New Alzheimer's Blood Test May Tell When Symptoms Are Around the Corner

A novel biomarker beats the leading diagnostic blood test at predicting disease progression.

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Small loops of genetic material may be strong indicators of imminent Alzheimer's disease (AD) symptoms. In a National Institutes of Health (NIH)-funded study, researchers showed that elevated levels of certain circular RNAs (circRNAs) in the blood nearly tripled patients' risk of developing symptoms, suggesting these molecules are more sensitive to symptom onset than traditional AD biomarkers.

Current AD blood tests offer reliable diagnoses by detecting markers of amyloid plaques, a hallmark of the disease. However, these tests, which can produce positive results potentially decades before cognitive impairment, are not highly informative of how a patient's disease will progress. This new research lays groundwork for a kind of test that could potentially predict symptom onset.

"In a clinical setting, being able to identify patients on the verge of symptom onset would be invaluable. Having this information could help us select the right patients for clinical trials and better determine which treatments are effective at preventing cognitive decline," said Richard Hodes, MD, director of NIH's National Institute on Aging (NIA).

Unlike amyloid plaques, which accumulate slowly in the brain, circRNAs are far more dynamic, reflecting the brain's more recent activity. In a previous stud, Carlos Cruchaga, PhD, and colleagues at the Washington University School of Medicine, St. Louis, linked circRNAs in the brain to dementia and neuropathological severity. To learn if these molecules held clinical promise, they needed to see if these associations held up among circRNAs circulating in blood, a far more accessible tissue.

Cruchaga and his co-authors analyzed blood data from more than 1,200 people from multiple independent cohorts, finding a set of 34 circRNAs that were associated with AD. Predictive models based on these associations successfully identified individuals with AD pathology, performing similarly to models trained on the protein pTau217 data — the leading clinical blood-based biomarker for AD.

The circRNA model far surpassed the pTau217 model when looking into the future, however. The 34 circRNAs were stronger predictors of a patient's progression to symptomatic AD, with additional experiments suggesting that their levels seem to diverge from normal about two to four years prior to symptom onset. Notably, the authors produced similar findings in samples from two independent cohorts.

These results may be foundational for tests that could not only help clinicians identify candidates for novel treatments but also monitor their response, especially for drugs that target amyloid plaques.

"Patients being treated with novel Aβ-removal therapies, can become pTau negative but still have Alzheimer's disease. These circular RNAs may grant us a more complete perspective of someone's overall disease biology," said Cruchaga, the study's corresponding author.

Together with commercial partners, the researchers are currently working to develop translatable clinical assays for blood-based circRNAs.

"It's nice to have good science and models, but we're ultimately doing this to help people," Cruchaga said.

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