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RESEARCH ARTICLE

Tau as a diagnostic instrument in clinical trials to predict amyloid in Alzheimer's disease

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Abstract

INTRODUCTION: Alzheimer's disease (AD) is characterized by the presence of both amyloid and tau pathology. In vivo diagnosis can be made with amyloid and tau positron emission tomography (PET) imaging. Emergent evidence supports that amyloid and tau accumulation are associated and that amyloid accumulation may precede that of tau. This report further investigates the relationship between amyloid and tau to assess whether elevated cortical tau can predict elevated amyloid in participants with early symptomatic AD.

METHODS: Florbetapir F18 and flortaucipir F18 uptake were evaluated from baseline PET scans collected in three multi-center studies with cognitively impaired participants, including A05 (N = 306; NCT02016560), TB (N = 310; TRAILBLAZER-ALZ; NCT03367403), and TB2 (N = 1165; TRAILBLAZER-ALZ 2; NCT04437511). Images were assessed using visual and quantitative approaches to establish amyloid (A+) and tau (T+) positivity, as well as a combination method (tauVQ) to establish T+. Associations between global amyloid and tau were evaluated with positive and negative predictive values (PPV, NPV) and likelihood ratios (LR+, LR−). Predictive values within subgroups according to ethnicity, race, cognitive score, age, and sex were also evaluated. The relationship between regional tau (four target and two reference regions were tested) and global amyloid was investigated in A05 participant scans using receiver-operating characteristic (ROC) curves.

RESULTS: PPV for amyloid positivity was ≥93% for all three trials using various A+ and T+ definitions, including visual, quantitative, and combination methods. Population characteristics did not have an impact on A+ predictability. Regional analyses (early tau ($E\tau$) volume of interest (VOI), temporal, parietal, frontal) revealed significant area under the ROC curve in $E\tau$ VOI compared to frontal region, regardless of reference region and consistent among visual and quantitative A+ definitions ($p < 0.001$).

DISCUSSION: These findings suggest that a positive tau PET scan is associated (≥93%) with amyloid positivity in individuals with early symptomatic AD, with the potential benefits of reducing clinical trial and health care expenses, radiation exposure, and participant time.

KEYWORDS
Alzheimer's disease, amyloid, correlation, diagnosis, imaging, prediction, tau

Highlights

- Positron emission tomography (PET) evaluates candidates for Alzheimer's disease (AD) research. A positive tau PET scan is associated (≥93%) with amyloid positivity.
- A positive amyloid PET is not necessarily associated with tau positivity.
- Tau PET could be the sole diagnostic tool to confirm candidates for AD trials.

1 | BACKGROUND

Amyloid plaques (extracellular, insoluble aggregations of amyloid beta [Aβ] peptides) and neurofibrillary tangles (NFTs; hyperphosphorylated, misfolded tau aggregates) are hallmark Alzheimer's disease (AD) proteinopathies that are considered essential for the neuropathologic diagnosis of AD.[1] Abnormal levels of biomarkers measuring Aβ and NFTs classify AD as a unique neurodegenerative disease that is biologically defined as such by the 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework.[2] Similarly, the International Working Group[3] defines the diagnosis of AD as clinical–biological, requiring the presence of clinical phenotype in addition to amyloid and tau positivity.

Accumulation of Aβ peptide in the brain parenchyma represents the earliest evidence of AD, as suggested by the amyloid-cascade hypothesis[4,5] and may cause downstream pathologic changes including tauopathy,[2] such that amyloidosis triggers the spread of tau beyond the medial temporal lobe and contributes to tau-mediated neurodegeneration. Rarely, tau pathology can also be driven independent of Aβ accumulation,[6] indicating both amyloid-independent and amyloid-facilitated tauopathies.

Although various types of biomarkers can be used to determine amyloid and tau positivity,[2] positron emission tomography (PET) constitutes a reference tool to diagnose both amyloid and tau pathologies in research settings. Florbetapir F18 (AMYVID) is a US Food and Drug Administration (FDA)–approved diagnostic radioactive agent used to estimate Aβ neuritic plaque density with PET imaging. A negative scan indicates sparse to no neuritic plaques, whereas a positive scan indicates moderate to frequent amyloid neuritic plaques.[7] Flortaucipir F18 (TAUVID) has also been approved by the FDA and estimates the density and distribution of aggregated tau NFTs.[8] A positive flortaucipir scan shows increased neocortical activity in the posterolateral temporal, occipital, or parietal/precuneus regions, with or without frontal activity.[8]

Growing evidence suggests that tau PET can serve as a single diagnostic test[9,10] to confirm both amyloid and tau pathologies. We reported previously[11] that the majority of participants with amyloid negative (A–) florbetapir scans also had low flortaucipir signal, suggesting that elevated cortical tau uptake can predict elevated amyloid. However, having an amyloid positive florbetapir scan did not necessarily indicate an elevated tau burden. Similar observations were reported using different amyloid and tau positivity definitions, and PET tracers.[12–14] A comprehensive analysis based on various amyloid and tau positivity definitions is still, to our knowledge, an important gap in the literature.

