Received: 12 August 2022 | Revised: 9 November 2022 | Accepted: 29 November 2022

DOI: 10.1002/dad2.12390

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Discriminative accuracy of the A/T/N scheme to identify cognitive impairment due to Alzheimer's disease

Tharick A. Pascoal[1,2,3] | **Antoine Leuzy**[4] | **Joseph Therriault**[3,5] | **Mira Chamoun**[3,5] | **Firoza Lussier**[1,3] | **Cecile Tissot**[2,4] | **Olof Strandberg**[4,6] | **Sebastian Palmqvist**[4,6] | **Erik Stomrud**[4,6] | **Pamela C. L. Ferreira**[1] | **João Pedro Ferrari-Souza**[1,7] | **Ruben Smith**[4,6] | **Andrea Lessa Benedet**[3,5] | **Serge Gauthier**[3] | **Oskar Hansson**[4,6] | **Pedro Rosa-Neto**[3,5]

[1]Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[2]Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[3]Translational Neuroimaging Laboratory, The McGill University Research Centre for Studies in Aging, Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Montreal, Québec, Canada

[4]Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden

[5]Montreal Neurological Institute, McGill University, Montreal, Québec, Canada

[6]Memory Clinic, Skåne University Hospital, Lund, Sweden

[7]Graduate Program in Biological Sciences: Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Correspondence
Tharick A. Pascoal, Assistant Professor of Psychiatry and Neurology, University of Pittsburgh, 3501 Forbes Ave, Pittsburgh, PA 15213, USA
Email: pascoalt@upmc.edu

Tharick A. Pascoal, Antoine Leuzy, Joseph Therriault, Oskar Hansson, and Pedro Rosa-Neto contributed equally to this study.

Funding information
National Institute of Health, Grant/Award Numbers: R01AG075336, R01AG073267; Alzheimer's Association, Grant/Award Number: AACSF-20-648075; Canadian Institutes of Health Research, Grant/Award Number: MOP-11-51-31; Swedish Research Council, Grant/Award Number: 2016-00906; Knut and Alice Wallenberg foundation, Grant/Award Number: 2017-0383; Swedish Alzheimer Foundation, Grant/Award Number: AF-939932; Swedish Brain Foundation, Grant/Award Number: FO2019-0326

Abstract

Introduction: The optimal combination of amyloid-β/tau/neurodegeneration (A/T/N) biomarker profiles for the diagnosis of Alzheimer's disease (AD) dementia is unclear.

Methods: We examined the discriminative accuracy of A/T/N combinations assessed with neuroimaging biomarkers for the differentiation of AD from cognitively unimpaired (CU) elderly and non-AD neurodegenerative diseases in the TRIAD, BioFINDER-1 and BioFINDER-2 cohorts (total $n = 832$) using area under the receiver operating characteristic curves (AUC).

Results: For the diagnosis of AD dementia (vs. CU elderly), T biomarkers performed as well as the complete A/T/N system (AUC range: 0.90–0.99). A and T biomarkers in isolation performed as well as the complete A/T/N system in differentiating AD dementia from non-AD neurodegenerative diseases (AUC range; A biomarker: 0.84–1; T biomarker: 0.83–1).

Discussion: In diagnostic settings, the use of A or T neuroimaging biomarkers alone can reduce patient burden and medical costs compared with using their combination, without significantly compromising accuracy.

KEYWORDS
Alzheimer's disease, A/T/N system, biomarker, diagnose, PET

1 | BACKGROUND

Alzheimer's disease (AD) is characterized by the aggregation of amyloid-beta (Aβ) plaques, neurofibrillary tangles consisting of hyperphosphorylated tau, and downstream neurodegeneration.[1] Accepted biomarker models of AD suggest that Aβ accumulates decades before the appearance of symptoms, with neocortical tau pathology and neurodegeneration occurring closer to the onset of cognitive impairment.[2,3]

The recently proposed unbiased biomarker classification system for AD provides three main classes of biomarkers: Aβ (A), Tau (T), and neurodegeneration (N), denoted as A/T/N.[4] In this framework, abnormal levels of Aβ and Tau are considered specific to AD, with neurodegeneration also being a feature of other neurodegenerative diseases.[5] This classification has numerous applications including enrichment of therapeutic trials[6] and prediction of cognitive decline.[7] With increasing clinical use of molecular imaging for the differential diagnosis of individuals with cognitive impairment,[8–10] it has often been speculated that this framework may also have practical applications in screening patients most likely to have AD and to help differentiate AD from non-AD dementia disorders. However, which A/T/N biomarker profiles are optimal for the accurate diagnosis of the etiology of cognitive impairment has not yet been determined.

While many research studies phenotype individuals according to the complete A/T/N system,[7,11–15] doing so in clinical settings is unlikely to be feasible given financial, practical, and patient-related constraints. A logical question is thus whether there is a single AD biomarker, or combination of two biomarkers, that can provide a level of diagnostic accuracy similar to the complete A/T/N system. Building on previous studies reporting high diagnostic accuracy of tau positron emission tomography (PET) biomarkers for the diagnosis AD,[16] we compared the performance of A/T/N biomarkers (combined or in isolation) for the separation of AD dementia from cognitively unimpaired (CU) controls and non-AD neurodegenerative diseases in three independent cohorts. We hypothesized that the biomarkers combinations would result in higher diagnostic performance as compared to the use of single biomarkers.

