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RESEARCH ARTICLE

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Acceptability and feasibility of plasma phosphorylated-tau181 in two memory services

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Abstract

Background: Plasma phosphorylated-tau181 (p-tau181) represents a novel blood-based biomarker of Alzheimer's disease pathology. We explored clinicians' experience of the utility of plasma p-tau181 in Camden and Islington Memory Services.

Methods: Patients were identified by their clinician as appropriate for p-tau181. Their p-tau181 result was plotted on a reference range graph provided to clinicians. This was discussed with the patient at diagnostic feedback appointment.

Results: Twenty-nine participants' plasma p-tau181 samples were included (mean age 74 SD 8.5, 65% female). Nine clinicians participated in the study. Eighty-six percent of clinicians found the p-tau181 result to be helpful and in 93% of cases it was clearly understandable. The p-tau181 result was useful in making the diagnosis in 44% of cases.

Conclusions: Plasma p-tau181 is a feasible test for use in memory services and acceptable to clinicians. Clinician feedback on utility in dementia diagnoses was mixed. Further work is required to provide education and training in understanding and interpreting ambiguity in biomarker results.

KEYWORDS
Alzheimer's disease, biomarker, blood, diagnosis, memory service, p-tau181

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Key points

- Results from this study show that plasma phosphorylated-tau181 (p-tau181) is feasible to incorporate in the diagnostic assessment of patients in a memory service and acceptable to clinicians.
- Clinicians require education and training in understanding and interpreting ambiguity in biomarker results.
- Further work is needed to establish the clinical utility of such a blood biomarker in UK Memory Services and to investigate the impact of p-tau181 results for Alzheimer's disease diagnoses, clinicians' diagnostic confidence and patient management.

1 | INTRODUCTION

Plasma phosphorylated-tau181 (p-tau181) is a blood-based biomarker of Alzheimer's disease (AD) pathology[1,2] While cerebrospinal fluid (CSF) biomarkers based on amyloid and tau, and amyloid-positron emission tomography (amyloid-PET) are used in specialist neurology centres, they are not routinely used in UK memory services.[3,4] Memory service clinicians currently use routine blood tests and brain imaging to exclude reversible causes of cognitive decline and to identify non-Alzheimer's disease causes of dementia such as vascular dementia.[5] A blood test, which is cheap and simple to perform could enhance the diagnostic assessment of patients with memory difficulties.[2,6]

The emergence of blood-based markers with high sensitivity and specificity for AD, comparable with that seen with CSF measures, has potential to support diagnosis within memory services.[7] The Alzheimer's Association recently published appropriate use recommendations for blood biomarkers in AD and identified a key research priority to investigate their use in specialised memory clinic settings.[6] This study was conducted at Camden and Islington Memory Services.

2 | METHODS

2.1 | Study design

We included data from 29 patient and 9 senior clinician participants. Patients were recruited prospectively from the Camden and Islington Memory Services over a 6-month period between January 2022 and July 2022.

In this study suitable patient participants were referred by their clinician after their initial assessment. Patient participants were consented to have an additional blood test appointment. The p-tau181 concentration was plotted by age on the reference range graph and sent to the referring clinician. The result was sent to the clinician prior to the patient's follow-up appointment at which clinicians provided the patient with their diagnosis. In most cases the clinician discussed their diagnosis with the patient after receiving the results of the p-tau181 results. In a minority of cases the diagnosis was communicated separately due to a delay in receiving the results of the plasma assay.

This study involved a mixed-methods design. Quantitative data for each p-tau181 result was collected from clinicians using a 5-point Likert scale scores on 3 domains. Semi-structured interviews were carried out with memory service clinicians to collect qualitative data and analysed using thematic analysis.

2.2 | Participants

Inclusion criteria for patient participants were any patient presenting with cognitive impairment to a Memory Clinic at Camden and Islington Foundation Trust where the clinician was interested to know if Alzheimer's disease pathology was involved in their diagnosis. The patient can give informed consent. Patient participant exclusion criteria comprised: patient unlikely to accept a blood test, had a previous positive biomarker test for AD through amyloid-PET/lumbar puncture, the patient or family did not want to take part in research, or they were unable to consent.

Senior clinicians were of Consultant and Senior Registrar grade. This comprised on average a range of years' experience of between 8 and 35 years. The clinician inclusion criteria included any clinician involved in the assessment and diagnosis of dementia, working within the Memory Services at Camden and Islington Foundation Trust were eligible to participate in this study. Clinician participants were excluded if their job role did not involve the diagnosis of dementia within the memory service, did not hold a senior grade position, or did not agree to participate in the study.