The objective of the analysis described herein was to evaluate tau and amyloid PET data using a comprehensive analysis approach from scans collected in several multi-center trials to further elucidate the relationship between amyloid and tau pathologic levels. Specifically, we evaluated the degree to which a positive flortaucipir scan predicts amyloid pathology as measured using florbetapir in cognitively impaired participants. Baseline amyloid and tau PET characteristics were determined from images acquired in one multi-center observational trial of flortaucipir (A05, NCT02016560) and two multi-center interventional trials of donanemab (TRAILBLAZER-ALZ [TB], NCT03367403 and TRAILBLAZER-ALZ 2 [TB2], NCT04437511).[15,16] The amyloid–tau PET relationship was evaluated using several definitions (visual and quantitative) of amyloid and tau positivity.

1.1 | Design and participant population

The observational study 18F-AV-1451-A05 (NCT02016560) was an open label, phase 2/3 (A05E/A05C) multicenter study, evaluating the safety and imaging characteristics of flortaucipir in cognitively healthy volunteers, participants with mild cognitive impairment (MCI), and participants with possible or probable AD dementia. Screening characteristics were published previously.[11,17,18] Participants with either

AD or MCI from both the A05 (E/C) studies were combined for a total of 306 participants ($N = 112$ with AD, $N = 194$ with MCI). All participants who qualified for the A05 studies were scheduled to undergo both amyloid and tau PET imaging, regardless of the outcome of either scan. The order of amyloid and tau PET scans varied and PET imaging sessions were performed 48 hours to 60 days apart. Only participants with both flortaucipir and florbetapir baseline PET scans were included in the current analyses.

TRAILBLAZER-ALZ (TB, NCT03367403) and TRAILBLAZER-ALZ 2 (TB2, NCT04437511) were multi-center, randomized, double-blind, placebo-controlled phase 2 and phase 3 trials, respectively, that assessed the safety and efficacy of donanemab in participants with early symptomatic AD.[16,19] In TB, only participants with low/medium-tau (described below) assessed by flortaucipir PET subsequently completed a florbetapir scan. Time between flortaucipir and florbetapir scans ranged from 2 to 287 days, with a 22-day median. From the TB trial, a total of $N = 310$ participant scans were assessed in this report.

The TB2 screening procedure did not prescribe a scan order (florbetapir first or flortaucipir first); thus we included all participants with "independently" performed scans in which the eligibility decision based on the first scan was issued later than the second scan was conducted. Time between flortaucipir and florbetapir scans ranged from 0 to 38 days, with a 2-day median, and time between florbetapir and flortaucipir scans similarly ranged from 0 to 40 days, with a 2-day median. From the TB2 trial, a total of $N = 1165$ met criteria for analysis in this report.

To summarize, we analyzed three data sets with cognitively impaired participants: two data sets (A05 and TB2) with unrestricted amyloid and tau pathologies and one data set (TB) where the amyloid scan was conducted only for the low/medium-tau population. All flortaucipir and florbetapir scans were reviewed and processed at a centralized PET imaging facility. Images were corrected for participant motion and spatially normalized to a brain atlas space using previously described florbetapir[20] and flortaucipir image processing procedures. In addition, flortaucipir images were corrected for the difference between tracer injection and acquisition times.[17]

Participants provided informed consent before starting study procedures. Studies were conducted in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

1.2 | Florbetapir

At each planned scan visit, A05 participants received a single intravenous (IV) bolus injection target dose of 370 MBq (10 mCi) of florbetapir followed by a saline flush. Approximately 50 minutes following injection, a continuous 10-minute brain scan (two frames of 5-minute duration) began. TB and TB2 trial participants also received a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir followed by a saline flush and underwent a 20-minute scan (four frames x 5 minutes) started ≈50 minutes post injection.

Florbetapir images were categorized as amyloid negative (A−) or amyloid positive (A+) using previously established visual[21] and quantitative[20] methods and as described in detail in S1. For quantitative assessment, a composite standardized uptake value ratio (SUVR) with whole cerebellum as a reference region was calculated[20] and converted to centiloid (CL) units.[22] A previously established cut-off of 24.1 CL[22] was used to quantitatively determine amyloid positivity.

RESEARCH IN CONTEXT

1. **Systematic review**: Literature was reviewed within traditional databases (PubMed) using the listed keywords. Several reports indicated that tau deposition is closely related to Alzheimer's disease (AD), despite amyloid positron emission tomography (PET) reported as the more common screening diagnostic. Reports have suggested correlations between amyloid and tau but lacked data-driven support that tau PET could be utilized as a sole screening diagnostic for AD pathology.
2. **Interpretation**: Our findings identify that a positive tau PET scan is indicative of a positive amyloid PET scan in the strong majority (≥93%) of individuals with AD with mild cognitive impairment (MCI), or mild dementia. These results suggest that both tau and amyloid positivity can be confirmed with a single tau PET scan.
3. **Future directions**: Future research is needed to verify that tau PET can confirm amyloid status using different populations and other amyloid and tau PET tracers.

1.3 | Flortaucipir

At each planned scan visit, A05 participants received a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir followed by a saline flush. At ≈80 minutes post injection, a continuous 20-minute brain scan (four frames of 5-minute duration) was obtained. In TB and TB2 trials participants also received a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir followed by a saline flush and a dynamic 30-minute brain scan (six frames x 5 minutes) was acquired ≈75 minutes post injection.

Tau positive (T+) and tau negative (T−) status was evaluated using visual,[23] quantitative,[23] and a combination of visual and quantitative[16,24] definitions (tauVQ) and as described in detail in the supplement (S1). For quantitative assessment, we used an AD-signature weighted neocortical tau SUVR[25] with respect to a reference signal intensity in subject-specific white matter (PERSI).[26] Cut-points 1.11[23] and 1.10[16,24] were used in quantitative and

tauVQ T+/T− categorizations, respectively. Flortaucipir scans were also visually interpreted[23] as inconsistent with AD (negative AD tau pattern, τAD−) or consistent with AD (moderate τAD+ or advanced τAD++ tau pattern). Detailed description of the visual read is in S1.

