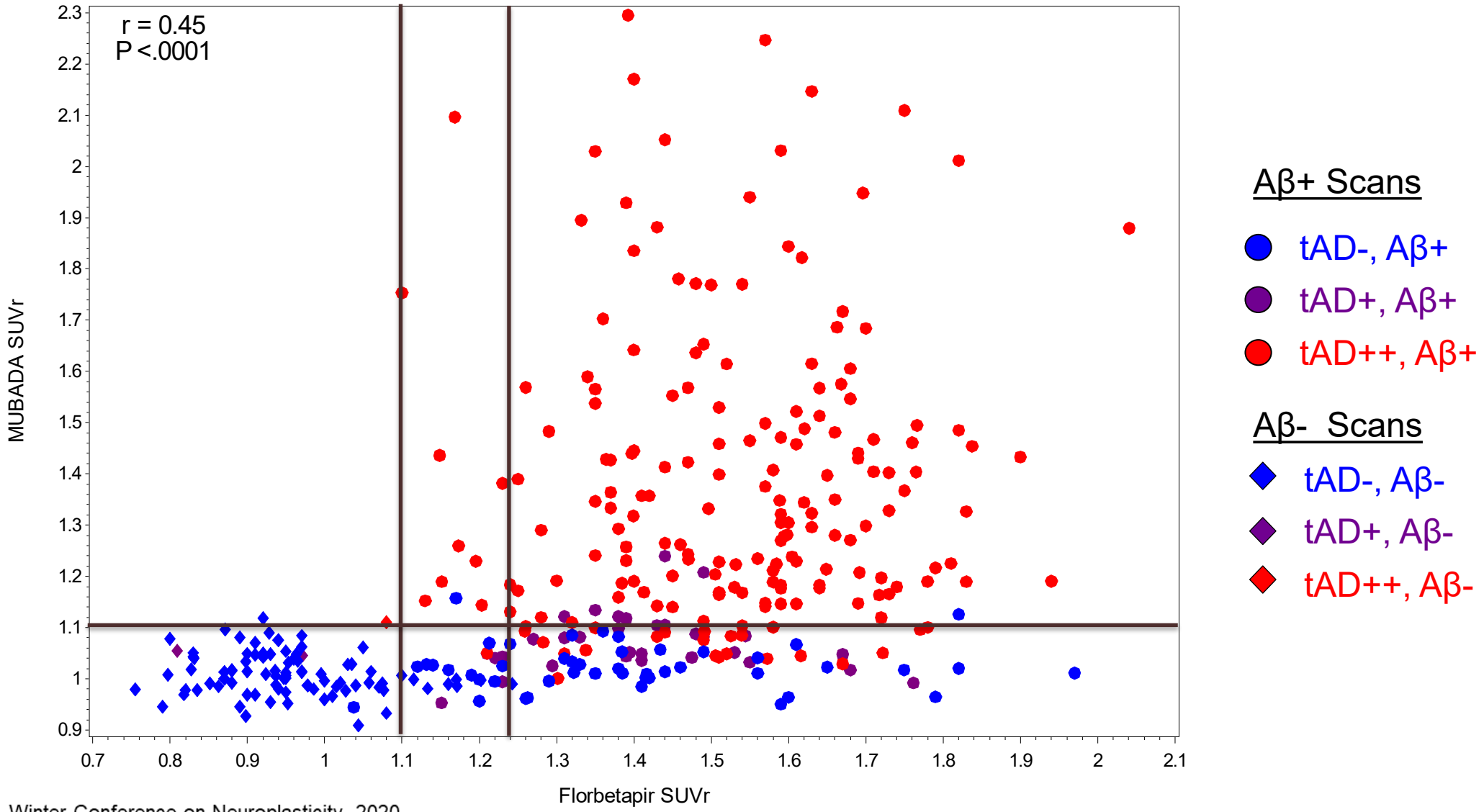
Classification	Centiloid	Hazard Ratio (95% Int)	p-value
Negative	<15		
Uncertain	15-25	1.6 (0.5-4.7)	
Moderate	26-50	3.2 (1.3-7.6)	p<0.05
High	51-100	7.0 (3.7-13.3)	p<0.001
Very High	>100	11.4 (5.1-25.8)	p<0.001

