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RESEARCH ARTICLE

# Survey among experts on the future role of tau-PET in clinical practice and trials

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## Abstract

**BACKGROUND:** Recent advancements in Alzheimer's disease (AD) biomarker research and clinical trials prompt reflection on the value and consequently appropriate use of tau positron emission tomography (tau-PET) in the future.

**METHODS:** We conducted an online survey among dementia and PET experts worldwide to investigate the anticipated future role of tau-PET in clinical practice and trials.

**RESULTS:** Two hundred sixty-eight dementia experts, comprising 143 clinicians and 121 researchers, covering six continents participated. The vast majority (90%) fostered a positive attitude toward the added value of tau-PET in clinical practice, particularly for staging, diagnosing, monitoring, and prognostication in a cognitively impaired memory clinic population. Experts anticipated an important role for tau-PET for participant selection (76%–100%) and measuring endpoints (75%–97%), in both anti-amyloid and anti-tau drug trials.

**DISCUSSION:** Our global survey study shows that dementia experts envision an important role for tau-PET in the future, both in clinical practice and in drug trials, beyond current guidelines and practices.

KEYWORDS
Alzheimer's disease, positron emission tomography, tau, trials

## Highlights

- Dementia experts envision an important role for tau-PET in the future.
- Experts indicate that a tau-PET scan could influence patient management.
- Experts anticipate the utility of tau-PET for participant selection and endpoints in drug trials.
- There is a gap between the anticipated usefulness of tau-PET and current clinical practices.

## 1 | BACKGROUND

Alzheimer's disease (AD) is pathologically characterized by the accumulation of amyloid-$\beta$ into plaques and of tau proteins into neurofibrillary tangles.[1] The AT(N) biomarker classification scheme identifies three biomarker categories: amyloid-$\beta$, tau, and neurodegeneration. Tau biomarkers include quantification of insoluble neurofibrillary tangles using positron emission tomography (PET), as well as soluble phosphorylated tau (p-tau) in cerebrospinal fluid (CSF) and plasma.[2] In the 2024 revised diagnostic criteria by the Alzheimer's Association Workgroup, tau PET (tau-PET) is proposed as a core 2 biomarker to stage biological disease severity, provide information on prognosis, and on the likelihood that AD is contributing to symptoms.[3]

Tau pathology is spatially and temporally tightly linked to neurodegeneration and the manifestation of clinical symptoms.[4–10] With tau-PET, the burden, and localization of AD-like tau pathology can be quantified and visualized in vivo.[5,11–20] The most widely used tau-PET tracers (i.e., [$^{18}$F]flortaucipir, [$^{18}$F]MK6240, [$^{18}$F]RO948, and [$^{18}$F]PI2620) show specific binding to the 3R/4R isoforms of the tau protein that are characteristic of AD.[18–21] These common tau-PET tracers have a lower affinity to 3R and 4R tau isoforms, observed in primary tauopathies and other neurodegenerative diseases, which enhances its diagnostic specificity.[14,17,20–23] Indeed, tau-PET shows excellent diagnostic performance for distinguishing AD versus other neurodegenerative disorders (specificity ~90%),[24–27] which is superior compared to other currently available biomarkers.[24,25,27–30] While soluble p-tau biomarkers also reflect AD-specific tau pathology, they appear to measure distinct neuropathological processes related to early alterations in tau metabolism, temporally much closer to amyloid abnormality.[31–34] Recently, the United States Food and Drug Administration (FDA) has approved the clinical use of the [$^{18}$F]flortaucipir (Tauvid) PET tracer in cognitively impaired patients assessed for AD.[12,35] And finally, in 2024, appropriate use criteria for tau-PET have been developed by the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup.[36]

Nonetheless, broad clinical implementation of tau-PET imaging is challenging due to high costs and limited availability. Moreover, the limited sensitivity of tau-PET for the detection of early tau pathology (Braak stages I–IV)[12–14] may have implications regarding which individuals qualify for an examination with tau-PET. Also, all tau-PET tracers are characterized by various sources of off-target binding, for example, to neuromelanin, monoamine oxidase B, and microhemorrhages. However, these off-target binding patterns usually do not interfere with uptake patterns of AD-specific tau pathology.[37] Currently, a common quantitative approach, cfr. the Centiloid scale for amyloid-PET,[38] is lacking for tau-PET. Efforts are ongoing to harmonize common tau-PET tracers into a universal quantitative scaling method[39,40] and to validate various visual read methods.

Recently, the advent of disease-modifying treatments for AD has urged the importance of an accurate biomarker-assisted diagnosis[37] and better prediction of clinical outcomes.[10] Questions remain regarding the appropriate use of tau-PET in clinical settings,[41] also taking the emergence of high-performing plasma p-tau assays into consideration. Moreover, advancements in therapeutical trials have prompted critical reflection on the use of tau-PET for participant inclusion criteria and measuring study endpoints. In this study, we investigate opinions of global dementia experts, in view of the future role of tau-PET in clinical practice and trials. Consequently, we aim to identify gaps between experts' perspectives and current practices and guidelines, and differences in opinions between clinicians and researchers.

**RESEARCH IN CONTEXT**

1. **Systematic review**: Extensive literature has demonstrated the favorable properties of tau-PET for clinical purposes (e.g., differential diagnosis and prognostication) and drug trials. However, some questions remain for tau-PET to be meaningfully implemented in clinical and drug development settings. This study collected expert opinions on the envisioned future role of tau-PET.
2. **Interpretation**: Findings from our global survey study suggest that dementia experts foresee a valuable role for tau-PET both in clinical practice and drug development trials.
3. **Future directions**: We identified a gap between the anticipated usefulness of tau-PET and current practices. Therefore, prospective studies designed to further investigate the validity and utility of tau-PET are needed to support the development of guidelines for the appropriate use of tau-PET.