In addition, exploratory analyses of regional tau PET SUVR in temporal composite volume of interest (early tau [Eτ] VOI[27]), lateral temporal, parietal, and frontal regions were performed in the A05 data set using both PERSI and cerebellum gray as reference regions.[11]

1.4 | Statistical analyses

All analyses were conducted independently for each individual trial data set. The ability to predict a pathologic amyloid level based on a positive tau PET scan was examined using positive predictive values (PPVs) to determine the portion of T+ participants with a positive florbetapir output (identified using either visual read assessment or quantitative threshold (CL ≥24.1). The negative predictive value (NPV) was also calculated based on a portion of T− participants with a negative florbetapir scan A−. The positive and negative likelihood ratio (LR+/LR−) were also included and defined in S1.

Because both quantitative and visual assessments for florbetapir were available in the A05 data set, the PPVs for amyloid positivity were calculated for both visual and quantitative (CL ≥ 24.1) amyloid positivity rules. In the TB and TB2, florbetapir visual assessments were not conducted, thus PPV for only quantitative amyloid positivity rules are available.

The corresponding 95% confidence intervals (CIs) for PPV were calculated using the Wilson method. Analyses for the subgroups with different baseline characteristics were performed with the pooled study data.

For regional tau PET SUVRs available in the A05 trial, the diagnostic performance of accurately classifying amyloid positivity was examined through the area under the curve of the ROC (AUROC).[28] PPVs and NPVs were not calculated within those regional analyses because regional tau PET thresholds were not previously established.

The data analysis for this report was performed using SAS System for Windows, version 9.4 (SAS Institute Inc).

1.5 | Characteristics

Baseline characteristics for participants included in these analyses are provided in Table 1. Parameters collected at screening visits in TB and TB2 trials and population characteristics for the A05 cohort are included. The average amyloid level in A05, TB, and TB2 data sets reflects the tau status in populations that underwent the florbetapir scan. Regardless of tau (≈52% of A05 and TB2 were τAD−), all A05 and TB2 participants underwent florbetapir scans and reported mean amyloid levels of ≈52 CL. In the TB trial, only low/medium-tau (tau positive according to tauVQ) participants with τAD+ or τAD++ patterns underwent florbetapir scan and mean amyloid was 99.2 CL. Mean AD-signature neocortical tau SUVR values were similar in A05 (1.164) and TB2 (1.161) and slightly higher in TB (1.213). Average Mini-Mental State Examination (MMSE) scores followed the same trend and were similar in A05 (25.4) and TB2 (24.5) and slightly lower in TB (23.7).

1.6 | Association between amyloid and tau pathologic levels

Table 2 summarizes the available PPV and NPV assessments for A05, TB, and TB2 data sets. We assessed PPV for all four T+ rules when A+ was defined quantitatively while only A05 data allowed us to examine PPVs when A+ was defined visually. We assessed NPVs in A05 and TB2 data sets. NPV values for the TB population were not reported due to 0% tau negativity (according to tauVQ) in cohort.

PPV results varied between 92.7% and 98.0% irrespective of the population, PET acquisition protocol, or A+ and T+ definitions (Table 2), suggesting that the majority (≥92.7%) of cognitively impaired participants with a positive flortaucipir scan would have a positive florbetapir scan. However, lack of a pathologic tau burden did not necessarily predict the absence of elevated amyloid. NPV results for A05 and TB2 data sets with independently performed florbetapir and flortaucipir scans varied between 54.6% and 77.3% (Table 2). In A05 data, NPV for the visual A+ assessment is consistently better (represented by a higher %) than for the quantitative A+ assessment for all four T+ criteria considered, and NPVs for visual or composite tauVQ T+ rules are larger than for quantitative assessment with tauSUVR. Overall, the highest NPV (77.3%) and sensitivity (80.8%) were achieved in A05 analysis where visual rules for both A+ and T+ were applied. NPVs for quantitative A+ rule in A05 and TB2 are similar to each other and confirm the robustness of our estimates. Sample binary confusion matrices were added (S2) to illustrate the aforementioned observations.

LR+ ratios calculated from A05 results showed a particularly high probability of A+, given that LR+ of >10 is indicative of a large increase in post-test probability of A+.[29] Similarly, a data-driven association between quantitative amyloid and tau measures (supplemented by a locally weighted scatterplot smoothing [LOWESS]) (Figure 1) confirms that an overwhelming majority of participants with tauSUVR ≥1.11 are amyloid positive (CL ≥24.1). Moreover, Figure 1 suggests that tauSUVR ≥1.11 is rarely seen with amyloid below ≈50 CL. The LOWESS curve showed minimal change in amyloid level with an increasing tauSUVR after reaching the 1.11 threshold. Only scans with available quantitative outputs (CL and tauSUVR) were included in these scatterplots.