Shaded regions= 95% CI

***p<0.001, **p<0.01 , *p<0.05 significantly different slope from “negative” baseline.

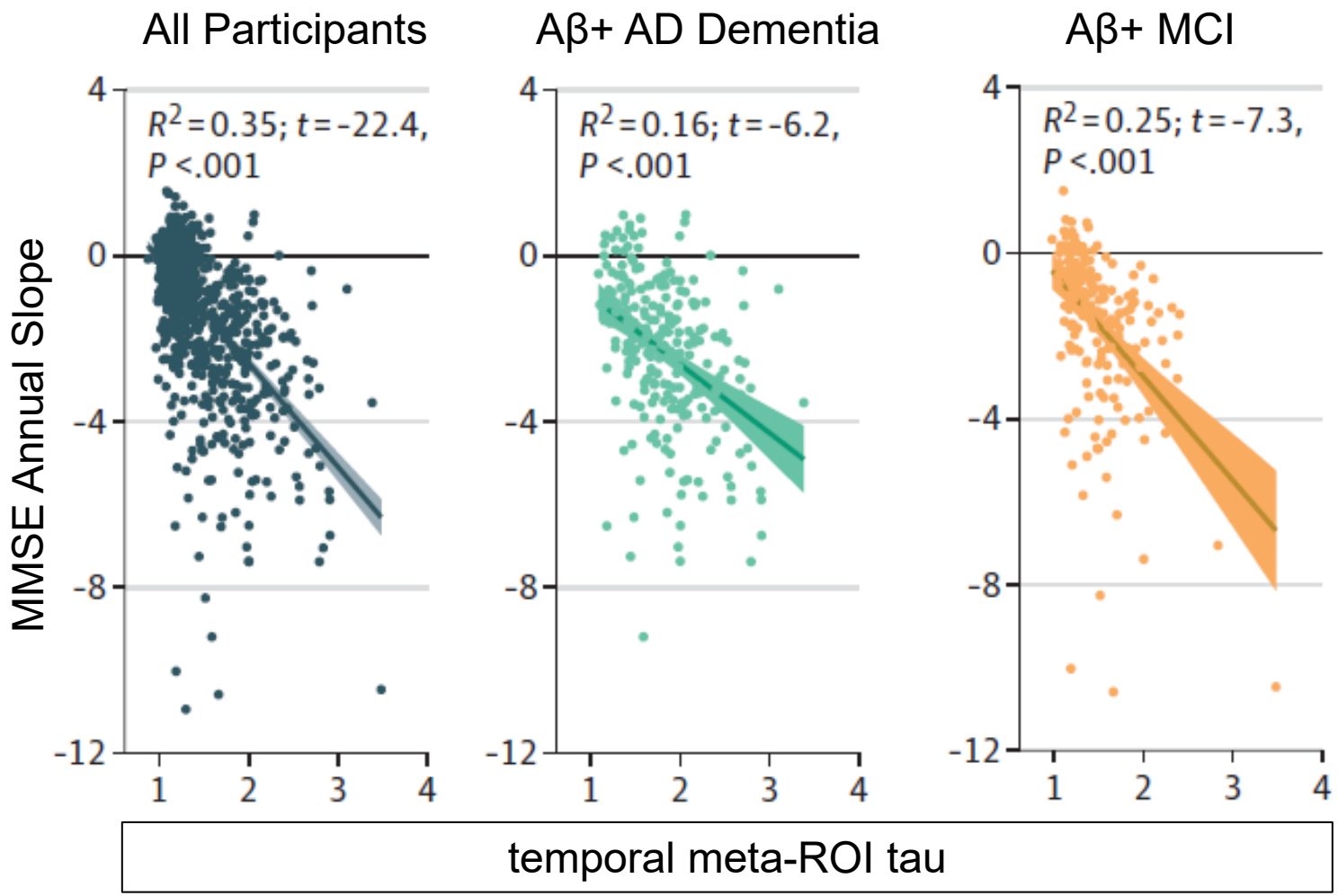
Adapted from Van der Kall et al., 2021

Distribution of Florbetapir and Flortaucipir reads with respect to Florbetapir and Flortaucipir SUVr



Data adapted from Pontecorvo, Winter Conference on Neuroplasticity, 2020
Cases from Pontecorvo et al., Brain 2017 and Lu et al., JAMA Neurol 2021

Relationship Between Tau at Baseline and Subsequent Cognitive Deterioration



Adapted from Ossenkoppele et al, JAMA Neurol, 2021.

