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Clinical validation of the LucentAD p-Tau 217 assay as a CLIA laboratory developed test (LDT) for clinical use

93% Accuracy | 98% Specificity | 90% Sensitivity

Background

With the arrival of FDA-approved therapeutics for Alzheimer's disease (AD), cost-effective and widely available blood-based biomarkers are urgently needed to facilitate diagnosis of AD and ease the health system log jam associated with traditional diagnostic modalities, which include PET and lumbar puncture. p-Tau 217 has emerged as the only blood-based biomarker exhibiting the requisite sensitivity and specificity supporting an AD diagnostic use-case as an alternative to PET and cerebrospinal fluid biomarkers.[2,3]

LucentAD p-Tau 217 assay, powered by Simoa® was validated for clinical use as an LDT, as described below.

Methods

Cohort description:
We included n=497 individuals of the Amsterdam Dementia Cohort[1] with known baseline amyloid-beta status by CSF biomarker testing. Diagnostic categories ranged from subjective cognitive decline, mild cognitive impairment, and Alzheimer's dementia.

Testing and analyses:
Plasma samples were tested in duplicate in the Quanterix CLIA laboratory using the LucentAD p-Tau 217 assay. A randomized subset of the cohort (n=298) was used as a training set to establish diagnostic thresholds, and the remaining samples (n=199) were used as a validation set. A 2-cutoff approach was utilized as recommended by draft NIA-AA guidelines[2] and Brum et al.[3] The use of two cutoffs establishes a three-zone test reflecting low, intermediate, and high risk of amyloid pathology. Samples reading below the lower cutoff are unlikely to have amyloid pathology, and samples reading above the upper cutoff are likely to have amyloid pathology. Test results in the intermediate range between the lower and upper cutoffs are considered uncertain and may require referral for evaluation by other methods, including CSF biomarker testing.

Results

The distribution of LucentAD p-Tau 217 results training and validation cohorts are exhibited in Figure 1.

Figure 1

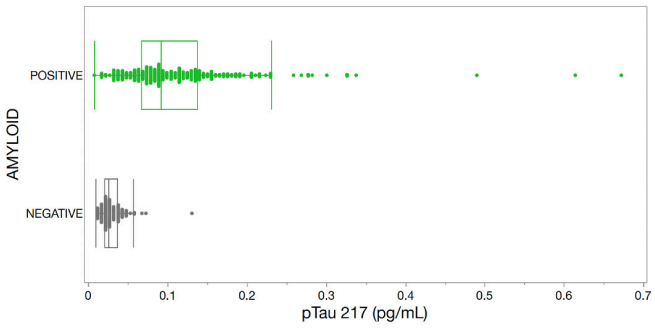

Fig. 1. *Plasma p-Tau 217 sample distributions by amyloid positivity (CSF) (n=498). All but 5 samples (0.1%) were above the lower limit of quantification of 0.006 pg/mL (not included).*

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The area under the curve of the validation cohort was 0.94, as depicted in Figure 2.

Figure 2

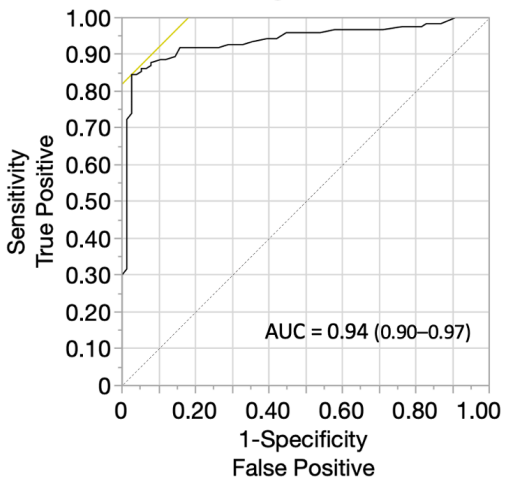

Fig. 2. *Receiver operating characteristic curve of validation cohort for LucentAD p-Tau 217 test. Area under the curve was 0.94. 95% boot strapped confidence intervals are also shown.*

With a two-cutoff approach limiting the intermediate range to less than 30%, the LucentAD p-Tau 217 test gave the performance characteristics exhibited in Table 1 below.

Table 1

Category	Performance
Sensitivity	90.0%*
Specificity	98.1%*
Accuracy (NIA-AA definition[2])	**93.1%**
AUC	94.0%
Intermediate range	27.6%**

*Excluding samples in the intermediate range.
**27.6% of the samples gave test results within this range.

The overall prevalence of amyloid positivity in the validation cohort was 61.8%.

Conclusions

The LucentAD p-Tau 217 blood test achieves an overall accuracy exceeding 90% which meets the stringent requirements set forth in most recent NIA-AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease.

The LucentAD p-Tau 217 test provides a blood-based method for accurate amyloid risk stratification of patients with cognitive concerns in memory clinic settings.

References

1. van der Flier WM, Scheltens P. Amsterdam Dementia Cohort: Performing Research to Optimize Care. J Alzheimers Dis. 2018;62(3):1091-1111.
2. NIA-AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease. Draft Oct 9, alz.org/NIA-AA.
3. Brum WS, Cullen NC, Janelidze S, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. Nat Aging. 2023;3(9):1079-1090.

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