In A05 and TB2 data sets with the whole spectrum of amyloid and tau PET results available, we estimated PPV as a function of the tauSUVR threshold (Figure 2B, D). Approximately 60% to 65% (minimal tauSUVR threshold) of symptomatic participants were amyloid positive according to either visual (A05) or quantitative (A05 and TB2) A+ criterion. As neocortical tau levels increase, an average greater prevalence of amyloid positivity is increased as well. For both visual and quantitative amyloid positivity criteria, the prevalence reaches >95% at tauSUVR ≈1.1 and plateaus. For comparison, we generated the opposite graph showing a prevalence of symptomatic T+

TABLE 1 Baseline characteristics for participants underwent both florbetapir and flortaucipir scans in three trials and included in current analyses.

	A05	TB	TB2
N	306	310	1165
Age, mean (SD)	72.4 (9.5)	75.9 (5.6)	72.3 (6.4)
Females, N (%)	150 (49.0)	164 (52.9)	609 (52.3)
MMSE, mean (SD)	25.4 (3.1)	23.7 (3.2)	24.5 (2.6)
Race			
White	288	294	1076
Black or African American	12	9	50
American Indian or Alaska Native	1	2	3
Asian	3	3	26
Other[a]	2	2	3
Ethnicity			
Not Hispanic or Latino	293	298	867
Hispanic or Latino	13	12	284
Amyloid level			
Centiloids, mean (SD)	52.0 (53.1)	99.2 (40.4)	51.7 (56.0)
<24.1 (A-), *N*	114	11	499
≥24.1 (A+), *N*	192	299	666
Negative by visual read, *N*	124	n/a	n/a
Positive by visual read, *N*	182	n/a	n/a
Tau level			
Neocortical SUVR, mean (SD)	1.164 (0.295)	1.213 (0.119)	1.161 (0.257)
<1.11 (T-), *N*	198	62	518
≥1.11 (T+), *N*	98	245	352
τAD− by visual read, *N* (%)	154 (50.3)	0 (0)	630 (54.1)
τAD+ by visual read, *N* (%)	21 (6.9)	17 (5.5)	95 (8.2)
τAD++ by visual read, *N* (%)	131 (42.8)	293 (94.5)	440 (37.8)

Abbreviations: A05, 18F-AV-1451-A05 (NCT02016560); A+ (A−), abnormal (not abnormal) amyloid level as measured using florbetapir PET; CL, Centiloid; MMSE, Mini-Mental State Examination; N, number of participants; T+ (T−), abnormal (not abnormal) tau level as measured using flortaucipir PET; TB, TRAILBLAZER-ALZ (NCT03367403); TB2, TRAILBLAZER-ALZ 2 (NCT04437511); SD, standard deviation; SUVR, standardized uptake value ratio; τAD−/+/++, negative/moderate/advanced AD tau pattern.
[a]Other specifies race category identified as "other," "multiple," or not specified.

participants as a function of the CL threshold (Figure 2A, C), which shows values of ≈50% to 75% T+ prevalence at CL ≥24.1 and increases with higher amyloid thresholds.

1.7 | Population subgroup analyses

We used pooled study data to analyze PPVs in five subgroups of participants, including ethnicity, race, cognitive score, age, and sex (Figure 3). Data available in the pooled data set allowed us to examine the impact of subgroups on the relationship between T+ (tauVQ criterion) and A+ (CL ≥ 24.1 criterion). Overall, PPV and amyloid distribution were similar between subgroups of ethnicity, race, cognitive score, age, and sex. A PPV of 94.3% to 96.6% was observed for all subgroups except for small groups of Hispanic/Latino participants (*N* = 47, PPV 78.7%) and Asian participants (*N* = 13, PPV of 84.6%). Distributions of amyloid levels for T+ participants (S3) were also similar for all subgroups.

1.8 | Regional tau PET SUVR

Exploratory analyses of regional tau PET SUVR were performed in the A05 data set, and predictability of amyloid positivity was compared within this data set. The constructed ROC curves (Figure 4) and AUROC values (S4) suggest that all regions of interest (ROIs) measured can be utilized to establish an amyloid positivity A+ with a specificity/negative agreement of 95%. However, the sensitivity/positive agreement corresponding to 95% specificity depends on both ROI and reference region. Better AUROC were observed for regions positioned earlier in the tau pathologic cascade. For instance, comparison