## 2 | METHODS

### 2.1 | Population and recruitment

Individuals were eligible to participate in this survey study if they had experience in the field of dementia, with or without experience in PET imaging. We aimed to reflect the opinions of professionals globally, as these are expected to be subject to local practices and the availability of tau-PET. To that end, recruitment for study participants occurred on social media platforms (X, LinkedIn), through international professional networks, and attendees at the Alzheimer's Association International Conference and the European Association of Nuclear Medicine Congress in 2023, were encouraged to contribute.

### 2.2 | Survey

Study participants filled out an online survey, enquiring about expert opinions on the future role of tau-PET (see Supplementary Materials). The survey was created in the eCastor electronic data capture

system. Questions were formulated by M.R.V., R.O., and E.vdG. The survey incorporated 34–36 questions, of which 3–5 were open questions (2 questions were follow-up questions depending on the previous answer), and all others were multiple choice. They encompassed clinical as well as trial related topics and were grouped into five categories: "Demographics", "Tau-PET in clinical practice", "Tau-PET in drug development and trials", "Tau-PET classification", and "Clinical cases". Respondents were categorized as clinician if they performed clinical work, independent of whether they also contributed to research. Respondents categorized as researchers were not involved in clinical work. Completing the survey took around 10 min.

### 2.3 | Ethics

This survey study is in accordance with the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects 2013, and has been reviewed by the Medical Ethics Committee from the Amsterdam UMC (Institutional Review Board [IRB] number 2023.0376). After an individual expressed their interest on a website, an online survey was sent to their e-mail address. Informed consent was obtained from all respondents before the survey. The handling of data was in agreement with the European Union (EU) General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Respondent's privacy and confidentiality were respected throughout the study. Respondents had the option to either fill out the survey anonymously or leave their full name and be mentioned in the acknowledgments of this article.

### 2.4 | Statistics

All analyses were performed in R version 4.2.1 and R Studio. Surveys with more than 50% of the questions completed were included in the analyses. For checkbox and multiple-choice questions proportions were calculated and compared between clinicians and researchers using Fisher's exact test or Pearson's chi-squared test. Results of questions on a 5-point Likert scale (1 = "strongly disagree"; 2 = "disagree"; 3 = "neither agree nor disagree", 4 = "agree"; 5 = "strongly agree") were expressed in medians with interquartile ranges. These were compared between clinicians and researchers utilizing the Mann–Whitney U test. For the overall group and relevant subgroups, summary mean scores were calculated and compared using an independent samples *t*-test. If, hypothetically, an individual responded "Neither agree nor disagree" (score = 3) to every Likert scale question ($n = 8$), a summary score of 24 would be reached. Consequently, a score > 24 was considered a positive attitude toward the future role of tau-PET. For the calculation of summary scores, missing scores in Likert scale questions were recoded as a neutral score 3. Proportions with a positive attitude were compared between clinicians and researchers using Pearsons' chi-squared test.

## 3 | RESULTS

### 3.1 | Respondents

The survey was launched online on June 8th, 2023, and closed on October 6th, 2023. We included 268 respondents, comprising 143 self-reported clinicians and 121 self-reported researchers (Figure 1, Table 1, and Table S1). Four individuals had professional duties other than clinical or research-related work. Experts from The United States of America were most represented with 27.6%, followed by The Netherlands (10.5%), Sweden (10.5%), Canada (6.7%), Germany (4.9%), Spain (4.9%), Brazil (4.5%), United Kingdom (4.1%), Italy (3.7%), Switzerland (3.7%), Belgium (3.4%), Argentina (3.0%), France (2.6%), Australia (1.5%), Denmark (1.5%), South Korea (1.5%) and China, Finland, Chile, Colombia, Costa Rica, Cuba, Democratic Republic of the Congo, Israel, Norway, Peru, Portugal, Singapore, Uruguay (< 1%). Overall, the sample reasonably represented demographical and professional diversity. Compared to researchers, clinicians were more often from the European or South American continent, more often specialized in neurology or neuropsychology, and had more years of professional experience.

### 3.2 | General view on the importance of tau pathology

First, we enquired opinions toward tau pathology in AD in general. The majority of respondents stated that in AD neocortical tau aggregation is closely associated with neurodegenerative processes (91.0%), strongly correlated with cognitive decline (90.3%), and a central event in the pathogenesis of AD (84.0%). More than half of respondents indicated that it is secondary to the accumulation of amyloid-$\beta$ (53.0%). Most respondents indicated that tau pathology in AD is not primarily driven by amyloid-$\beta$ independent pathways (85.1%) or that it is a meta-phenomenon in AD (93.0%). This question was answered by all participants ($n = 268$).

### 3.3 | Value of tau-PET in clinical practice

Overall, 89.9% of respondents fostered a positive attitude (mean summary score 30.2) toward the added value of tau-PET, with no difference present between the views of clinicians (88.1%) versus researchers (91.7%, $p = 0.44$). In clinical practice, most experts indicated that tau-PET is valuable for pathophysiological staging (79.7%), identifying tau aggregation patterns in suspected atypical AD (76.7%), monitoring disease progression (75.6%), predicting future cognitive decline (74.4%), and differentiating AD from non-AD pathologies (70.7%) (Figure 2A, Table S2). A smaller proportion considered tau-PET valuable for early detection of AD (42.5%). Compared to clinicians, researchers envisioned greater value in the role of tau-PET for predicting cognition (67 .8% vs. 83.2% resp., $p = 0.004$). Nine individuals