All participants included in this study gave written informed consent and the study was approved by the local research ethics committee.

2.3 | Plasma phosphorylated tau 181

P-tau181 plasma samples were collected in 2 × 10 mL EDTA vacutainer tubes and centrifuged within a 2-h period. Plasma samples were frozen at −80°C and stored until analysis. P-tau181 analysis was conducted per protocol using 15 × 500 µL aliquots of plasma per patient in a batch process. Plasma p-tau181

concentrations were measured by the Single molecule array (Simoa) technique using the Simoa pTau181 Advantage kit on an HD-X Analyzer (Quanterix). Identical calibration curves were used for all plates. Measured kit controls and internal controls were used to validate each run. The same machine was used for all plates to avoid variability. P-tau181 plasma level was reported in pg/mL.

Plasma pre-analytics were performed by the Dementia Research Institute (DRI) laboratory staff. The Simoa p-tau181 V2 Advantage Kit is commercially available through Quanterix. Other commercially available p-tau assays are available through Eli Lilly and ADx NeuroSciences.

2.4 | Reference range graph

Participating clinicians were provided with a graph of plasma p-tau181 ranges in AD and control subjects[8–12] (Figure 1).

2.5 | Statistical and qualitative analysis

Ninety-five percent confidence intervals were generated for plasma p-tau-181 data used in the reference range graph. All statistical analysis was undertaken in Microsoft Excel.

Quantitative data for each p-tau181 result were collected using a 5-point Likert scale scores on 3 domains: (1) comprehension of test function, (2) clarity of result interpretation and (3) usefulness in dementia diagnosis. Data were analysed and presented in frequency histograms.

Qualitative data were collected from end of study semi-structured clinician interview using the following questions:

- How easy was it for you to understand the marker and what it meant about the likely diagnosis in your patients?
- Was there a difference before and after receiving the biomarker for the diagnosis you considered likely in your patients?
- Would you want to have this information on every patient assessed or only on a proportion of patients seen in the Memory Service? If so which proportion of patients would this test be useful for?
- Are there any suggestions for how the test is made available to you or how the results are presented?

Qualitative data were analysed using thematic analysis.

2.6 | Outcome measures

Qualitative data regarding clinician's experience of the p-tau181 result for individual patients, using three domains which they rated on a 5-point Likert scale: (1) comprehension of test function, (2) clarity of result interpretation and (3) usefulness in dementia diagnosis.

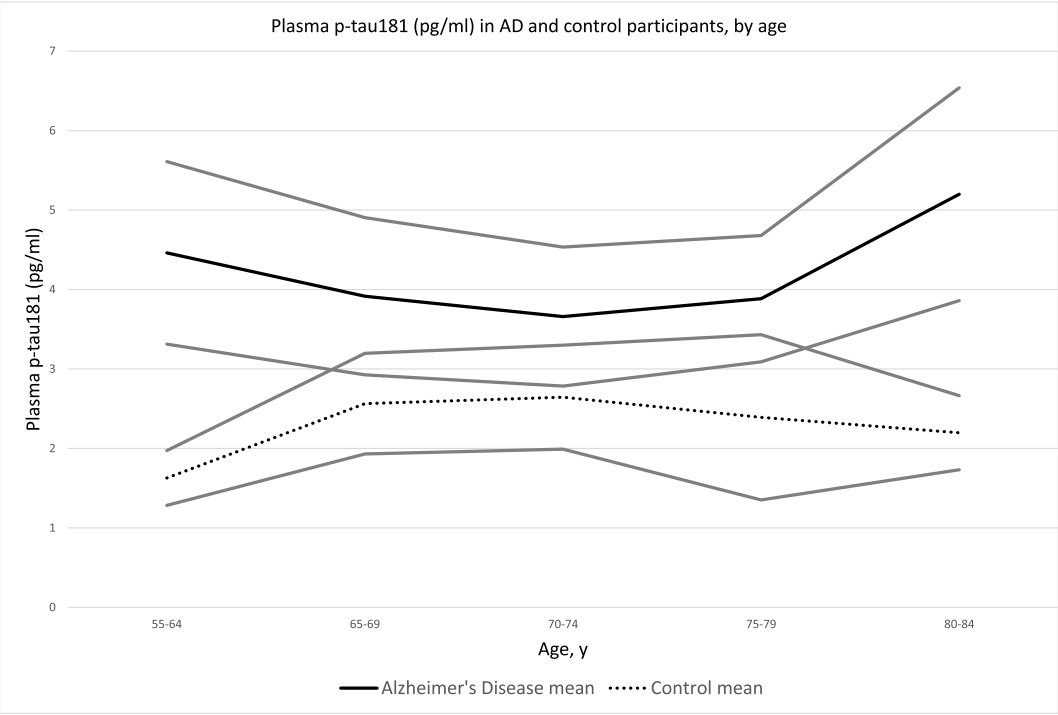

FIGURE 1 Reference range graph of concentrations of plasma phosphorylated-tau181 (p-tau181) (pg/mL) in Alzheimer's disease participants (black) and control participants (dotted) stratified by age. Data shown as mean plasma p-tau181 with 95% confidence intervals (grey).