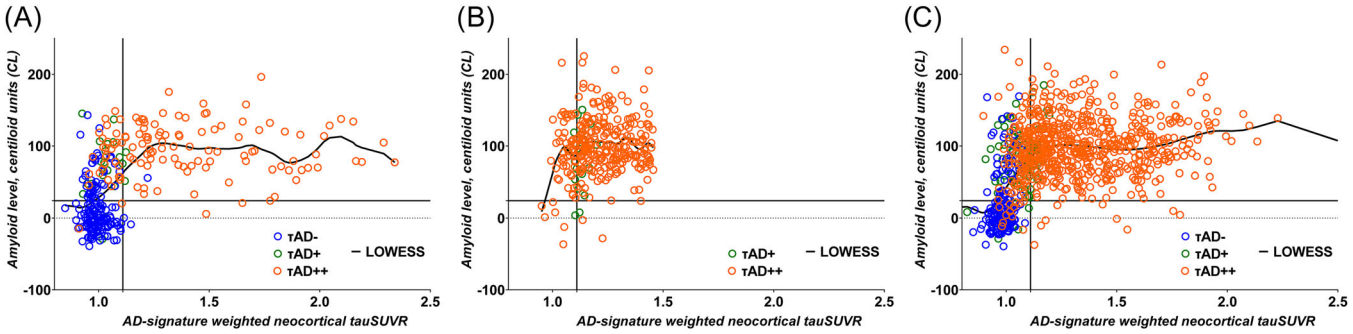

FIGURE 1 Association between composite quantitative measures of amyloid and tau levels in three data sets: (A) A05; (B) TB; (C) TB2. Only florbetapir and flortaucipir with quantitative measures (CL and tauSUVR) available are included. AD-weighted composite neocortical SUVR is calculated using PERSI as a reference region. A data-driven association between amyloid and tau measures is illustrated using LOWESS. The horizontal solid line corresponds to the amyloid positivity threshold CL = 24.1; the vertical line corresponds to the tau positivity threshold tauSUVR = 1.11. Abbreviations: AD, Alzheimer's Disease; CL, centiloids; LOWESS, locally weighted scatterplot smoothing; PERSI, parametric estimation of reference signal intensity; SUVR, standardized uptake value ratio; τAD-, negative AD tau pattern; τAD+, moderate AD tau pattern; τAD++, advanced AD tau pattern; TB, TRAILBLAZER-ALZ; TB2, TRAILBLAZER-ALZ2.

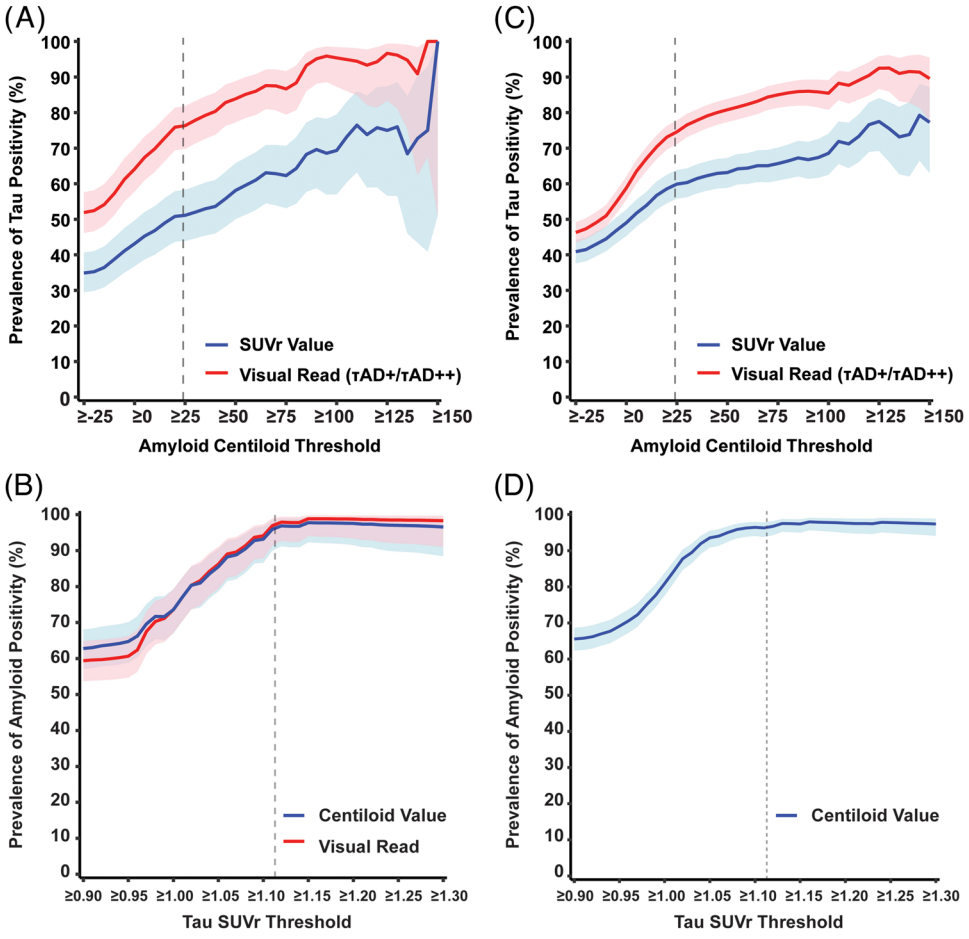

FIGURE 2 Probability of (A) tau positivity as a function of amyloid Centiloids and (B) amyloid positivity as a function of tauSUVR screening threshold within A05 population ($N = 306$). Probability of (C) tau positivity as a function of amyloid CL screening threshold and (D) amyloid positivity as a function of tauSUVR screening threshold within TB2 population ($N = 1165$). Gray dotted line refers to amyloid positivity threshold = 24.1 Centiloids (*A* and *C*) or tau positivity threshold tauSUVR = 1.11 (*B* and *D*). Shaded blue and red refer to corresponding Wilson confidence intervals. Abbreviations: CL, centiloids; N, number of participants; SUVR, standardized uptake value ratio; τAD+, moderate AD tau pattern; τAD++, advanced AD tau pattern; TB2, TRAILBLAZER-ALZ2.

TABLE 2 Predictive values and likelihood ratios calculated using various A+ and T+ definitions.