2 | METHODS

2.1 | Participants

This study included three separate research cohorts. The first cohort was the Translational Biomarkers in Aging and Dementia (TRIAD) study[17] recruiting from the McGill Centre for Studies in Aging in Montreal, Canada. The second and third cohorts were the Swedish BioFINDER-1[18] and BioFINDER-2[19] studies, both recruiting from Skåne University Hospital and the Hospital of Ängelholm, Sweden. In all three cohorts, inclusion was based on (i) being cognitively unimpaired (CU)—that is, did not have MCI or dementia—and above age 60, (ii) fulfilling clinical criteria for probable AD[20] or a non-AD dementia disorder, and (iii) availability of all three ATN biomarkers. Table S1 presents a breakdown of the non-AD neurodegenerative diseases in each cohort. Participants were excluded if they had inadequately treated systemic conditions, active substance abuse, recent head trauma, major surgery, or presented with magnetic resonance imaging (MRI)/PET safety contraindications. Full details of inclusion and exclusion criteria for all studies have been published previously[17–19] and are provided in Supplementary Methods 1.

Written informed consent was obtained for all participants. The TRIAD study was approved by the Montreal Neurological Instituted PET Working Committee and the Douglas Mental Health University Institute Research Ethics Board. Ethical approval for the BioFINDER-1 and BioFINDER-2 studies was given by the Regional Ethical Committee in Lund, Sweden. Approval for PET imaging was obtained from the Swedish Medicines and Products Agency and the local radiation safety committee at Skåne University Hospital, Lund, Sweden.

2.2 | MRI/PET acquisition and processing

Details of the MRI and PET acquisition and processing for TRIAD,[17] BioFINDER-1,[21] and BioFINDER-2[22] studies are provided in Supplemetary Methods 2. Briefly, all participants from the three cohorts underwent 3.0T MRI scans. In the TRIAD study, Aβ-PET standardized uptake value ratio (SUVR) was acquired using [^{18}F]AZD4694 from 40 to 70 min post-injection normalized to the full cerebellum[23] and tau PET was acquired using [^{18}F]MK6240 from 90 to 110 min post-injection normalized to the inferior cerebellum gray matter.[24] In the BioFINDER-1 study, Aβ PET SUVR was acquired using [^{18}F]flutemetamol from 90 to 100 min post-injection normalized to the pons and tau PET was acquired using [^{18}F]flortaucipir from 80 to 100 min post-injection normalized to the inferior cerebellum gray matter. In the BioFINDER-2 study, tau PET was acquired using [^{18}F]RO948 from 70 to 90 min post-injection normalized to the inferior cerebellum gray matter. In BioFINDER-2, Aβ PET is not performed on individuals with dementia with the cerebrospinal fluid (CSF) Aβ42/40 ratio instead used as an Aβ biomarker.[25] Tau PET SUVR values (T) for all tracers were extracted from a composite region of interest (ROI) consisting of the entorhinal cortex and hippocampus. Aβ PET SUVR (A) levels for all tracers were extracted from a composite ROI comprising frontal, temporal, and parietal cortices. In all cohorts, a high-resolution T1-weighted MRI was acquired on a 3T scanner for the purposes of PET image

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources. While most research studies phenotype individuals according to the complete amyloid-β/tau/neurodegeneration (A/T/N) biomarker system, doing so in clinical settings is unlikely to be feasible given financial and patient burden constraints.
2. **Interpretation**: Our findings led us to investigate the diagnostic performance of established A/T/N biomarkers to determine the optimal combination of biomarkers for AD diagnosis. We observed that A and T biomarkers alone had similar performance to the full A/T/N system when differentiating AD from non-AD neurodegenerative diseases, and that T biomarkers were best for differentiating AD from cognitively unimpaired (CU) elderly individuals.
3. **Future directions**: The use of A or T neuroimaging biomarkers alone in diagnostic settings can reduce patient burden and medical costs compared with using AD biomarker combinations, without significantly compromising accuracy. Future studies should aim to investigate whether same pattern of results are observed with plasma biomarkers of AD pathophysiology.

coregistration and template normalization, and for the extraction of hippocampal volume as a measure of neurodegeneration (N).

2.3 | Statistical analyses

Statistical analyses were performed using R Statistical software v4.0.4. The receiver operating characteristic (ROC) curves comparing groups provided the area under the curve (AUC) to determine biomarker performance using clinical diagnosis as the standard of truth. Logistic regressions were used to generate test variables representing the intended biomarker combinations, which were then used as an input in the ROC AUC analyses. Cutoff values were determined using the Youden index maximizing the separation between groups. We then used these optimized cutoffs to generate confusion matrices summarizing diagnostic performance. In these models, each AUC value indicates overall biomarker (or combination of biomarkers) performance, with 50% indicating no difference from chance and 100% indicating a biomarker with sensitivity and specificity of 100%. We tested whether there were statistically significant differences between AUC values for biomarkers or combinations of biomarkers by comparing 95% confidence intervals using the DeLong method.[26]

3 | RESULTS

A total of 832 individuals were evaluated from three prospective cohorts (TRIAD: $n = 225$; BioFINDER-1: $n = 123$; BioFINDER-2: $n = 484$), including 418 CU elderly individuals, 221 patients with AD dementia, and 193 patients with various non-AD neurodegenerative disorders. Summary demographic, clinical and biomarker information are provided in Table 1. Specific diagnoses of the subjects categorized as "non-AD neurodegenerative diseases" are reported in Table S1. Average tau PET SUVR images across diagnostic groups for each cohort are shown in Figure 1.