At the end of the study, semi-qualitative interviews were conducted with clinician participants to identify themes.

3 | RESULTS

Twenty-nine patients (mean age 74 SD 8.5 years, 65% female) and 9 clinicians participated in the study (Figure 2).

There was on average a 3-month period between plasma p-tau181 sample collection and result availability. A summary of clinician's rating score per p-tau181 result is provided in Figure 3.

3.1 | Semi-structured interviews

Eight clinician participants participated in semi-qualitative interviews. Established themes included: interpreting ambiguity or conflict, using a result without established reference ranges, certainty of diagnosis and diagnostic re-appraisal.

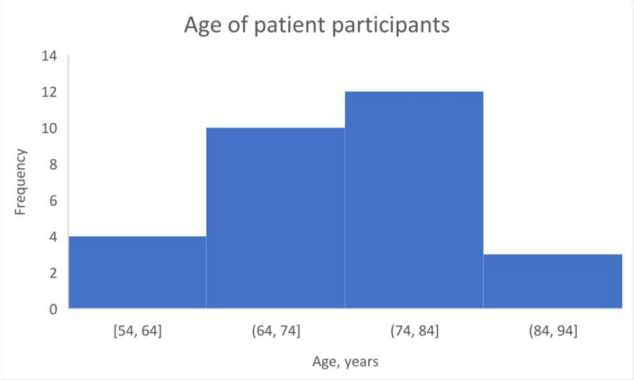

FIGURE 2 A histogram of the ages of participants, showing frequency stratified by age, with 10-year age categories.

3.1.1 | Interpretating blood biomarker results

Most clinicians reported that results were easy to understand, and they had enough information to interpret the results.

3.1.2 | Using a result without established reference ranges

A common theme was the need for comprehensive information alongside the result to aid in interpretation, with suggestion of an accompanying leaflet or informative video. '*I didn't understand it initially until it was explained. There was no validated reference range values or cut-offs which changed my expectation of its use. You also must factor in the patient's age when interpreting the result. My understanding of the result changed once I got back some of the results and I understood how better to use it clinically*'. It was suggested that simplifying the reference range graph would help patients and family members to understand the result '*Displaying the data and where patient sits on that in a more user-friendly way*'.

3.1.3 | Certainty of diagnosis

Some clinicians reported it would be useful to have P-tau181 in all patients '*I wouldn't think it was a bad thing for everyone. The more information we have the between and for some patients it will change the diagnosis which will be helpful as well as making it more certain*'. Others suggested it could be more helpful in patients where there

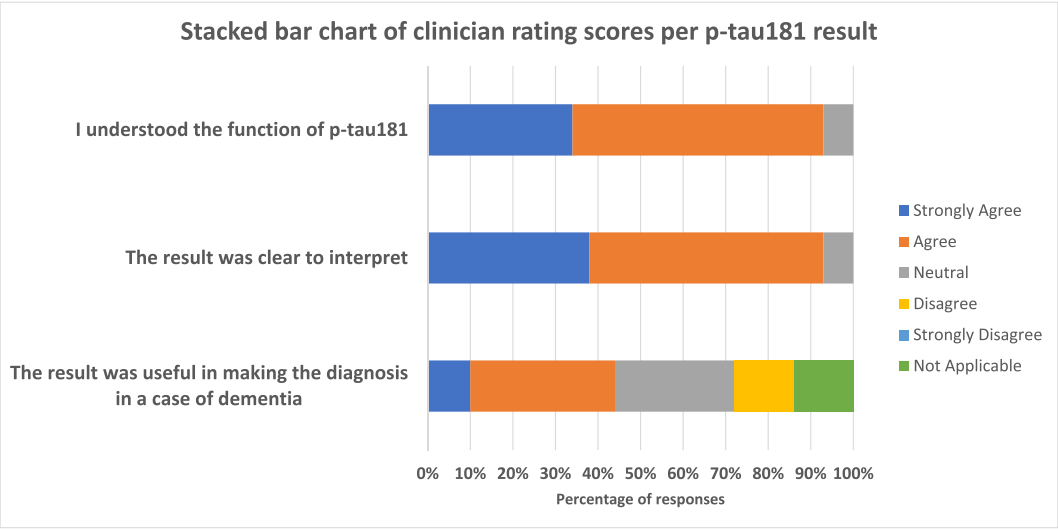

FIGURE 3 Stacked bar chart of clinician's rating score per phosphorylated-tau181 (p-tau181) result (A) I understood the function of p-tau181, (B) The result was clear to interpret (C) The result was useful in making the diagnosis in a case of dementia.