Positive Predictive Values (PPV)			
T+ definition	**Trial**	**A+ by visual assessment[a] (LR+)**	**A+ by quantitative assessment CL ≥24.1, (LR+)**
τAD+ or τAD++ (visual read)	A05	147/152 = 96.7% (20.0)	146/152 = 96.1% (14.5)
	TB	-	299/310 = 96.5% (1.0)
	TB2	-	496/535 = 92.7% (9.52)
τAD++ (visual read)	A05	128/131 = 97.7% (29.1)	127/131 = 97.0% (18.9)
	TB	-	284/293 = 96.9% (1.2)
	TB2	-	415/440 = 94.3% (12.44)
tauSUVR ≥1.11	A05	95/98 = 96.9% (22.2)	94/98 = 95.9% (14.3)
	TB	-	249/254 = 98.0% (1.9)
	TB2	-	339/352 = 96.3% (13.99)
tauVQ	A05	132/135 = 97.8% (30.0)	131/135 = 97.0% (19.4)
	TB	-	299/310 = 96.5% (1.0)
	TB2	-	431/457 = 94.3% (12.5)
Negative predictive values (NPV)			
T+ definition	**Trial**	**A− by visual assessment[a] (LR-)**	**A− by quantitative assessment CL < 24.1 (LR-)**
τAD+ or τAD++ (visual read)	A05	119/154 = 77.3% (0.2)	108/154 = 70.1% (0.3)
	TB	-	-
	TB2	-	460/630 = 73.0% (0.28)
τAD++ (visual read)	A05	121/175 = 69.1% (0.3)	110/175 = 62.9% (0.4)
	TB	-	-
	TB2	-	474/725 = 65.4% (0.4)
tauSUVR ≥1.11	A05	119/198 = 60.1% (0.5)	108/198 = 54.6% (0.5)
	TB	-	-
	TB2	-	291/518 = 56.2% (0.4)
tauVQ	A05	121/171 = 70.8% (0.3)	110/171 = 64.3% (0.3)
	TB	-	-
	TB2	-	472/702 = 67.2% (0.4)

Abbreviations: A+ (A−), abnormal (not abnormal) amyloid level as measured using florbetapir PET; A05, 18F-AV-1451-A05 (NCT02016560); CL, Centiloid; NPV, negative predictive value, PPV, positive predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; T+ (T−), abnormal (not abnormal) tau level as measured using flortaucipir PET; τAD+/++, moderate/advanced AD tau pattern; TB, TRAILBLAZER-ALZ (NCT03367403); TB2, TRAILBLAZER-ALZ 2 (NCT04437511); tauVQ, visual and quantitative assessment of tau PET images; SUVR, standardized uptake value ratio.
[a]Amyloid PET visual assessments were not available for TB and TB2 trial cohorts.

between Eτ VOI and frontal ROI showed significant ($P < 0.001$) advantage of Eτ VOI for both PERSI and cerebellum gray references. Moreover, Eτ VOI showed an advantage over other estimates when PERSI was used as a reference region. Alternatively, parietal and frontal ROIs showed the worst performance in all considered situations.

2 | DISCUSSION

2.1 | Summary

Amyloid and tau relationships were evaluated *post hoc* from baseline scans collected from cognitively impaired participants in three separate clinical trials. Several methods were incorporated to evaluate amyloid and tau levels and provided high confidence by means of robust evaluation of both amyloid and tau. The results herein indicate high predictivity(≥93% for all trials) of amyloid A+ status within T+ participants, regardless of visual or quantitative definition of amyloid positivity or by method of tau positivity, trial population (especially, on the amyloid positivity rate), PET acquisition protocols, or ethnicity, race, cognitive score, age, and sex. Overall, these findings suggest that the preponderance of amyloid-positive, cognitively impaired individuals can be evaluated for clinical research studying AD solely from flortaucipir imaging, with the exception that some symptomatic A+ participants do not exhibit T+.

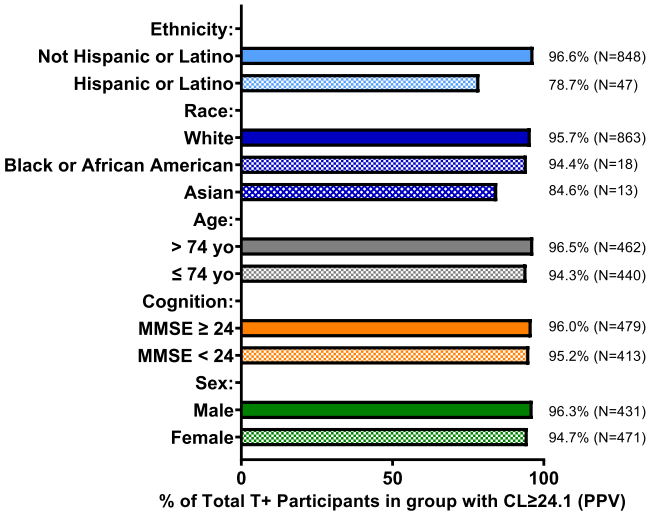

FIGURE 3 Positive predictive value in population subgroups. T+ (according to tauVQ criterion) participants ($N = 135$ from A05, $N = 310$ from TB, and $N = 457$ from TB2) from a pooled data set were used. Numbers shown in figure are the T+ participants in each subgroup with data available. Abbreviations: CL, centiloids; MMSE, mini—mental state examination; N, number of participants; PPV, positive predictive value; T+, abnormal tau level as measured using flortaucipir PET; tauVQ, visual and quantitative assessment of tau PET images; TB, TRAILBLAZER-ALZ; TB2, TRAILBLAZER-ALZ2; yo, years old.