We tested the discriminative accuracy of various A/T/N biomarker combinations for the classification of AD dementia versus CU elderly. In the TRIAD cohort (Figure 2A), no significant difference in diagnostic accuracy was observed among A/T/N, A/T, and T biomarkers, while A in isolation and N in isolation had significantly lower discriminative accuracy ($p < 0.05$). In the BioFINDER-1 cohort (Figure 2B), there were no significant differences between A/T/N and other biomarker combinations in differentiating AD dementia from CU elderly individuals. In the BioFINDER-2 cohort (Figure 2C), A/T/N, A/T, and T had similar diagnostic accuracy, while A in isolation had significantly lower discriminative accuracy ($p < 0.05$).

Subsequently, we tested the discriminative accuracy of A/T/N combinations for the classification of AD dementia versus non-AD neurodegenerative diseases. In all three cohorts, we observed no significant difference in diagnostic accuracy for A/T/N, A/T, A, and T biomarkers, while N biomarkers in isolation had significantly lower diagnostic accuracy ($p < 0.05$) (Figure 3).

4 | DISCUSSION

In summary, we found that the discriminative accuracy of tau PET or Aβ PET in isolation was similar to the combination of Aβ, tau and neurodegeneration biomarkers in differentiating AD dementia from CU individuals and those with non-AD degenerative disorders. These results support the diagnostic utility of both tau and Aβ biomarkers in patients with cognitive impairment.

For the diagnosis of AD dementia (vs. CU elderly), the combination of A and T biomarkers, as well as T in isolation, had similar performance as the full A/T/N classification system. Because Aβ pathology accumulates for decades before the onset of cognitive symptoms,[2,3] Aβ abnormality is observed in about 30% of older CU individuals.[27,28] Consequently, the discriminative accuracy of Aβ biomarkers for AD is likely to be lower than for biomarkers of tau, which become abnormal much closer to cognitive impairment.[29] Since ~ 30% of CU elderly are Aβ positive, the use of Aβ biomarker thresholds merely indicating cerebral amyloidosis will have a specificity no greater than 70%. To circumvent this, studies have used different techniques, such as the Optimal Operating Point for ROC, to optimize the discriminative accuracy of Aβ biomarkers, resulting in better diagnostic performance due to a more balanced trade-off between sensitivity and specificity. In our study, the difference between the global concentrations between Aβ positive CU and Aβ positive subjects with cognitive impairment allowed optimization of Aβ thresholds and resulted in better diagnostic performance compared to the use of standard Aβ thresholds.