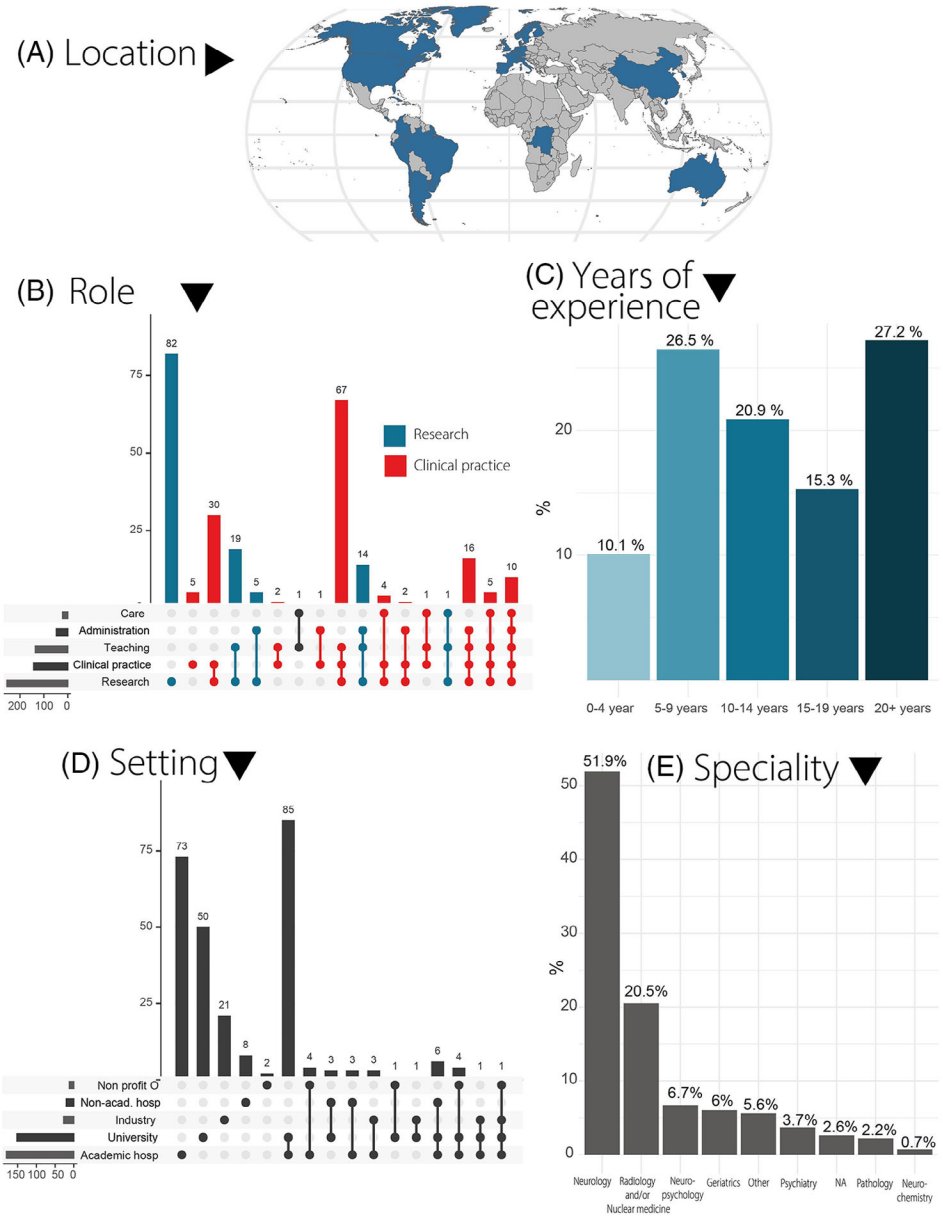


**FIGURE 1** Respondent demographics. (A) Map displaying respondents' locations by country. (B) Upset plot illustrating the roles and tasks of the respondents: horizontal bars represent the frequency of each activity, while vertical bars show the frequency of task combinations. Colors differentiate between clinicians and researchers. (C) Bar graph showing the relative frequency of respondents by years of experience. (D) Upset plot summarizing the work setting of each respondent. (E) Bar plot showing the main professional specialty fields of the respondents. academic hosp, academic hospital; non-acad. hosp, non-academic hospital; Non profit O, non-profit organization.

(3.4%), of which eight clinicians, responded that there is no place for tau-PET in clinical settings.

### 3.3.1 | Patient population

Respondents considered tau-PET to be most valuable for clinical use in the prodromal stage (90.7%), followed by the dementia stage (48.1%) and preclinical stage (37.1%, Table S3). Two clinicians and two researchers (1.7%) indicated that tau-PET is not useful to them in any of these clinical stages.

### 3.3.2 | Differential diagnosis

Clinicians and researchers largely agreed that tau-PET is a helpful tool for discriminating symptomatic AD from behavioral variant frontotemporal dementia (68.1%), vascular dementia (61.7%), and suspected corticobasal degeneration (60.0%) (Figure 2B, Table S4). Over half of respondents indicated that tau-PET can support in discriminating AD from limbic age-related TDP-43 encephalopathy (LATE, 56.6%), progressive supranuclear palsy (57.0%), semantic variant primary progressive aphasia (55.7%), non-fluent variant primary progressive aphasia (53.6%), Parkinson's disease (53.6%), and Lewy body dementia