is diagnostic uncertainty, or in patients under the age of 65 years. Some clinicians found it useful when trying to establish if there was underlying AD pathology in patients presenting with mild cognitive impairment (MCI). '*I tended to refer younger patients where I wasn't sure if it was MCI or otherwise. In one case I felt clinically she didn't have AD and the biomarker supported this. It helped the patient understand*'.

3.1.4 | Interpreting ambiguity or conflict

Several clinicians reported the result increased their level of diagnostic certainty. '*The other results supported my clinical diagnosis, and it was nice to have this information and increase my certainty*' and *'it did move the needle towards dementia*'. In other cases, there was a conflict between clinicians' clinical impression and the p-tau181 result. This resulted in clinicians feeling the result held less clinical utility. '*There was one patient that it didn't impact on the diagnosis as it didn't help, it came back low but she clinically had a progressive AD*'. Several clinicians explained that, in such a scenario '*when clinical presentation conflicts with biology for example, biomarker or scan result, I would mark it down and go with the clinical presentation*'.

3.1.5 | Diagnostic re-appraisal

Two clinicians reported a reappraisal of their initial diagnosis once they received the biomarker result. '*There was case in particular I made a diagnosis of AD when I initially said MCI*'. In another patient the initial differential diagnosis was '*Depression versus dementia, also increased my needle towards dementia*'.

4 | DISCUSSION

It was feasible to use a plasma biomarker as an additional test in the diagnostic assessment of patients within two London memory services. Clinicians reported that presentation of the results was satisfactory, although simplifying the reference data to include only p-tau181 in control/non-AD participants was suggested. Clinicians found biomarker levels useful in some patients in the diagnostic assessment process. Utility of the biomarker was reduced when there was perceived conflict between the result and the clinician's clinical impression.

A limitation reported by some clinicians was the length of time in getting the plasma result back, which was restricted by the samples being analysed in a batch process.

In this study a single plasma assay, p-tau181 was used. In the future, if these blood biomarkers are utilised in memory clinics, it may be that a combination of markers are introduced. Other candidate blood biomarkers include amyloid beta42/40 ratio, neurofilament light (NfL) and Glial fibrillary acidic protein (GFAP). Future studies should address the impact of blood biomarkers on clinical decision making, particularly when patients have had multiple investigations such as neuroimaging or neuropsychological testing.

A proportion of clinicians reported difficulty in interpreting intermediate or ambiguous results. In contrast to an amyloid-PET result which is binary negative or positive, p-tau181is a continuous variable with no established cut-points and must be considered as one piece of additional information in the context of the whole clinical presentation and any other available investigations.

To date there is little published literature on the clinical utility of blood biomarkers in memory services. There is greater information regarding the clinical utility of another fluid biomarker, cerebrospinal fluid (CSF), where some comparisons can be drawn. Albeit collecting CSF biomarkers involves a lumbar puncture which is a more invasive and challenging procedure.[13–15]

When interpreting a CSF biomarker profile, a clinician may find that a typical AD profile increases their diagnostic confidence by a small percentage in favour of an AD diagnosis. For example, in a study where clinicians were given simulated clinical vignettes, an AD clinical presentation along with AD CSF results led to a significantly increased odds of an AD diagnosis, however if clinicians received borderline CSF values, they used other clinical information to reach a diagnosis.[16,17]

In a systematic review and meta-analysis of the clinical utility of CSF biomarkers in the diagnostic evaluation of cognitively impaired patients, clinicians' use of CSF biomarkers resulted in a pooled percentage change in diagnosis of 25%, an increase in diagnostic confidence of 14% and a pooled proportion of patients whose management changed of 31%.[16] This highlights that despite limitations in the data, the biomarker results still had the power to push diagnostic certainty and change management.

Only one study to date has assessed the clinical utility of a serum biomarker, neurofilament light protein in the diagnosis of dementias.[18] Having established feasibility and acceptability, further studies are needed to establish the clinical utility of a blood biomarker such as plasma p-tau181 in UK NHS Memory Services. This is of particular importance when considering the impact that disease modifying therapies may have in the future on the value of a more secure, diagnosis of AD.

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CONFLICT OF INTEREST STATEMENT

Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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