



Clinical Utility of Plasma Biomarkers of Alzheimer’s Disease (CLiPAD)

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Background & Aims

The **Clinical Utility of Plasma Biomarkers of Alzheimer’s Disease (CLiPAD)** study evaluates the real-world utility of plasma phosphorylated tau (p-tau) biomarkers for Alzheimer’s disease (AD). This study aims to determine the diagnostic accuracy of plasma p-tau by comparing it to the independent clinical diagnoses and clinical amyloid- β (A β) PET imaging. Additionally, it assesses how plasma p-tau influences treatment decisions in routine care. We will examine demographic and clinical factors that affect diagnostic concordance and analyze *longitudinal* changes in plasma p-tau to evaluate its potential in tracking disease progression. A longitudinal component of the study will monitor changes in plasma p-tau over time, providing insights into its utility for tracking disease progression and potentially identifying early markers of cognitive decline. Findings from the CLiPAD study will support the integration of plasma p-tau into clinical practice and inform the development of future care guidelines.

Methods

Study Design and Recruitment:

CLiPAD is an ongoing observational study enrolling up to **200 participants**, aged **40–90**, referred through UPMC-affiliated clinics. Eligible participants present with **objective cognitive impairment** as determined by the referring clinician.

Clinical Referral and Assessment:

Referring clinicians are asked to provide:

- A **primary etiologic diagnosis** for the cognitive impairment.
- Their **diagnostic confidence**
- **Planned clinical actions** post-test, including candidacy for **amyloid-targeting therapy**

Study Visit Procedures:

Each participant completes a study visit that includes:

- **Blood sampling**
- **Cognitive assessment** using the **Montreal Cognitive Assessment (MoCA)**
- **Informant-based questionnaires**, completed by a study partner:
 - Neuropsychiatric Inventory Questionnaire (NPI-Q)
 - Geriatric Depression Scale (GDS)
 - Alzheimer’s Disease 8-item Screener (AD8)
 - Functional Assessment Scale (FAS)

Biomarker Analysis:

Plasma p-tau assays are performed in a **CLIA-certified laboratory**:

- **Lucent Diagnostics:** p-tau 181, p-tau 217
- **ALZpath:** p-tau 217
- **Quest Diagnostics:** p-tau 181, p-tau 217, and A β 42/40 ratio
- Lumipulse p-tau217 (pending results)

Referring clinicians receive test results within **14 business days** of sample collection.

Follow-Up and Longitudinal Data Collection:

Participants are invited to return for follow-up visits at **12, 24, and 36 months** to repeat cognitive testing and blood collection. Clinicians complete a **post-test survey** to assess the impact of plasma biomarker results on clinical management. **Ongoing review of participants’ medical records** is conducted throughout the study.

Patients receiving anti-amyloid therapy who are enrolled in the study may enroll in a subgroup collecting blood samples at 1month intervals.

Current Status:

227 referrals have been received from **20 clinicians**, primarily from **Neurology** and **Geriatrics**, with additional referrals from **Family Medicine**.

Current Sample

To date, **169 participants** have been enrolled (**71.5 ± 9.58 years, 58% Female**).

At the time of referral, clinicians indicated a **suspected primary etiology** of either **Alzheimer’s disease (AD)** or **non-AD dementia (Figure 1)**, which includes categories such as **vascular, mixed, and other dementias**. Clinician confidence of their diagnostic hypothesis is also rated **1-10**.

Figure 1 summarizes the sample size for each assay.

All participants are administered the **MoCA** (19.08 ± 5.58) and **GDS** (2.52± 2.57). Informants provide information to complete the **NPI-Q** (2.85 ± 2.53), **AD8** (4.95 ± 2.45), and **FAQ** (9.15 ± 7.41). To contextualize sample depth, **Figure 3** provides sample size for each group and clinician confidence at time of referral.

N= 55 participants enrolled are receiving anti-amyloid therapy treatment (Kisunla or Leqembi), N=19 individuals completed at least 1 blood draw prior to receiving treatment. N=29 individuals who are receiving treatment are enrolled in the study subgroup to complete blood collection, cognitive assessment, and informant-based questionnaires at monthly intervals during their infusion treatment program. If or when individuals discontinue treatment, they are asked to complete blood collection and assessments at 3-month intervals.