When comparing global amyloid and tau quantitative measures with corresponding visual assessments, we noticed an advantage of visual assessments in terms of NPV (Table 2). Among A05 cases that received a positive read using the flortaucipir visual interpretation method previously established for clinical use,[8] 96.7% were classified as amyloid positive using the florbetapir visual interpretation method recommended for clinical use,[30] whereas NPV and sensitivity reached 77.3% and 80.8%, correspondingly. NPVs were lower (55%–70%) for comparisons using global quantitation and include regions such as frontal cortex that may not yet have accumulated substantial tau, despite visual positivity in early regions like the temporal cortex. Furthermore, regional tau quantifications (Figure 4) suggest that regions positioned earlier in the tau pathologic cascade may perform better in differentiating amyloid positivity. Thus regions expected to accumulate tau early in the disease may outperform global tau SUVR measures and require further investigation with established positivity thresholds and PPV/NPV evaluations.

2.2 | The amyloid–tau relationship

A summary was created on previously published studies with both amyloid and tau measurements in individuals from various diagnostic groups, with various PET tracers and analysis methods (S5). Among all listed studies, the calculated PPVs ranged from 72% to 100%. The wide range is likely due to differences in enrollment criteria including order of PET imaging, methods used to measure amyloid and tau, target and reference regions used, and various A+ and T+ definitions. For example, lower PPVs of 72% reported by Weigand et al.[31] and 81% reported by Schwarz et al.[32] both used less stringent tau positivity criteria, which categorized subjects with uptake on Braak I/II+ regions as T+. Alternatively, we report PPVs of 93% and higher for symptomatic participants. This is not surprising given that pathology data show that the probability of being amyloid positive is lower in early Braak stage cases than in later Braak stages, as identified by the methods in the present study.[33]

2.3 | The amyloid cascade hypothesis

The finding that tau deposition can predict amyloid deposition corroborates the original amyloid cascade hypothesis, which proposes that accumulation of Aβ is a key event in AD and widespread NFT deposition.[34] From a mechanistic perspective, dominant mutations known to cause early-onset AD occur in either the amyloid precursor protein or presenilin, the protease that cleaves the amyloid precursor protein and generates Aβ. Oligomers of Aβ induce hyperphosphorylation of tau at AD-relevant epitopes,[35] resulting in amyloid-driven deposition of tau. Furthermore, amyloid plaques are surrounded by dystrophic neurites with high concentrations of tau-laden axons and dendrites. The hypothesis then posits that a subject must first pass through an amyloid phase, followed by a tau phase. It is the later tau phase that is in greater proximity to the onset of cognitive decline. The high predictability of amyloid deposition by tau reported here is in strong support for this temporal relationship within the amyloid cascade hypothesis.

2.4 | A+T− participants

With current tau PET analysis methodologies, tau PET cannot be used as a single diagnostic instrument for both amyloid and tau pathologies in order to distinguish "A−T−" (normal biomarkers) and "A+T−" (Alzheimer's or suspected concomitant non-Alzheimer's pathologic change) subgroups[2] with high confidence. Our previous analyses with quantitatively (global SUVR for amyloid and tau levels) determined subgroups[36] showed that both baseline and longitudinal ADAScog-11 scores of the "A+T−" subgroup were more similar to the "A−T−" than to the "A+T+" group in that there were no significant differences between A−T− and A+T− subgroups.[36] However, the "A+T+" sub-group had significantly higher ADAScog-11 score and significantly greater decline than the "A+T−" subgroup. Recent analyses[13] also suggest that tau PET is superior to amyloid PET for predicting cognitive change.

2.5 | A−T+ participants

A small percentage (3%–4%) of participants with low amyloid of <24.1 CL (A−) also exhibited high tau (T+), representing a small subset of participants who may have Aβ-independent tau deposition.[6] Using tau PET as a diagnostic for this subset of participants and for prediction of amyloid could result in misinterpretation of amyloid levels in these participants. Additional analysis of the baseline characteristics within the $N = 41$ A05, TB, and TB2 A−T+ participants are shown in Table S6.