**TABLE 1** Summary of respondent demographics.

| Characteristics | Overall N = 268* | Clinicians N = 143* | Researchers N = 121* | Others N = 4* | p-value† |
|---|---|---|---|---|---|
| **Age** | | | | | 0.003 |
| < 35 | 68 (25.4%) | 23 (16.1%) | 43 (35.5%) | 2 (50.0%) | |
| 35 to 44 yo | 88 (32.8%) | 53 (37.1%) | 35 (28.9%) | 0 (0.0%) | |
| 45 to 54 yo | 64 (23.9%) | 37 (25.9%) | 26 (21.5%) | 1 (25.0%) | |
| 55 to 64 yo | 30 (11.2%) | 21 (14.7%) | 8 (6.6%) | 1 (25.0%) | |
| > 65 | 18 (6.7%) | 9 (6.3%) | 9 (7.4%) | 0 (0.0%) | |
| **Gender** | | | | | 0.10 |
| Female | 102 (38.1%) | 47 (32.9%) | 53 (43.8%) | 2 (50.0%) | |
| Male | 165 (61.6%) | 95 (66.4%) | 68 (56.2%) | 2 (50.0%) | |
| Prefer not to say | 1 (0.4%) | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | |
| **Continent** | | | | | < 0.001 |
| Africa | 1 (0.4%) | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | |
| Asia | 8 (3.0%) | 7 (4.9%) | 1 (0.8%) | 0 (0.0%) | |
| Oceania | 4 (1.5%) | 3 (2.1%) | 1 (0.8%) | 0 (0.0%) | |
| Europe | 137 (51.1%) | 81 (56.6%) | 54 (44.6%) | 2 (50.0%) | |
| North America | 92 (34.3%) | 31 (21.7%) | 61 (50.4%) | 0 (0.0%) | |
| South America | 26 (9.7%) | 20 (14.0%) | 4 (3.3%) | 2 (50.0%) | |
| **Field of specialty** | | | | | 0.021 |
| Neurology or neuropsychology | 157 (58.6%) | 95 (66.4%) | 60 (49.6%) | 2 (50.0%) | |
| Radiology and/or nuclear medicine | 55 (20.5%) | 24 (16.8%) | 30 (24.8%) | 1 (25.0%) | |
| Other specialty | 56 (20.9%) | 24 (16.8%) | 31 (25.6%) | 1 (25.0%) | |
| **Experience in dementia field** | | | | | 0.021 |
| 0–4 years | 27 (10.1%) | 9 (6.3%) | 18 (14.9%) | 0 (0.0%) | |
| 5–9 years | 71 (26.5%) | 35 (24.5%) | 33 (27.3%) | 3 (75.0%) | |
| 10–14 years | 56 (20.9%) | 26 (18.2%) | 30 (24.8%) | 0 (0.0%) | |
| 15–19 years | 41 (15.3%) | 25 (17.5%) | 16 (13.2%) | 0 (0.0%) | |
| 20 + years | 73 (27.2%) | 48 (33.6%) | 24 (19.8%) | 1 (25.0%) | |

*Note*: Respondents are grouped as "Others" if they reported not to be involved in either clinical or research related work.
*n (%).
†Fisher's exact test; Pearson's chi-squared test for comparison between clinicians and researchers.

(53.2%). The majority of clinicians and researchers agreed that tau-PET is not helpful to discriminate AD from primary age-related tauopathy (PART, 71.9%). Eleven individuals (4.7%) indicated that tau-PET is of no assistance when discriminating AD from any of the aforementioned diseases.

We also presented three clinical case vignettes (Figure 3) and asked whether in current clinical practice respondents would request a tau-PET scan. In the first case, an 80-year-old male patient with a typical amnestic-predominant AD presentation and amyloid positivity in CSF, only one-quarter (57/227) of respondents would request a tau-PET scan (clinicians 24.5% vs. researchers 26.4%, $p = 0.70$). In the second case, a 55-year-old female patient presenting with behavioral symptoms and an abnormal amyloid-PET scan, most experts (77.9%, 176/226) would request a tau-PET scan (clinicians 73.4% vs. researchers 84.9%, $p = 0.04$). Finally in the third case, a 55-year-old-male patient suspected of mixed pathology including vascular and AD dementia and an abnormal amyloid-PET scan, a considerable proportion (65.4%, 144/220) would request a tau-PET scan (clinicians 61.5% vs. researchers 72.6%, $p = 0.09$).

### 3.3.3 | Clinical setting

Most respondents agreed that tau-PET will have added value on top of routine diagnostic procedures in specialized memory clinics (median score 4 corresponding to "agree" on a Likert scale 1–5 [IQR 4-5], Table S5). However, for non-academic settings, clinicians were less confident than researchers (median score 3 corresponding to "neither agree nor disagree" [2–4] vs. 3 [3–4], $p = 0.006$). Respondents agreed that, in the future, tau-PET will be of additional value on top of more cost-effective and feasible biomarkers like CSF and/or plasma p-tau (median score 4 [3–5]). In Figure 2B proportions per Likert category are shown.