Acknowledgement:

We sincerely thank all CLiPAD research participants and their family members for their time, commitment, and valuable contributions to this study. Their participation is essential to advancing our understanding of Alzheimer’s disease and improving care for future patients.



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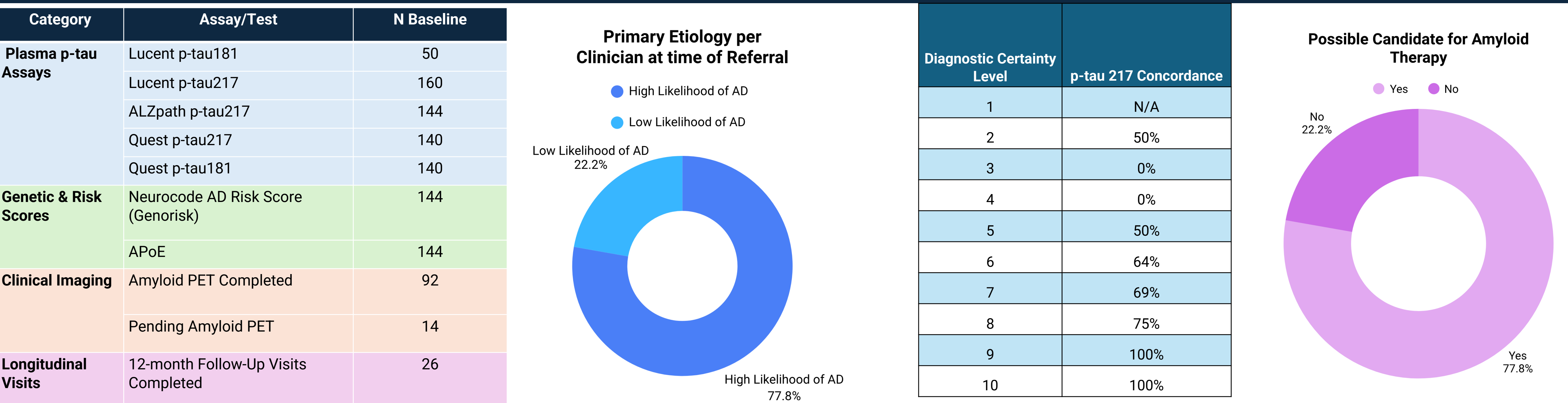
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Figure 1: CLiPAD Study Progress & Clinical Referral Information



A sample size summary is shown above. At the time of referral, clinicians designate their diagnostic hypothesis; the two designations of primary etiology are AD and non-AD. Reflected above is the distribution of primary etiology. Physicians are asked to score their confidence level in their suspected primary etiology (1-10).. Greater diagnostic certainty correlates to greater assay concordance. Clinicians are asked to determine if the patient is a possible candidate for anti-amyloid therapy. Currently, of our enrolled participants N=55 are receiving either Leqembi or Kisunla. N=29 are completing monthly blood draws