TABLE 1 Demographic and key characteristics of the samples

(A) TRIAD Cohort	CU	AD dementia	Non-AD
No.	156	39	30
Age, y, mean (SD)	71.33 (5.97)[a]	66.59 (9.07)	66.16 (9.22)[b]
Female, no. (%)	105 (67.3%)	19 (48.7)	15 (50)
Education, y, mean (SD)	15.25 (3.51)	14.58 (3.43)	14.17 (3.78)
APOE ε4 carriers, %	43 (27.5%)	21 (53.8%)	5 (16.6%)
MMSE, mean (SD)	29.12 (1.05)[a,d]	18.34 (6.58)	25.96 (5.91)[c]
Neocortical [^{18}F]AZD4694 SUVR (SD)	1.40 (0.31)[j]	2.28 (0.34)[e,f]	1.21 (0.14)
Braak I-II [^{18}F]MK6240 SUVR (SD)	0.98 (0.23)	2.07 (0.51)[e,f]	0.86 (0.18)
Braak III-IV [^{18}F]MK6240 SUVR,(SD)	0.95 (0.08)	2.63 (0.91)[e,f]	0.9 (0.08)
Braak V-VI [^{18}F]MK6240 SUVR (SD)	0.97 (0.09)	2.25 (0.92)[e,f]	0.96 (0.11)
Hippocampal volume, cm^3 (SD)	3.50 (0.38)[a,b]	2.79 (0.46)[e]	3.19 (0.54)
(B) BioFINDER-1 Cohort	**CU**	**AD dementia**	**Non-AD**
No.	57	43	23
Age, y, mean (SD)	75.77 (4.45)[a]	71.51 (7.14)	69.61 (5.65)[b]
Female, no. (%)	28 (49)	20 (46.5)	11 (48)
Education, y, mean (SD)	12.18 (3.86)	12.44 (3.85)	14.17 (3.78)
APOE ε4 carriers, %	23 (40)	24 (58%; 2 NA)	7 (36; 4 NA)
MMSE, mean (SD)	28.91 (1.06)[a,d]	20.69 (3.06)	25.56 (4.6)[c]
Neocortical [^{18}F]Flutemetamol SUVR (SD)	0.64 (0.16)	0.90 (0.17)[e,f]	0.59 (0.11)
Braak I-II [^{18}F]Flortaucipir SUVR (SD)	1.2 (0.14)	1.53 (0.20)[e,f]	1.16 (0.16)
Braak III-IV [^{18}F]Flortaucipir SUVR (SD)	1.18 (0.10)	1.95 (0.44)[e,f]	1.24 (0.27)
Braak V-VI [^{18}F]Flortaucipir SUVR (SD)	1.03 (0.06)	1.47 (0.36)[e,f]	1.06 (0.15)
Hippocampal volume, cm^3 (SD)	3.39 (0.37)[a]	2.89 (0.48)	3.15 (0.66)[c]
(C) BioFINDER-2 Cohort	**CU**	**AD dementia**	**Non-AD**
No.	205	139	140
Age, y, mean (SD)	75.19 (5.86)[h]	74.09 (6.69)[g]	70.4 (8.97)
Female, no. (%)	113 (55)	76 (54)	56 (40)
Education, y, mean (SD)	12.04 (3.73)	12.16 (4.6)	12.59 (3.68)
APOE ε4 carriers, %	89 (43)	100 (72)	53 (38)
MMSE, mean (SD)	28.77 (1.24)[a,d]	20.27 (4.25)	25.42 (4.38)[c]
CSF Aβ 42/40 ratio	0.86 (0.28)[a]	0.48 (0.13)	0.93 (0.23)
Braak I-II [^{18}F]RO948 SUVR (SD)	1.12 (0.16)	1.61 (0.29)[e,f]	1.07 (0.21)
Braak III-IV [^{18}F]RO948 SUVR (SD)	1.07 (0.09)	1.51 (0.42)[e,f]	1.07 (0.14)
Braak V-VI [^{18}F]RO948 SUVR (SD)	1.21 (0.18)	2.15 (0.69)[e,f]	1.21 (0.19)
Hippocampal volume, cm^3 (SD)	3.53 (0.43)[a]	2.88 (0.43)	3.43 (0.60)[d]

Abbreviations: ; AD, Alzheimer's disease; CSF, cerebrospinal fluid; CU, cognitively unimpaired; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio; non-AD, neurogenerative diseases other than Alzheimer's disease.
A = CU > AD ($p < 0.005$); B = CU > nonAD ($p < 0.005$); C = non-AD > AD ($p < 0.005$); D = CU > nonAD ($p < 0.005$); E = AD > CU ($p < 0.005$); F = AD > non-AD ($p < 0.005$); J = CU > non-AD ($p < 0.05$).

When differentiating AD from non-AD neurodegenerative dementia disorders, we observed that the combination of A and T biomarkers, as well as A and T biomarkers in isolation performed nearly as well as the complete A/T/N classification system in all three cohorts. This supports the use of either Aβ or tau PET for the differential diagnosis of neurodegenerative diseases in individuals with cognitive impairment.[9] N, as a nonspecific biomarker that characterizes AD as well as non-AD neurodegenerative disease, performed significantly worse than biomarkers that were specific to AD pathology (i.e., A and T).

