With Plasma p-tau217 Clocks Predicting Onset of Symptomatic Alzheimer's Disease

Researchers developed and validated plasma biomarker-based clock models using plasma %p-tau217 to estimate when cognitively unimpaired individuals with evidence of underlying Alzheimer's pathology may progress to symptomatic Alzheimer's disease (AD). The resulting mathematical models forecast symptom onset across two independent cohorts, with a median absolute error of just over 3 years, offering a probabilistic framework to estimate not only whether but also when symptoms may emerge.

Study

The study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and analyzed longitudinal data from two independent cohorts: The Knight Alzheimer's Disease Research Center (Knight ADRC; n = 258) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; n = 345). Participants were cognitively unimpaired at baseline but had available plasma %p-tau217 measurements. Both cohorts were predominantly composed of non-Hispanic White individuals, potentially limiting generalizability.

The biomarker %p-tau217 represents the ratio of phosphorylated to non-phosphorylated tau at position 217. Plasma levels were quantified using high-throughput liquid chromatography–mass spectrometry (LC-MS). Blood samples were collected multiple times over a median interval of approximately 6.5 years in Knight ADRC and 4.5 years in ADNI, enabling modeling of biomarker trajectories over time.

Findings

Researchers developed two mathematical clock models, Temporal Integration of Rate Accumulation (TIRA) and Sampled Iterative Local Approximation (SILA), to map longitudinal increases in plasma %p-tau217. These models estimated the age at which an individual's biomarker would cross a threshold considered positive for Alzheimer's pathology.

The predicted age of biomarker positivity was then used to estimate the projected onset of symptomatic AD. Model predictions were compared with participant-specific clinical assessments, including Clinical Dementia Rating (CDR) staging and adjudicated diagnoses, to evaluate temporal accuracy.

The clock models demonstrated consistent disease progression trajectories across both cohorts. Adjusted R2 values ranged from 0.337 to 0.612, indicating moderate explanatory strength. The models achieved median absolute errors of 3.0-3.7 years when predicting symptom onset.

This level of predictive precision suggests plasma-based biomarker clocks can approximate the timeline of Alzheimer's progression within a clinically meaningful margin, although not with deterministic certainty. The models provide probabilistic rather than exact predictions for individuals.

Chronological age significantly influenced the duration between biomarker positivity and clinical symptom onset. Older individuals had shorter intervals between plasma %p-tau217 positivity and cognitive decline than younger individuals.

Participants who became biomarker-positive at age 60 had a median of 20.5 years before developing symptomatic AD. Those who reached positivity at age 80 had a median symptom-free interval of 11.4 years. These findings may reflect age-related co-pathologies or cumulative neurodegenerative processes that accelerate clinical expression in older adults.

The study evaluated whether similar clock modeling approaches could be applied across different immunoassay platforms. Assays examined included Fujirebio Lumipulse p-tau217/Aβ42, C2N Diagnostics PrecivityAD2 p-tau217, Janssen LucentAD Quanterix p-tau217, ALZpath Quanterix p-tau217, and Fujirebio Lumipulse p-tau217.

Clock modeling was feasible across platforms, but performance varied depending on assay characteristics and analytical methods. Concordance was not equivalent across assays, and differences in analytical sensitivity and calibration influenced predictive performance.

Conclusion

This study demonstrates that plasma %p-tau217-based biological clock models can estimate the timeline of Alzheimer's symptom onset with a median error of approximately three to four years. Although this margin limits immediate use for definitive individual prognoses, the approach provides a valuable research tool.

The authors caution that the models are not yet suitable for routine clinical decision-making. However, they propose immediate utility in research settings. By identifying individuals most likely to develop symptoms within a defined timeframe, plasma-based clocks could improve participant selection for prevention trials and therapeutic studies.

As future models incorporate additional biomarkers and health data, this blood-based forecasting approach may evolve into a practical tool for guiding preventive interventions and personalized monitoring strategies in Alzheimer's disease.

Source:

https://www.news-medical.net/news/20260222/Blood-test-models-predict-when-Alzheimere28099s-symptoms-may-start-years-in-advance.aspx