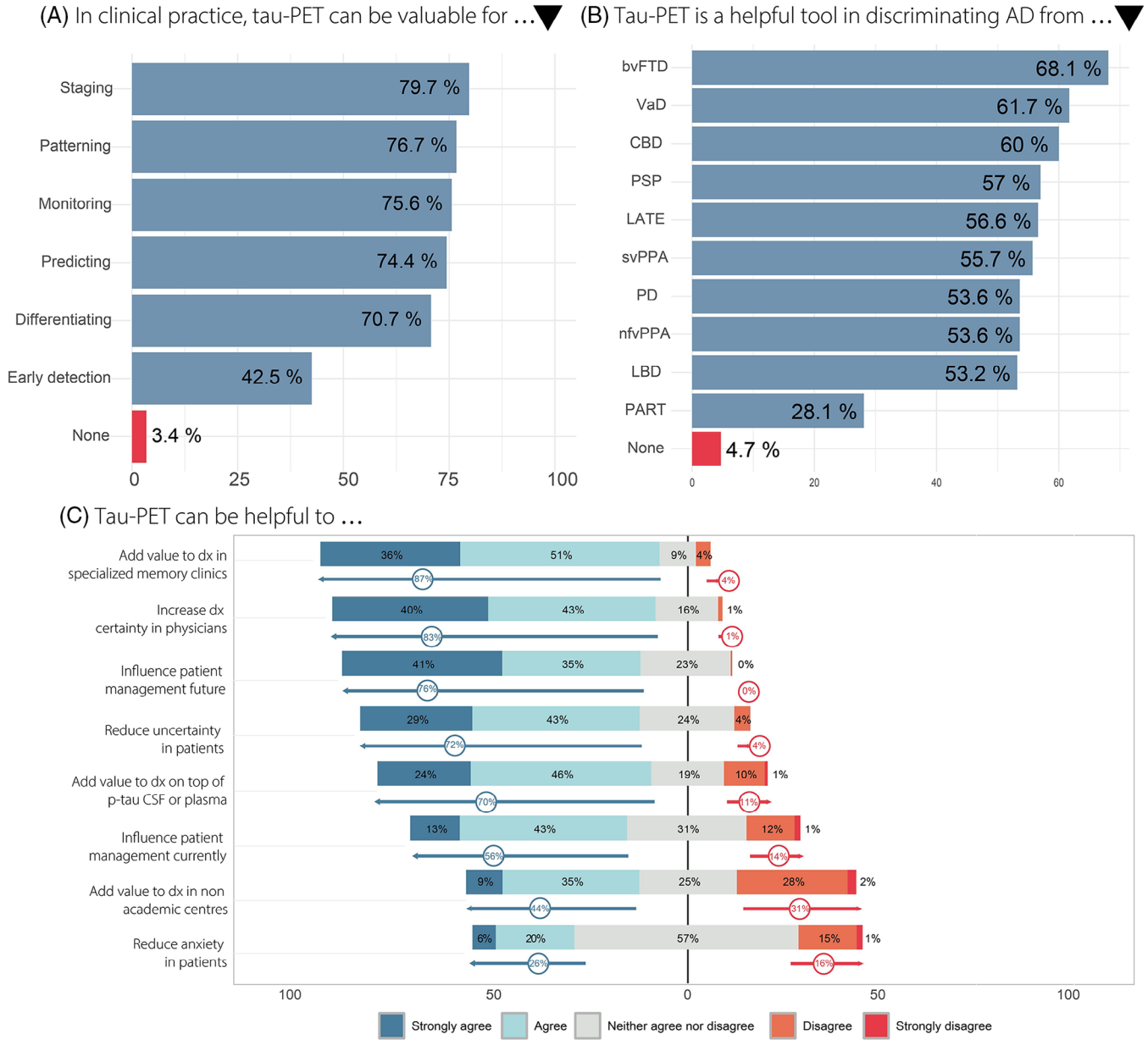


**FIGURE 2** Summary findings on the envisioned future role of tau-PET in clinical practice. (A) Envisioned value of tau-PET per clinical purpose. (B) Envisioned utility of tau-PET to differentiate between various neurodegenerative pathologies. (C) Proportions of responses of (dis)agreement on a Likert scale to eight statements regarding the added value of tau-PET. Arrows indicate the combined proportion of agreement or disagreement. AD, Alzheimer's disease; CSF, cerebrospinal fluid; dx, diagnosis/diagnostic; p-tau, phosphorylated tau; tau-PET, tau positron emission tomography.

### 3.3.4 | Clinical impact

While respondents agreed that tau-PET can improve the diagnostic certainty of physicians (median score 4 [4–5]) and reduce uncertainty in patients (median score 4 [4–5]), reduction of anxiety in patients was deemed less certain (median score 3 [3–4], Table S5). Experts were in agreement that tau-PET can influence patient management, currently (median score 4 [3–4]), and especially when effective disease modifying therapies are/become available (median score 5 corresponding to "strongly agree" [4–5]). In Figure 2B, proportions per Likert category are shown. While 96.8% (211/218) of respondents stated that a physician should know the tau-PET status of their patient before initiating disease-modifying treatment targeting tau, a smaller yet substantial proportion of 62.7% (138/220) responded that the tau-PET status should be determined before amyloid-$\beta$ treatment.

### 3.3.5 | TW.M.vdF.au-PET tracer of choice in the clinic

Most experts ($n$ = 182, 67.9%) did not express a preference for a particular tau-PET tracer to differentiate AD dementia from