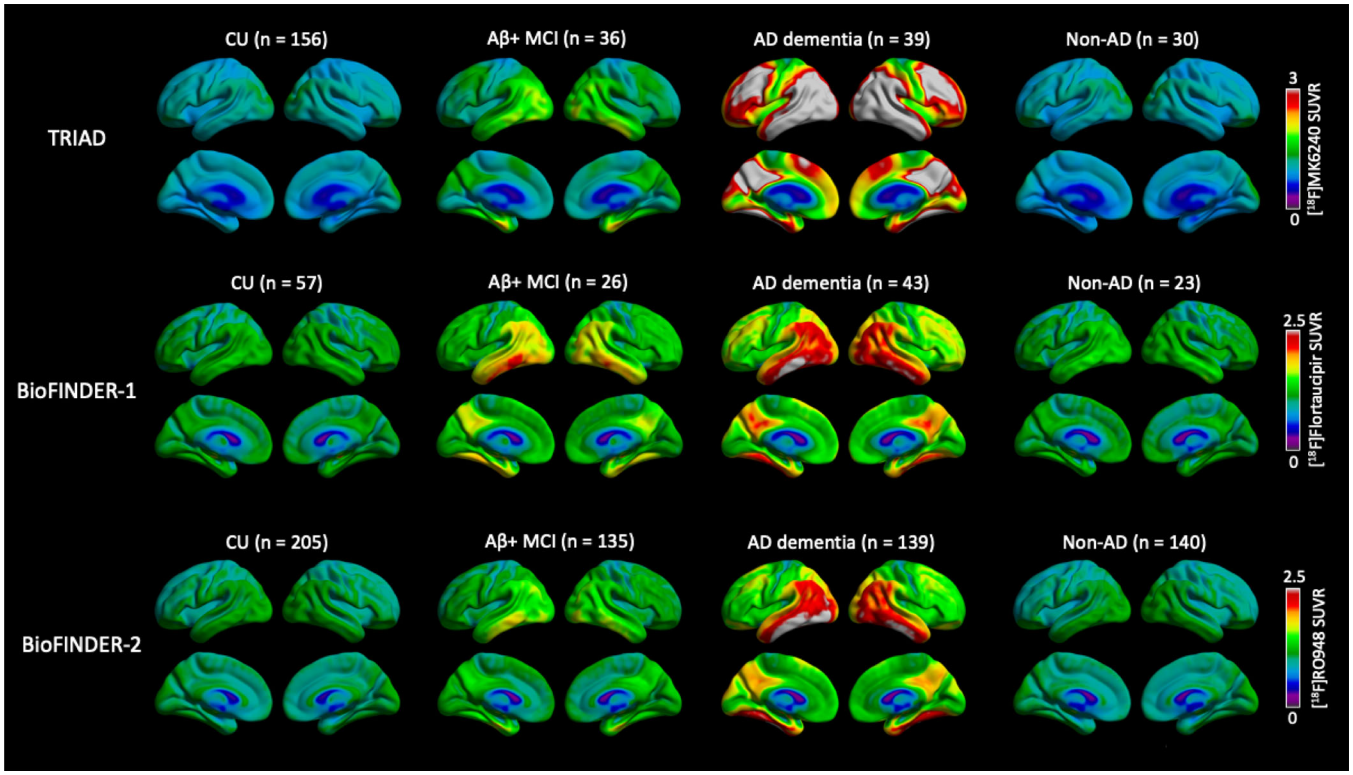

FIGURE 1 Mean tau-PET SUVRs from each diagnostic group in TRIAD, BioFINDER-1, and BioFINDER-2 cohorts. Average voxel-wise tau-PET images from each cohort. Participants in TRIAD were evaluated with [18F]MK6240. Participants in BioFINDER-1 were evaluated with [18F]flortaucipir. Participants in BioFINDER-2 were evaluated with [18F]RO948

Overall, we observed a relatively consistent pattern of results across the three cohorts investigated in this study. T biomarkers in isolation performed as well as the complete A/T/N system in distinguishing between AD dementia and CU elderly. Both A and T biomarkers in isolation performed as well as the complete A/T/N system in distinguishing AD dementia and CU elderly. Similarly, in all three cohorts, both A and T biomarkers in isolation performed as well as the complete A/T/N system in differentiating between individuals with AD dementia and those with non-AD neurodegenerative diseases.

It is important to emphasize that this study was designed to test the diagnostic accuracy of A/T/N biomarkers in individuals with cognitive impairment. Biomarker phenotyping with the full A/T/N system is useful in a number of other situations, including clinical trial enrichment[6] and prediction of cognitive decline.[7] While the use of A or T biomarkers alone in diagnostic settings could reduce patient burden and medical costs compared with using AD biomarker combinations if A, T, and N are completely or partially defined using neuroimaging, the combined use of A, T, and N CSF measures has been shown to carry prognostic value in memory clinic settings[30] and can easily be obtained without increasing patient burden and at only a mildly increased cost compared to individual measures. In addition to high diagnostic performance, tau PET offers the potential to stage individuals based on their pattern of tau deposition.[24,31] Because both the topography and the magnitude of tau PET uptake vary according to the severity of AD, it is conceivable that a tau PET scan may prove advantageous in providing additional information to clinicians regarding patient management, including identifying atypical phenotypic presentations of AD.[32] Future studies are needed to determine the feasibility of this concept, however.

This study has several limitations. One important limitation is the lack of autopsy data; hence, clinical diagnoses were considered as the reference standard. Because of imperfect agreement between clinical diagnoses and presence of Aβ plaques and neurofibrillary tangles at autopsy,[33] the reference standard for ROC analyses can be considered suboptimal. Second, diagnoses were made in secondary (BioFINDER) and tertiary (TRIAD) care clinical settings by dementia specialists and may not reflect diagnostic accuracy of more typical clinical settings. Third, applying cutoffs to binarize biomarkers inevitably results in trade-offs between sensitivity and specificity.[33] Fourth, we used hippocampal volume as our measure of neurodegeneration as this was the measure common to both cohorts; future should assess the importance of other neuroimaging and fluid neurodegeneration biomarkers, such as [^{18}F]FDG PET or CSF neurofilament light. Last, we did not include patients with MCI due to AD because of the potential circularity of including AD-biomarker positive individuals in an analysis of the discriminative accuracy of specific biomarkers. Future work should focus on this population. Strengths of this study include the investigation of three large and well-defined cohorts, replication of results across different PET tracers for Aβ and tau, and multimodal imaging biomarkers used to determine diagnostic performance.