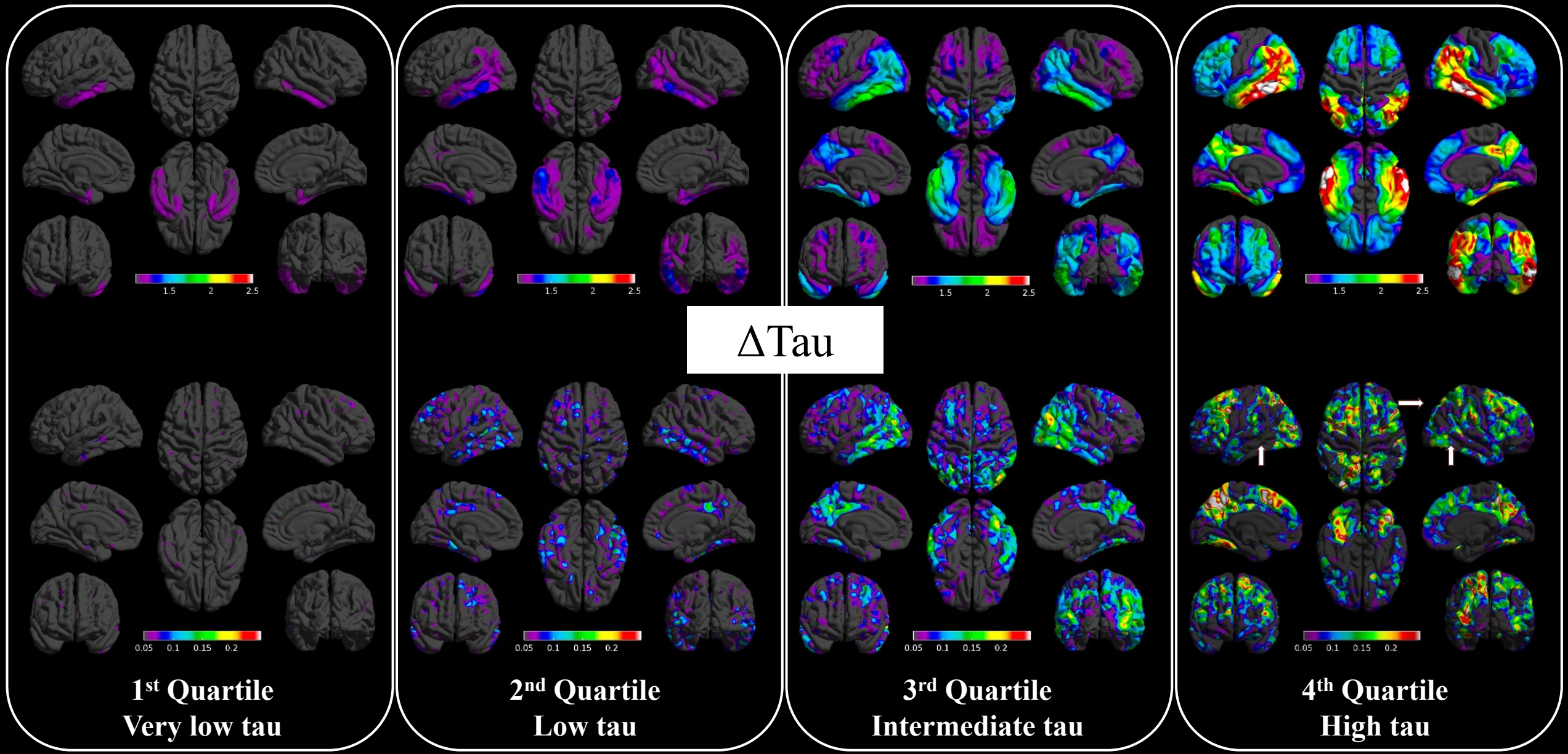
Is a Centiloid-like Approach for Tau Quantitation Possible?

- Amyloid burden appears well correlated and increases relatively consistently across all neocortical brain regions as the disease progresses, with the possible exception of the occipital lobe (LaPoint et al., 2022; Whittington et al., 2018).

- In contrast, Tau PET signal may be evident in different regions as disease progresses, may appear in heterogeneous and asymmetrical patterns, appears to decrease with advanced age (>75 years of age) in Aβ+ patients (Pontecorvo et al., 2017; Pontecorvo et al., 2019), and there may be tracer differences in off-target binding (Gogola et al., 2022; Smith et al., 2020).