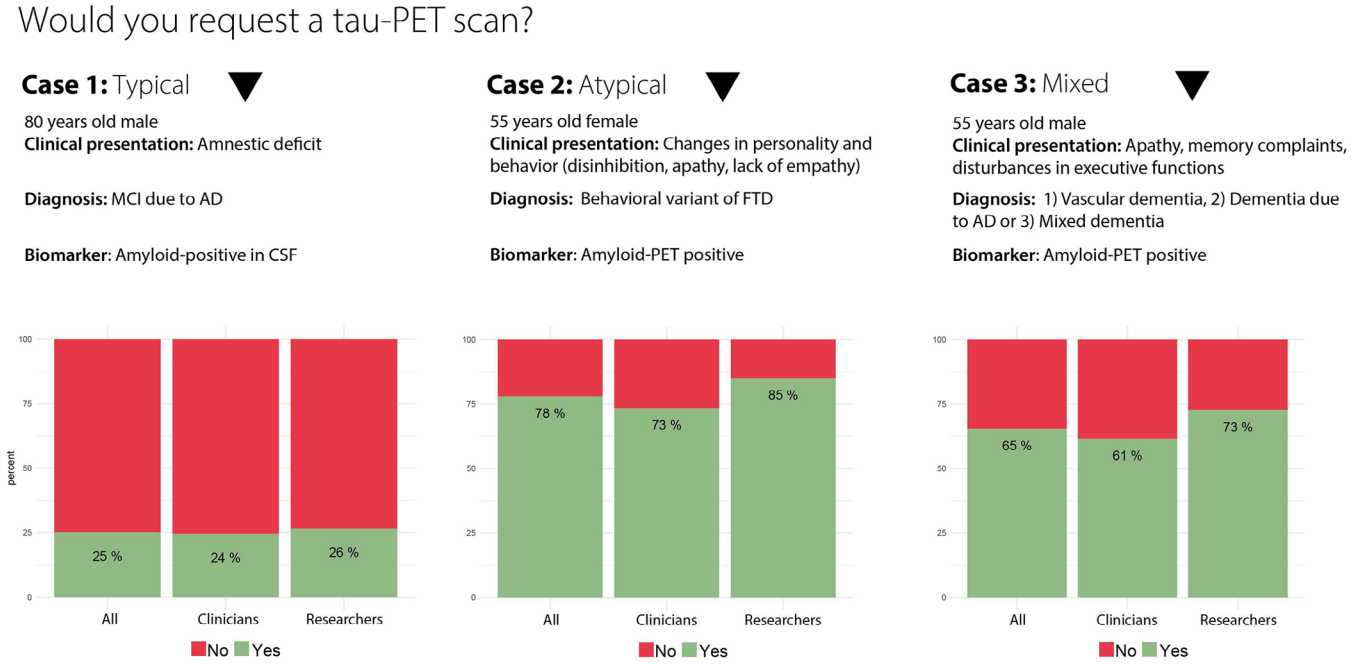


**FIGURE 3** Responses to three clinical case vignettes. Proportions of respondents who would request a tau-PET scan in a typical AD patient (case 1), a patient with an atypical presentation (case 2), and a patient with suspected mixed pathology (case 3). AD, Alzheimer's disease; amyloid-PET, amyloid positron emission tomography; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; FTD, frontotemporal dementia; tau-PET, tau positron emission tomography.

other neurodegenerative disorders in the clinic. Some indicated a preference for [$^{18}$F]MK6240 (n = 43, 16.0%), [$^{18}$F]flortaucipir (*n* = 22, 8.2%), [$^{18}$F]PI2620 (*n* = 11, 4.1%), [$^{18}$F]RO948 (*n* = 4, 1.5%), [$^{18}$F]GTP1 (*n* = 1, < 1%), and [$^{18}$F]PM-PBB3 (*n* = 1, < 1%). Four individuals valued two of the previously mentioned tracers equally.

### 3.3.6 | Tau-PET assessment in clinic

According to the respondents, in clinical practice tau-PET scans should be assessed using a visual read method in combination with a quantitative measure (81.0%, 209/258). A smaller proportion (11.6%, 30/258) preferred assessment with only a quantitative measure, for example, based on a SUVR cutoff. Only 7.4% (19/258) opted for a purely visual read method.

## 3.4 | Value of tau-PET in therapeutic trials

### 3.4.1 | Purpose of tau-PET in trials

We asked whether tau-PET would be useful for participant selection and measuring endpoints in drug trials targeting a variety of biological targets.[42,43] Respondents stated that tau-PET can be used for participant selection in anti-tau (99.6%) and anti-amyloid trials (76.1%) and were less confident regarding other drug classes, such as inflammation and immunity (40.0%), synaptic plasticity and neuroprotection (38.4%), proteostasis and proteinopathies (32.2%), metabolism and bioenergetics (25.1%), neurotransmitter receptors (20.8%), epigenetic (18.4%), oxidative stress (18.0%), vasculature (16.5%), and neurogenesis (15.7%) (Figure 4A, Table S6). More clinicians than researchers indicated a role for tau-PET to aid participant selection in proteostasis and proteinopathy drug trials (36.8% vs. 27.0%, $p = 0.01$). Similarly, experts agreed that tau-PET can be useful to measure endpoints in anti-tau (97.2%) and anti-amyloid trials (75.0%) and less so for other drug classes, such as inflammation and immunity (48.0%), synaptic plasticity and neuroprotection (34.3%), proteostasis and proteinopathies (30.2%), metabolism and bioenergetics (23.8%), oxidative stress (22.6%), epigenetic (21.4%), neurotransmitter receptors (18.1%), neurogenesis (16.5%), and vasculature (15.3%) (Figure 4A, Table S7).

When focusing on anti-amyloid trials in particular, experts indicated a role for tau-PET for participant selection (79.2%) and monitoring (80.4%), but less for target engagement (25.3%, Figure 4C). In anti-tau trials testing tau immunotherapies, tau aggregation inhibitors, targeting intracellular tau levels, and reversing post-translation modifications,[4] overall, an important role for tau-PET was envisioned in participant selection and monitoring (all > 85%, Figure 4B). Regarding target engagement, most respondents indicated usefulness in anti-tau trials testing tau immunotherapies (89.0%), followed by trials testing tau aggregation inhibitors (78.1%), trials targeting intracellular tau levels (66.8%), and trials reversing post-translation modifications (62.4%).