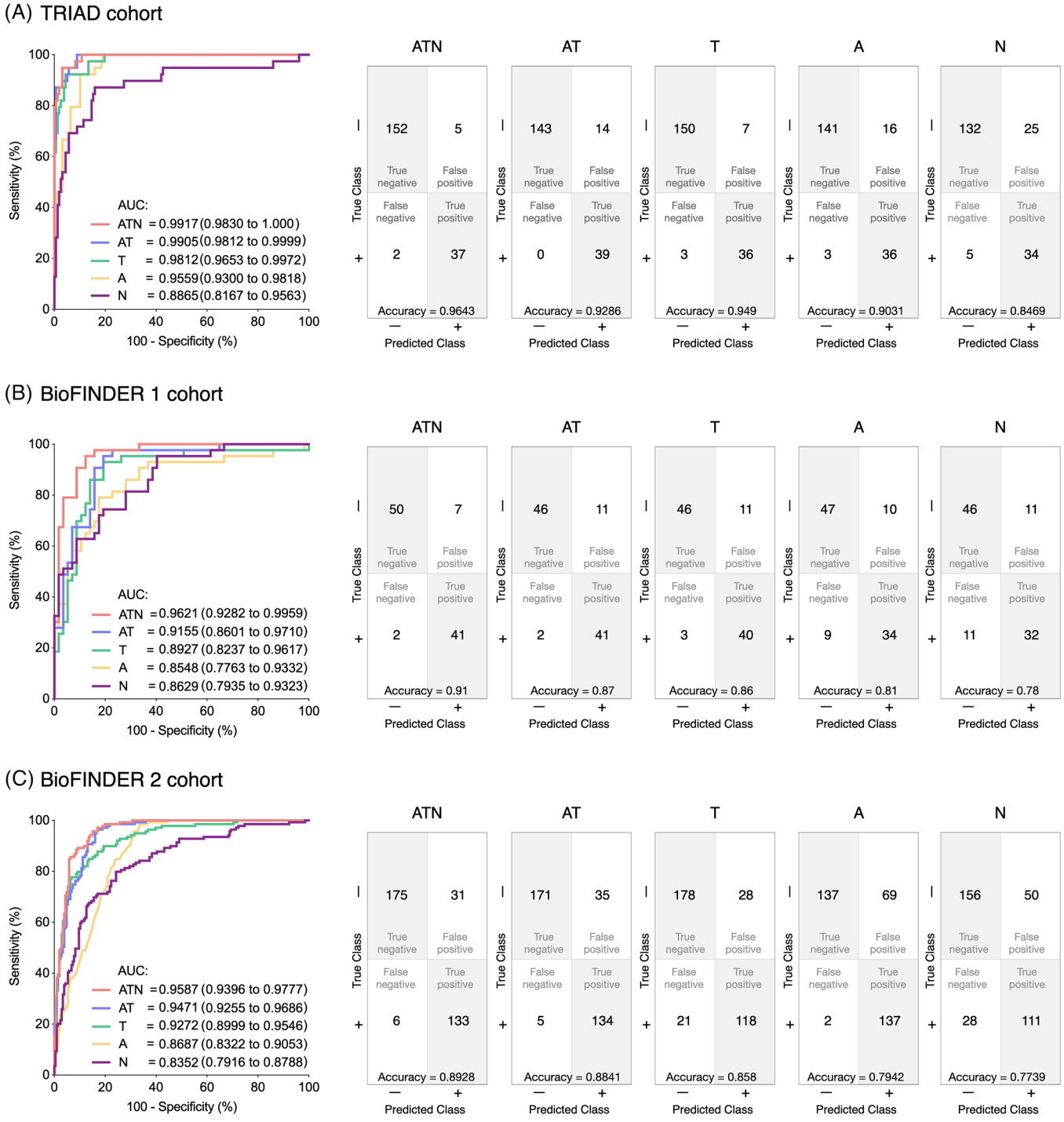

FIGURE 2 Tau PET has similar diagnostic performance to complete ATN biomarker classification for distinguishing AD dementia from CU elderly. Plots from ROC analyses illustrating diagnostic performance of A/T/N as well as individual biomarkers and biomarker combinations for distinguishing CU elderly individuals from individuals with AD dementia. Boxes illustrate the confusion matrices with the accuracy (predicted vs true class) of each biomarker or biomarker combination. In the TRIAD cohort (A) as well as the BioFINDER-2 cohort (C), the combination of AT, as well as T in isolation, performed nearly identically as the complete A/T/N system in differentiating CU elderly from individuals with AD dementia. A in isolation and N is isolation had significantly lower accuracy. In the BioFINDER-1 cohort (B), A in isolation had lower accuracy than the complete A/T/N system (81%), although this difference was not statistically significant. Similar to the TRIAD and BioFINDER-2 cohorts, N in isolation performed significantly worse (accuracy = 78%) than the complete A/T/N system