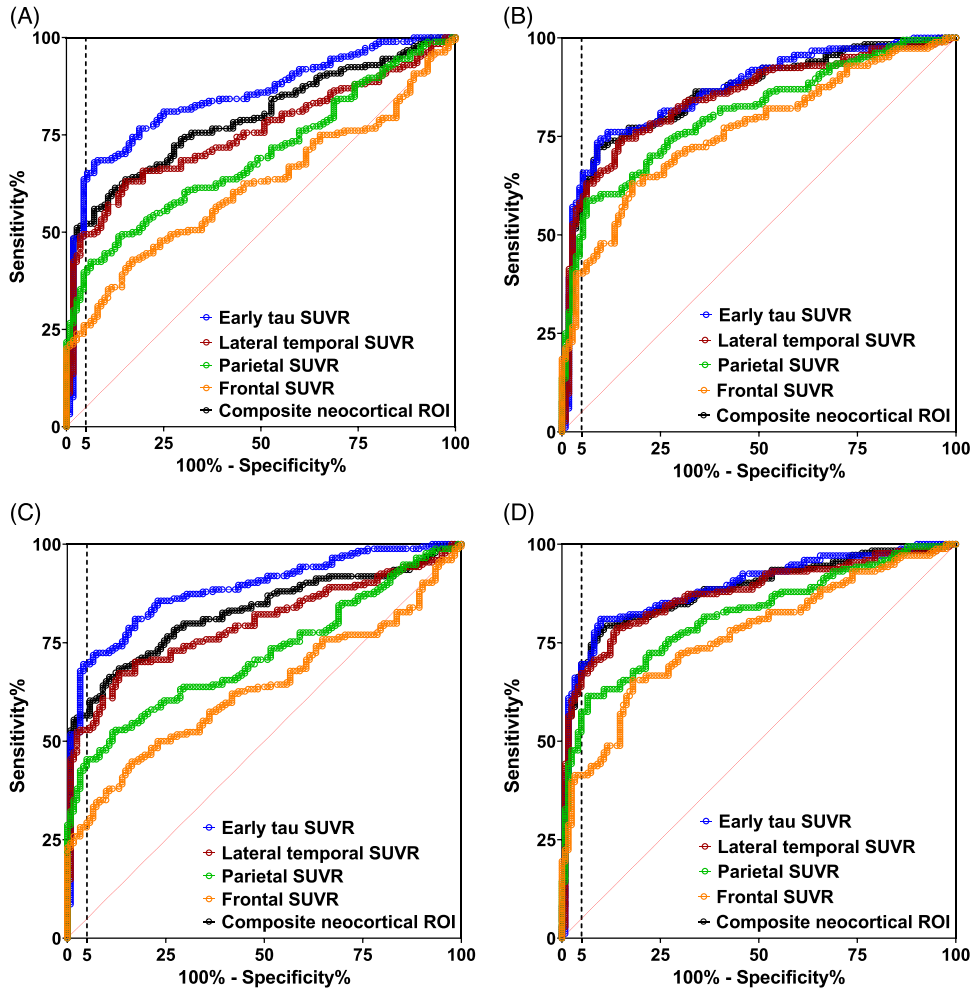

FIGURE 4 Receiver-operating characteristic (ROC) curves for various regional tau PET SUVR and A+ criteria using A05 data ($N = 306$). (A) PERSI as a reference region for T+ and quantitative (CL ≥24.1) criterion for A+; (B) cerebellum gray as a reference region for T+ and quantitative (CL ≥24.1) criterion for A+; (C) PERSI as a reference region for T+ and quantitative visual assessment for A+; (D) cerebellum gray as a reference region for T+ and visual assessment to determine A+. Vertical dashed line corresponds to the 95% specificity. Abbreviations: A+, abnormal amyloid level as measured using florbetapir PET; CL, centiloids; PERSI, parametric estimation of reference signal intensity; PET, Positron emission tomography; ROC, receiver-operating characteristic; ROI, region of interest; SUVR, standardized uptake value ratio; T+, abnormal tau level as measured using flortaucipir PET.

Tau levels were primarily within the τAD++ category by visual read. Of the 15 A−T+ participants in A05 and TB, 9 (60%) had lateral AD-like imaging patterns, primarily with left dominant and medial temporal and occipital uptake (S7). Specific uptake patterns may be associated with specific cognitive symptoms associated with tau pathology, particularly in individuals with atypical symptom expression of AD.[37] About 6% of individuals diagnosed with late-onset AD present with atypical symptoms, specifically non-memory symptoms,[38] and may be identifiable based on amyloid and tau presentation and uptake patterns.

2.6 | Implications for AD therapies

In an era where therapies targeting amyloid pathology in the symptomatic stage of the disease are being evaluated in clinical trials,[39] it is logical to consider that a tau scan can efficiently achieve multiple goals. As reported previously, a positive tau PET scan essentially rules in the presence of amyloid pathology for targeted treatment and the presence of AD since it can establish both pathologies (amyloid and tau). Finally, a large body of literature currently exists demonstrates the potential utility for predicting the speed of future decline as greater amounts of tau portend faster decline.[11,18,40,41] Nevertheless, tau PET cannot substitute for amyloid PET in all applications. Tau scans will not be useful in monitoring patients on amyloid-targetting therapies to determine when or if to stop treatment or to conclude whether an individual is responding to therapy but, should have utility in establishing the presence of tau and amyloid pathology of symptomatic patients.

In consideration of the increasing interest in plasma assays for trial screening,[42] tau PET may be most valuable in cases with borderline plasma results to confirm both amyloid and tau presence.

3 | LIMITATIONS

Our examinations were performed for symptomatic participants only and conclusions cannot be made for preclinical AD stages or A+ clinically normal participants. The utility of tau scans for identifying candidates for anti-amyloid treatment would be expected to decrease as therapies move earlier in the disease process, particularly for asymptomatic or secondary prevention trials where the amyloid pathology has not yet precipitated a robust tau pathology. Although baseline characteristic parameters were investigated, certain relevant parameters like apolipoprotein E (*APOE*) status were not systematically collected at screening and, therefore, limit meaningful conclusions about other parameters that may impact amyloid predictivity by tau PET. In terms of A+/A− and T+/T− distribution in the analyzed cohorts, the A05 and TB2 populations had balanced distribution in A+/A− and T+/T− categories. However, enrollment selection criteria limited the TB cohort to primarily A+/T+ participants. The interpretation of the TB cohort with low/medium-tau level supplemented confirmation of the PPVs reported, but no NPV was reported due to limitations of this cohort. Racial and ethnic diversity are also limited in trial populations.

4 | CONCLUSIONS

Analyses of florbetapir F18 and flortaucipir F18 scans collected from three multi-center studies with various amyloid and tau positivity criteria suggest that a positive tau PET scan is associated (≥93%) with amyloid positivity in early symptomatic individuals with the potential benefits of reducing clinical trial and health care expenses, radiation exposure, and participant time.

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CONFLICT OF INTEREST STATEMENT

All authors are employees and shareholders of Eli Lilly and Company. No other disclosures were reported. Any author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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