# Title: Clinical decision points for two plasma p-tau217 laboratory developed tests in neuropathology confirmed samples

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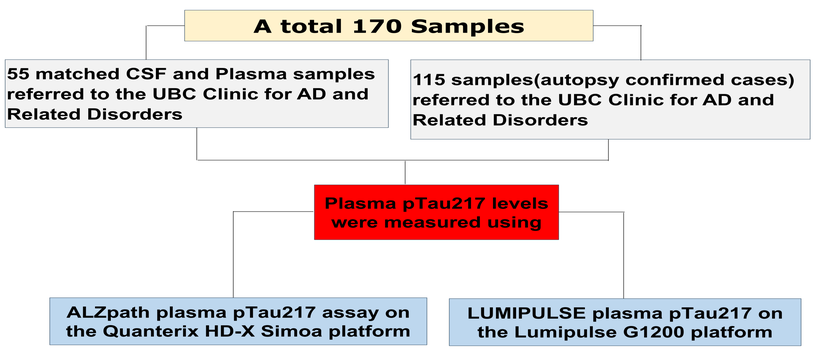
## Background

Measurement of AD biomarkers will be a key factor in determining eligibility for disease-modifying therapy in clinical practice.

Plasma p-tau217 has demonstrated high efficacy in identifying Aβ pathology and its levels change before tau-PET abnormalities, making it a feasible test for AD screening in clinical practice.[1]

Several assays including the ALZpath p-tau217 assay Fujirebio plasma p-tau217 assay have been made commercially available as a research use assay. [2] To determine the clinical decision points for plasma p-tau217 immunoassays in clinical practice, we assessed the diagnostic performance of both assays in comparison to CSF testing for Aß42/40 ratio and p-tau181, as well as postmortem neuropathological evaluation of cases who had plasma samples at diagnosis of dementia.

## Methods




CSF Aβ 42 to 40 ratio and p-tau181 levels were measured using commercially available Lumipulse G β-Amyloid 1-40, Lumipulse G β-Amyloid 1-42, and Lumipulse G p-tau181 kits (Fujirebio Europe N.V., Belgium) on the Lumipulse G1200 platform. Performance assessment of β-Amyloid 1-40, β-Amyloid 1-42, and p-tau181 was verified by Neurocode USA, Inc.

## Results

**Table 1: ALZpath plasma p-tau217 cut-offs**

**Amyloid pathology - CSF Ab 42/40 - AUC 0.95**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.34 | 90.0% | 93.4% | 92.5% | 93.9% | 90.0% |
| 0.40 | 95.0% | 84.8% | 88.7% | 96.6% | 79.2% |
| 0.63 | 95.0% | 72.7% | 81.1% | 96.0% | 67.9% |

**Tau pathology - CSF Ab p-tau181 - AUC 0.95**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.34 | 75.0% | 93.1% | 84.9% | 81.8% | 90.0% |
| 0.40 | 83.3% | 86.2% | 84.9% | 86.2% | 83.3% |
| 0.63 | 87.5% | 75.9% | 81.1% | 88.0% | 75.0% |

**Amyloid neuropathology - AUC 0.94**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.34 | 67.4% | 95.8% | 85.2% | 83.1% | 90.6% |
| 0.40 | 76.7% | 87.5% | 83.5% | 86.3% | 78.6% |
| 0.63 | 95.3% | 79.2% | 85.2% | 96.6% | 73.2% |

## Results

**Table 2: Fujirebio plasma p-tau217 cut-offs**

**Amyloid pathology - CSF Ab 42/40 - AUC 0.94**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.13 | 84.2% | 87.5% | 86.3% | 90.3% | 80.0% |
| 0.18 | 94.7% | 81.3% | 86.3% | 96.3% | 75.0% |
| 0.37 | 94.7% | 59.4% | 72.5% | 95.0% | 58.1% |

**Tau pathology - CSF Ab p-tau181 - AUC 0.94**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.13 | 82.6% | 96.4% | 90.2% | 87.1% | 95.0% |
| 0.18 | 87.0% | 85.7% | 86.3% | 88.9% | 83.3% |
| 0.37 | 95.7% | 67.9% | 80.4% | 95.0% | 71.0% |

**Amyloid neuropathology - AUC 0.90**

| Threshold | Spec. | Sens. | Acc. | PPV | NPV |
|---|---|---|---|---|---|
| 0.13 | 46.5% | 96.6% | 75.5% | 71.3% | 90.9% |
| 0.18 | 67.4% | 88.1% | 79.4% | 78.9% | 80.5% |
| 0.37 | 93.0% | 67.8% | 78.4% | 93.0% | 67.8% |

## Conclusion

The sensitivity of the ALZpath assay was higher than that of the Fujirebio assay at the lower reference value for both assays. The Fujirebio assay exhibits higher specificity for tau pathology at the upper reference value. This could be beneficial in primary care settings, where the positivity rate is expected to be lower than in specialized memory clinics.

For the ALZpath p-tau217, the upper cut-point by our study was lower than in another study (0.63 pg/mL compared to 0.92 pg/mL)[3]. This discrepancy may be due to differences in methodology in determining amyloid status or demographic differences in study cohorts. This suggests that further revaluation of the cut-points for both p-tau217 assays through prospective research studies is required before their widespread clinical implementation.

## References

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2. Mammel AE, Hsiung GYR, Mousavi A, et al. Title: Alzheimer's disease clinical decision points for two plasma p-tau217 laboratory developed tests in neuropathology confirmed samples Abbreviated. doi:10.1101/2024.07.27.24310872

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