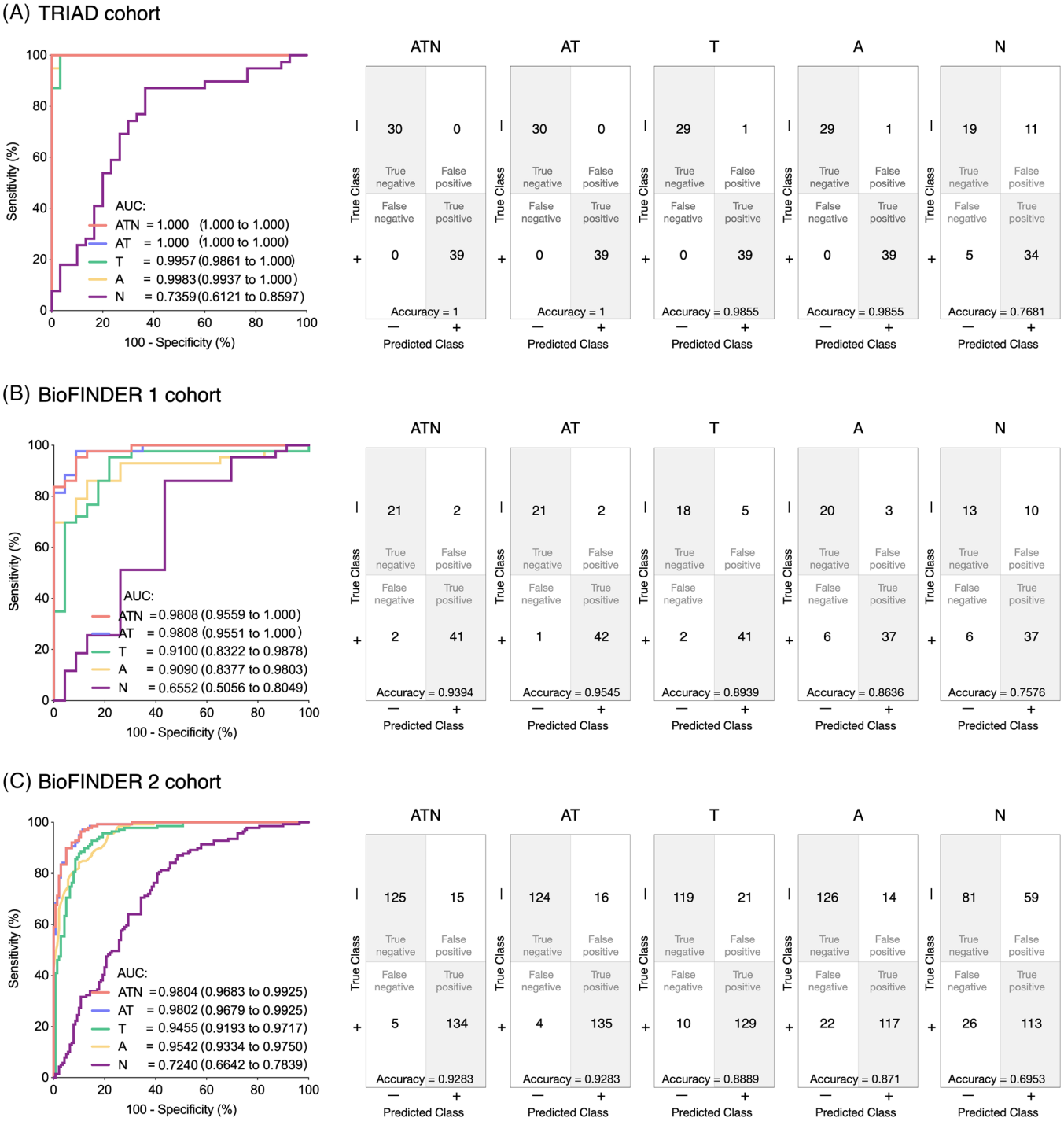

FIGURE 3 Aβ PET and tau PET alone have similar diagnostic performance to complete ATN biomarker classification for distinguishing AD dementia from non-AD neurodegenerative diseases. Plots from ROC analyses illustrating diagnostic performance of A/T/N as well as individual biomarkers and biomarker combinations for distinguishing individuals with AD dementia from individuals with non-AD neurodegenerative disorders. Boxes illustrate the confusion matrices with the accuracy (predicted vs true class) of each biomarker or biomarker combination. In all three cohorts (A-C), the combination of AT, as well as T in isolation and A in isolation performed with similar accuracy to the complete A/TN system. Only N in isolation performed significantly worse

To conclude, our study provides evidence from three independent cohorts that Aβ or tau PET biomarkers provide similar diagnostic accuracy to the full A/T/N system for the diagnosis of AD.

ACKNOWLEDGEMENTS

We thank the funding agencies that supported this work. T.A.P. is supported by the National Institute of Health (R01AG075336 and R01AG073267) and the Alzheimer's Association (AACSF-20-648075). P.R.-N. is supported by the Canadian Institutes of Health Research (CIHR) (MOP-11-51-31, P.R.-N.), the Alzheimer's Association (NIRG-12- 92090, NIRP-12-259245, PR-N), Fonds de Recherche du Québec – Santé (FRQS; Chercheur Boursier, PR-N and 2020-VICO-279314). PCLF is supported by Alzheimer's Association (AARFD-22-923814). The BioFINDER studies were supported by the Swedish Research Council (2016-00906), the Knut and Alice Wallenberg foundation (2017-0383), the Marianne and Marcus Wallenberg foundation (2015.0125), the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Swedish Alzheimer Foundation (AF-939932), the Swedish Brain Foundation (FO2019-0326), The Parkinson foundation of Sweden (1280/20), the Skåne University Hospital Foundation (2020-O000028), Regionalt Forskningsstöd (2020-0314) and the Swedish federal government under the ALF agreement (2018-Projekt0279).