Figure 2: Clinical Plasma Assay Results

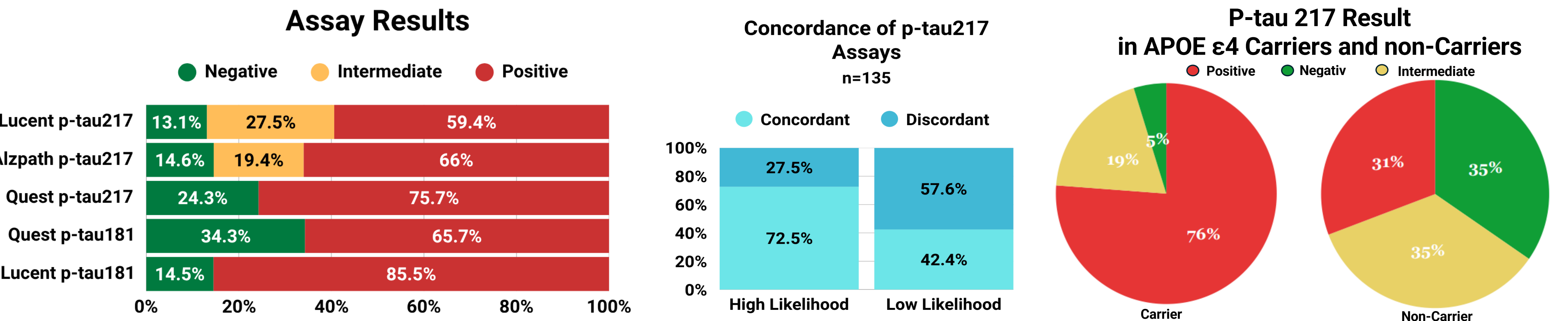
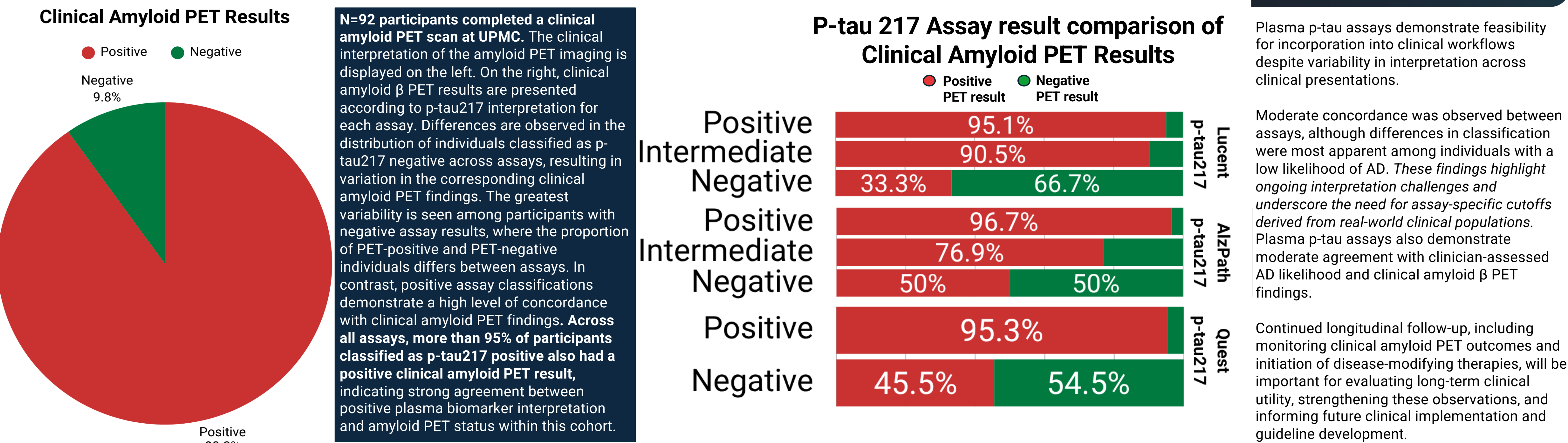


Fig 2. shows the clinical interpretation of each clinical assay, noting differences in interpretation. Quest A β 42/40 ratio interpretation differs the most from p-tau assay results. We also show p-tau 217 interpretation based on suspected primary etiology. Assay concordance for cases of high likelihood of AD is greater than low likelihood cases, though low-likelihood demonstrates considerable discordant results. Lucent -217 and Quest -217 concentrations show the largest difference between high and low likelihood of AD. APOEε4 carriers demonstrate greater portion of p-tau 217 positivity.

Figure 4: Agreement between Clinical Amyloid β and p-tau 217 Assays



Conclusion

Plasma p-tau assays demonstrate feasibility for incorporation into clinical workflows despite variability in interpretation across clinical presentations.

Moderate concordance was observed between assays, although differences in classification were most apparent among individuals with a low likelihood of AD. *These findings highlight ongoing interpretation challenges and underscore the need for assay-specific cutoffs derived from real-world clinical populations.* Plasma p-tau assays also demonstrate moderate agreement with clinician-assessed AD likelihood and clinical amyloid β PET findings.

Continued longitudinal follow-up, including monitoring clinical amyloid PET outcomes and initiation of disease-modifying therapies, will be important for evaluating long-term clinical utility, strengthening these observations, and informing future clinical implementation and guideline development.