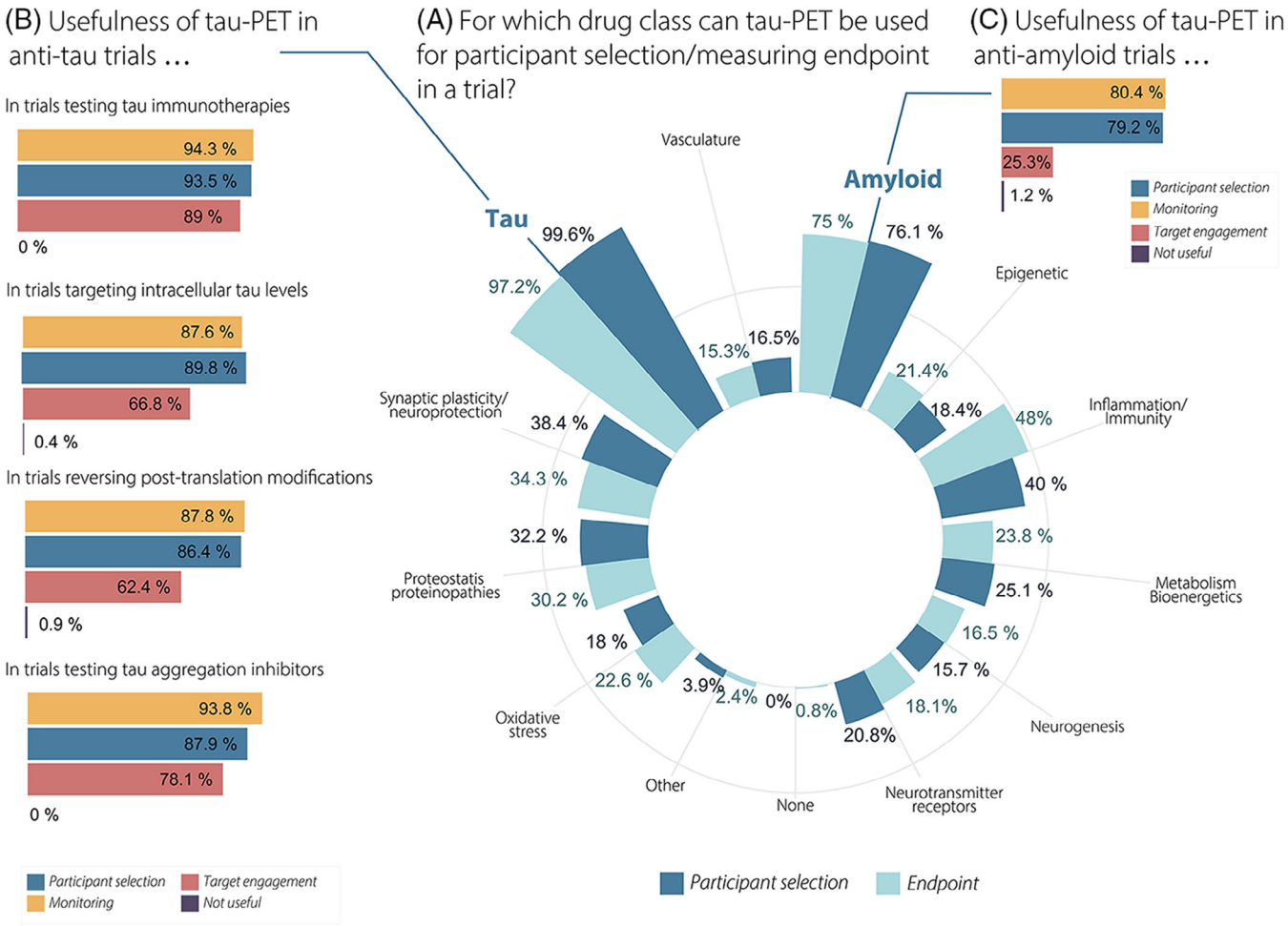


**FIGURE 4** Summary findings on the envisioned future role of tau-PET in drug trials. (A) Circular bar plot showing proportions of respondents envisioning a role for tau-PET for participant selection and measuring endpoints across different drug classes. (B) Bar plots showing proportions of respondents envisioning a role for tau-PET for participant selection, monitoring and target engagement within four anti-tau trial classes specifically. (C) Bar plots showing proportions of respondents envisioning a role for tau-PET for participant selection, monitoring and target engagement within anti-amyloid drug trials specifically. tau-PET, tau positron emission tomography.

### 3.4.2 | Tracer of choice in trials

Most respondents ($n$ = 190, 70.9%) did not express a preference for a particular tau-PET tracer for use in trials. Some indicated a preference for [$^{18}$F]MK6240 ($n$ = 46, 17.2%), [$^{18}$F]PI2620 ($n$ = 12, 4.5%), [$^{18}$F]flortaucipir ($n$ = 10, 3.7%), [$^{18}$F]RO948 ($n$ = 5, 1.9%), and [$^{18}$F]PM-PBB3 ($n$ = 1, < 1%). Four individuals valued two of the previously mentioned tracers equally.

### 3.4.3 | Tau-PET assessment in trials

Of all experts, 63.5% (165/260) indicated that in trials tau-PET scans should be assessed using a visual read method in combination with a quantitative measure. A smaller proportion of 36.5% (95/260) preferred assessment with only a quantitative measure, for example, based on a SUVR cutoff. None of the respondents opted for a purely visual read method for use in trials.

## 4 | DISCUSSION

In this survey study, 268 dementia experts from 29 different countries provided their perspectives on the future role of tau-PET in clinic and trials. The vast majority (~90%) fostered a positive attitude toward the added value of tau-PET, particularly for staging, diagnosing, monitoring, and predicting in a cognitively impaired memory clinic population. From a set of clinical cases, our findings suggest that a tau-PET scan is perceived particularly useful in patients with an atypical presentation or suspicion of mixed pathology. Furthermore, experts indicated that a tau-PET scan could influence patient management in current practice, and stated that this would further increase when effective disease-modifying treatments are/become available. Experts foresee great utility of tau-PET for participant selection and measuring endpoints, in both anti-amyloid and anti-tau drug trials.