CONFLICT OF INTEREST

O.H. has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from Alzpath, Biogen, Cerveau and Roche. S.G. has served as a scientific advisor to Cerveau Technologies, Inc. A.L. is a scientific advisor to Cerveau Technologies, Inc. T.A.P., J.T., M.C., F.L., C.T., O.S., S.P., E.S., P.C.L.F., J.P.-F.S., R.S., A.L.B. and P.-R.N. declare no competing interests. Author disclosures are available in the supporting information.

ORCID

Tharick A. Pascoal https://orcid.org/0000-0001-9057-8014

REFERENCES

1. Sperling RA, Laviolette PS, O'Keefe K, et al. Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron*. 2009;63:178–188.
2. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367:795–804.
3. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12:207–216.
4. Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016;87:539–547.
5. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535–562.
6. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6: 228fs13.
7. Jack CR Jr, Wiste HJ, Therneau TM, et al. Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *JAMA*. 2019;321:2316–2325.
8. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement*. 2013;9: e-1-16.
9. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019;321:1286–1294.
10. Jie C, Treyer V, Schibli R, Tauvid MuL. The first FDA-approved PET tracer for imaging tau pathology in Alzheimer's disease. *Pharmaceuticals (Basel)*. 2021;14(2): 110.
11. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med*. 2020: 12.
12. Mattsson-Carlgren N, Leuzy A, Janelidze S, et al. The implications of different approaches to define AT(N) in Alzheimer disease. *Neurology*. 2020;94:e2233–e44.
13. Sepulcre J, Schultz AP, Sabuncu M, et al. In vivo tau, amyloid, and gray matter profiles in the aging brain. *J Neurosci*. 2016;36:7364–7374.
14. Kern S, Zetterberg H, Kern J, et al. Prevalence of preclinical Alzheimer disease: comparison of current classification systems. *Neurology*. 2018;90:e1682–e91.
15. Ossenkoppele R, Leuzy A, Cho H, et al. The impact of demographic, clinical, genetic, and imaging variables on tau PET status. *Eur J Nucl Med Mol Imaging*. 2021;48:2245–2258.
16. Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative accuracy of [18F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2018;320:1151–1162.
17. Therriault J, Benedet AL, Pascoal TA, et al. Association of apolipoprotein E epsilon4 with medial temporal tau independent of amyloid-beta. *JAMA Neurol*. 2020;77:470–479.
18. Gustavsson AM, Stomrud E, Abul-Kasim K, et al. Cerebral microbleeds and white matter hyperintensities in cognitively healthy elderly: a cross-sectional cohort study evaluating the effect of arterial stiffness. *Cerebrovasc Dis Extra*. 2015;5:41–51.
19. Leuzy A, Smith R, Ossenkoppele R, et al. Diagnostic performance of RO948 F 18 tau positron emission tomography in the differentiation of Alzheimer disease from other neurodegenerative disorders. *JAMA Neurol*. 2020;77:955–965.
20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939–944.
21. Smith R, Schain M, Nilsson C, et al. Increased basal ganglia binding of (18) F-AV-1451 in patients with progressive supranuclear palsy. *Mov Disord*. 2017;32:108–114.
22. Smith R, Scholl M, Leuzy A, et al. Head-to-head comparison of tau positron emission tomography tracers [(18)F]flortaucipir and [(18)F]RO948. *Eur J Nucl Med Mol Imaging*. 2020;47:342–354.
23. Therriault J, Benedet AL, Pascoal TA, et al. Determining amyloid-beta positivity using (18)F-AZD4694 pet imaging. *J Nucl Med*. 2021;62:247–252.
24. Pascoal TA, Therriault J, Benedet AL, et al. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. *Brain*. 2020;143:2818–2830.
25. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's disease. *Alzheimers Res Ther*. 2019;11:34.

26. Brown L, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Med*. 2001;16:101–133.
27. Jack CR Jr, Therneau TM, Weigand SD, et al. Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA Neurol*. 2019;76(10): 1174–1183.
28. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol*. 2003;62:1087–1095.
29. Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. *JAMA Neurol*. 2019;76:915–924.
30. Delmotte K, Schaeverbeke J, Poesen K, Vandenberghe R. Prognostic value of amyloid/tau/neurodegeneration (ATN) classification based on diagnostic cerebrospinal fluid samples for Alzheimer's disease. *Alzheimers Res Ther*. 2021;13:84.
31. Lowe VJ, Wiste HJ, Senjem ML, et al. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*. 2018;141:271–287.
32. La Joie R, Visani AV, Lesman-Segev OH, et al. Association of APOE4 and clinical variability in Alzheimer disease with the pattern of tau- and amyloid-PET. *Neurology*. 2021;96:e650–e61.
33. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol*. 2012;71:266–273.

SUPPORTING INFORMATION

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

How to cite this article: Pascoal TA, Leuzy A, Therriault J, et al. Discriminative accuracy of the A/T/N scheme to identify cognitive impairment due to Alzheimer's disease. *Alzheimer's Dement*. 2022;00:e12390.
https://doi.org/10.1002/dad2.12390