- Consequently, different target regions and thresholds may be relevant depending on the goals/intended use of the scan for:
  - Diagnosis
  - Staging
  - Prognosis

Baseline Tau



Data from Pontecorvo et al., Brain 2019

A First Step Toward Harmonization of Tau PET Quantitation (Centaur – Ct)

- Neocortical target region mask derived from the intersection of regions showing elevation in AD patients across six putative tau tracers (Dore et al., 2021).
- Anchor points for each tracer based on mean of clinically normal Aβ- controls (0 Ct) and amyloid positive (>50 CL), visually tau positive, or cognitively impaired subjects <75 years of age (100Ct).
- SUVr mapped to anchor points for each tracer, for both a global composite and regional/staging VOI.
- Performance across tracers will be evaluated in head-to-head studies.

Key Points

- Amyloid imaging appears critical for the accurate prognosis and management of patients being evaluated for AD.
- Amyloid quantitative imaging has shown benefits over visual read, including no inter-rater disagreements, more accurate prognostic value for pre-clinical AD, and comparatively better consistency across time.
- Overcoming challenges in tau quantitative imaging is important for broad use of tau imaging for the prediction and evaluation of patient disease diagnosis, progression, and management.

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U.S. FOOD & DRUG ADMINISTRATION

Session IV: Quantitative Imaging in Staging of Disease, Prognosis, and Monitoring Disease Progression: Implications for Diagnostic Imaging Drug Labeling

FDA-CDER-CDRH, SNMMI, and MITA Workshop:

Quantitative PET Brain Amyloid

November 17, 2022

Session IV Speakers

Regulatory considerations

- **Sue-Jane Wang**, FDA – Evaluation of Qualitative and Quantitative Imaging: Implications for Diagnostic Imaging Drug Labeling

Industry and academic perspectives on brain amyloid PET

- **Val Lowe**, Mayo Clinic – Quantitative Amyloid Imaging: Mayo Clinic Aging Research
- **Gill Farrar**, GE Healthcare – Value of Quantitation in Diagnostic Imaging of Amyloid: Experience from European Labelling Activities
- **Andrew Stephens**, Life Molecular Imaging – Amyloid early detection / prognostic issues and how the Centiloid metric can help
- **Mark A. Mintun**, Avid Radiopharmaceuticals – Quantitative Amyloid & Tau PET Imaging in Clinical Trial Research

Patient perspective

- **Maria C. Carrillo**, Alzheimer's Association – Patient perspective

Session IV Panel Members

- **Tammie Benzinger**, Washington University
- **Gregory Klein**, Roche
- **Jonathan McConathy,** SNMMI
- **Mark Mintun,** Avid Radiopharmaceuticals
- **Stephen Salloway,** Brown University
- **Reisa Sperling,** Massachusetts General Hospital

Panel Question 1

- Should there be a standard quantitative definition for “amyloid positive” in staging of disease?

Panel Question 2

- It seems like quantitative amyloid PET will be most useful for detecting early amyloid accumulation (Sperling 50.1% of amyloid + preclinical participants were visual read negative) and for monitoring disease progression. Can the panelists comment on this?

Panel Question 3

- Current data suggest that the centiloid concordance with current visual reads is somewhere in the 25-35 centiloid range, yet quantitative analysis indicates that an amyloid load of greater than about 12 centiloid is predictive of future amyloid accumulation or disease prognosis. In a scenario with a hybrid visual/quantitative read, how should a reader/clinician be guided by the centiloid value? Should the aim be maximum concordance for the 24 centiloid cutoff that was used in histopath studies?

Panel Question 4

- Is there a consensus of age-related threshold of measuring amyloid PET accumulation?

Panel Question 5

- Do we need a sex and/or race specific centiloid?

Panel Question 6

- What do you see as the value of the approach used by European authorities, viz-a-viz, quantitative amyloid PET imaging supplementing the initial visual read?

Panel Question 7

- What level of precision would be appropriate for quantitative amyloid PET software?

Panel Question 8

- With enthusiastic research interests in developing diagnostic imaging drug for earlier stage neurological condition, please opine “what could serve as standard of reference for such diagnostic imaging drug development?”

Thank you for participation