While the majority of the viewpoints by the dementia experts are in line with the state-of-the-art literature and/or clinical practice, there are a few areas where there is a potential disconnect between

them. First, both researchers and clinicians indicated that tau-PET is most valuable in the prodromal stage of AD (90.7%). However, the literature consistently shows that the diagnostic performance of tau-PET is highest in the dementia stage, where the extent of tau-PET uptake is most pronounced. In fact, between ~33%–50% of amyloid-positive individuals with MCI have a negative tau-PET scan, whereas this is ~10%–20% at the dementia stage of AD.[12,24–27] Next, while the only currently FDA-approved method for the interpretation of tau-PET scans in clinical practice is a visual read,[12,35] experts indicated that tau-PET scans should be rated visually in combination with (non-approved) quantitative measures like a threshold approach (81%). Such an approach could resemble how [$^{18}$F]FDG PET is used in the diagnosis of neurodegenerative disorders, where a visual rating is often accompanied by an automated tool that provides additional quantitative information.[44,45] Likewise, amyloid-PET scans are increasingly assessed by visual read combined with a quantitative measure such as SUVR. The question remains whether tau-PET, given its great variability in spreading patterns, would benefit from additional quantitative information.

The outcomes of this tau-PET survey are largely in agreement with the Updated Appropriate Use Criteria for Amyloid and Tau PET by the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging.[36] For example, both the Workgroup and dementia experts agreed that a tau-PET scan can be useful in the diagnosis of patients with an atypical clinical presentation and suspicion of underlying mixed pathology. Indeed, the identification of the primary etiology causing cognitive symptoms becomes increasingly important in the context of treatment decisions. Moreover, respondents and the Workgroup agreed that eligibility for anti-amyloid drug treatment can be determined with tau-PET. This is in line with findings from the TRAILBLAZER clinical trial, where participants with low to intermediate tau-PET tracer uptake had a more favorable response to the treatment compared to the high tau-PET group, suggesting a theragnostic role for tau-PET.[46] While overall experts and the Workgroup additionally see value in tau-PET as an aid in prognostication in clinical practice, a significantly smaller proportion of clinicians (67.8%) compared to researchers (83.2%) indicated so. Large prospective studies, in both cognitively impaired and unimpaired populations, have provided evidence that tau-PET holds strong predictive value with clinical relevance.[47–49] This expert opinion may thus reflect the uncertainty of how tau-PET can be utilized in the clinic as a prognostic tool, rather than its prognostic performance in a research setting. Finally, the survey respondents foresaw an even broader window for the clinical application of tau-PET in the future, as they additionally anticipated tau-PET to be used as a tool for staging disease severity and monitoring disease progression. Nonetheless, currently, wide clinical application of tau-PET imaging is hampered by high costs and limited availability. Therefore, it will most likely be used selectively in patients benefiting most from a tau-PET scan, in addition to more accessible tests.

Notably, experts anticipated a valuable role for tau-PET for participant selection and measuring of endpoints in both anti-amyloid and anti-tau drug trials. This viewpoint is supported by the literature. For example, the aforementioned findings from the donanemab trial TRAILBLAZER suggested a putative role of tau-PET for participant selection.[46] Also, a recent phase-1 study with a tau-targeting antisense oligonucleotide therapy demonstrated proof-of-concept for tau-PET as a trial endpoint, as temporal tau-PET uptake was substantially reduced following treatment.[50] On the topic of target engagement in anti-tau trials, experts foresaw the utility of tau-PET for this purpose in tau immunotherapies (89.0%), which gradually decreased for tau aggregation inhibitors, therapies targeting intracellular tau levels, and reversing post-translation modifications, reflecting the differing mechanisms-of-action of these drug classes. In general, the experts had a positive attitude toward use of tau-PET in anti-tau (near-unanimous) and anti-amyloid (~75%) trials, which dropped substantially for other drug classes like inflammation, synaptic plasticity, and proteostasis. This has important potential ramifications for the future role of tau-PET in trials as the 2024 AD drug development pipeline[43] showed broad diversification of the drug portfolio, going well beyond anti-amyloid and anti-tau therapies.

A major strength of our survey study is that through our global outreach dementia experts from six different continents with diverse backgrounds responded. However, our recruitment strategy may constitute a participant selection bias. Moreover, experts from The Netherlands and Sweden are relatively overrepresented. In our attempt to keep the survey comprehensible and recruit a sufficient number of respondents, we were obliged to compromise on profoundness and nuances of the questions. For example, in some scenarios, it is not further specified whether alternative biomarkers, such as amyloid-PET, FDG-PET, or the complete CSF panel, were available.

In conclusion, our global survey study shows that dementia experts envision an important role for tau-PET in the future, both in clinical practice and in drugs trials, beyond current guidelines and clinical practices. Prospective clinical studies investigating the impact of tau-PET on clinical practice and identifying patients that benefit most from tau-PET are needed to support guidelines in the appropriate use of tau-PET.[41] Future findings from drug development will further direct meaningful implementation of tau-PET in trials.

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E.vdG. has received research support from NWO, ZonMw, Hersenstichting, Alzheimer Nederland, Health~Holland, and KWF. E.vdG. has performed contract research for Heuron Inc. and Roche. E.vdG. has a consultancy agreement with IXICO and Life Molecular Imaging for reading PET scans. Research programs of W.M.vdF. have been funded by ZonMW, NWO, EU-JPND, EU-IHI, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc, Novartis-NL, Life-MI, AVID, Roche BV, Fujifilm, Eisai, Combinostics. W.M.vdF. holds the Pasman chair. W.M.vdF. is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). W.M.vdF. is recipient of TAP-dementia (www.tap-dementia.nl), receiving funding from ZonMw (#10510032120003). TAP-dementia receives co-financing from Avid Radiopharmaceuticals and Amprion. WMvdF has been an invited speaker at Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, European Brain Council. W.M.vdF. is consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc, and Eisai. W.M.vdF. participated in advisory boards of Biogen MA Inc, Roche, and Eli Lilly. W.M.vdF. is member of the steering committee of EVOKE/EVOKE+ (NovoNordisk). All funding is paid to her institution. W.M.vdF. is member of the steering committee of PAVE,

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## CONSENT STATEMENT

All respondents provided 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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