Blood-based circular RNAs emerge as a breakthrough early diagnostic tool for Alzheimer's disease

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For decades, early detection of Alzheimer's disease (AD) has remained one of the most intractable challenges in neurodegenerative medicine. Clinical symptoms of dementia typically emerge only after years of irreversible neuronal damage, by which point many disease-modifying therapies can no longer deliver maximum benefit. Now, a landmark study published this month in *Nature Medicine* introduces a blood-based panel of 34 circular RNAs (circRNAs) that outperforms the widely used plasma phosphorylated Tau-217 (pTau217) biomarker in identifying biomarker-confirmed AD, with exceptional specificity for Alzheimer's pathology over other common neurodegenerative disorders.[1-3]

The multi-institutional research team, led by Dr. Carlos Cruchaga and colleagues at Washington University in St. Louis, analyzed blood samples from a total of 3,539 participants across three large, well-characterized cohorts: the Knight Alzheimer Disease Research Center (ADRC) discovery and replication cohorts, and the national Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) study. The work builds on the unique biological properties of circRNAs, a class of highly stable, covalently closed non-coding RNAs that are heavily enriched in the brain and capable of crossing the blood-brain barrier-traits that make them uniquely suited to serve as peripheral reporters of central nervous system pathology.[4]

MOVING BEYOND the LIMITS of CURRENT AD BIOMARKERS

Current gold-standard AD biomarker workflows rely on cerebrospinal fluid (CSF) sampling via lumbar puncture or amyloid positron emission tomography (PET) scans, both of which carry significant practical barriers: lumbar puncture is invasive and not suitable for repeated routine screening, while PET imaging is extremely expensive and unavailable to broad patient populations globally. The more recently developed plasma pTau217 assay represented a major advance for blood-based AD testing, but the research team notes that its performance can be confounded by changes following anti-amyloid antibody therapies, creating gaps in long-term monitoring capacity in the era of disease-modifying treatments.

"Even the best existing blood biomarkers today only capture a partial slice of the full AD pathological cascade," explained senior investigator Dr. Laura Ibanez. "We desperately needed a marker that could reflect overall disease status, track ongoing neurodegeneration, and remain reliable even after patients receive targeted amyloid-lowering treatments—and that is exactly what our circRNA panel delivers."

Unlike linear messenger RNAs that degrade rapidly in circulation, circRNAs have a half-life double that of their linear counterparts, making them far more stable for clinical testing. Prior small-scale studies had hinted that circRNA levels differ between the brains and blood of symptomatic AD patients and healthy controls, but no prior work had validated these signals in multi-cohort, large-population analyses or developed a panel robust enough for clinical translation.

A 34-CIRCRNA PANEL VALIDATED ACROSS MORE THAN 3,500 PARTICIPANTS

The research team first generated high-quality RNA sequencing data from 1,221 participants in the Knight-ADRC discovery cohort, including 405 individuals with clinical AD and 816 cognitively unimpaired (CU) controls. After applying rigorous multi-tool bioinformatic quality control using DCC, CIRI2 and CIRI3 pipelines to eliminate technical artifacts, the team identified 34 distinct circRNA transcripts that remained significantly associated with AD status after strict false discovery rate correction.

Cross-referencing these 34 candidates against the CircAtlas 3.0 tissue expression database confirmed that 30 of the 34 circRNAs ranked above the 80th percentile for brain expression across 33 human tissues, and 14 out of 21 circRNAs validated via quantitative PCR showed significantly higher expression in brain tissue than peripheral organs—supporting the hypothesis that these blood-detected circRNAs originate primarily in the central nervous system and can cross the blood-brain barrier to enter circulation. Critically, more than 87% of these circRNAs showed associations with AD that were fully independent of their corresponding linear mRNA transcripts, meaning their disease signals are not just passive byproducts of altered host gene expression.

When the team tested the 34-circRNA predictive model on biomarker-confirmed samples defined by CSF amyloid and Tau status, it achieved an outstanding area under the ROC curve (AUC) of 0.945 for distinguishing AD cases from cognitively unimpaired biomarker-negative controls—markedly higher than the 0.877 AUC measured for plasma pTau217 in the same sample set. Combining the circRNA panel with plasma pTau217 further elevated diagnostic performance to an AUC of 0.977, approaching near-perfect classification accuracy.

The model showed nearly identical diagnostic power across demographic subgroups, with AUCs of 0.903 for women and 0.909 for men, and 0.856 in APOE4 carriers (the highest genetic risk group for AD) and 0.883 in non-carriers. Most notably, the panel performed consistently well across diverse ancestral backgrounds, delivering AUCs of 0.906 for European ancestry participants, 0.934 for African ancestry participants, and 0.922 for admixed cohorts-an extremely rare level of cross-population robustness that addresses a major shortcoming of many prior AD biomarker studies that heavily overrepresent white participants （Figure 1）.

UNPRECEDENTED SPECIFICITY for ALZHEIMER'S DISEASE

One of the most clinically valuable features of the new circRNA panel is its exceptional specificity for AD over other neurodegenerative conditions. When the researchers applied the full 34-circRNA model to cohorts of patients with Parkinson's disease (PD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB), the model produced non-informative near-random AUC scores of just 0.413 for PD, 0.545 for DLB, and 0.404 for FTD. This near-zero predictive power for non-AD dementias is a major advance over existing blood biomarker assays, which frequently show elevated signals across multiple forms of neurodegeneration and lead to costly, unnecessary follow-up testing.

"Most current AD blood biomarkers struggle to tell the difference between Alzheimer's and other dementias, which creates real confusion in neurology clinics when a patient presents with mild cognitive impairment," noted Dr. Timothy J. Hohman, co-investigator on the study. "Our circRNA panel almost completely ignores non-AD neurodegeneration, which means it can give clinicians far more confidence that a positive test result actually signals underlying Alzheimer's pathology."

Only 3 of the 34 circRNAs showed even nominally significant associations across all tested neurodegenerative diseases, confirming that the vast majority of the panel's components are uniquely tied to the specific pathological processes of amyloid and Tau aggregation that define Alzheimer's disease.

PREDICTING PROGRESSION to SYMPTOMATIC AD YEARS BEFORE ONSET

The most transformative finding from the study came from longitudinal survival analysis tracking 688 initially cognitively unimpaired participants over extended clinical follow-up. The 34-circRNA model achieved a hazard ratio of

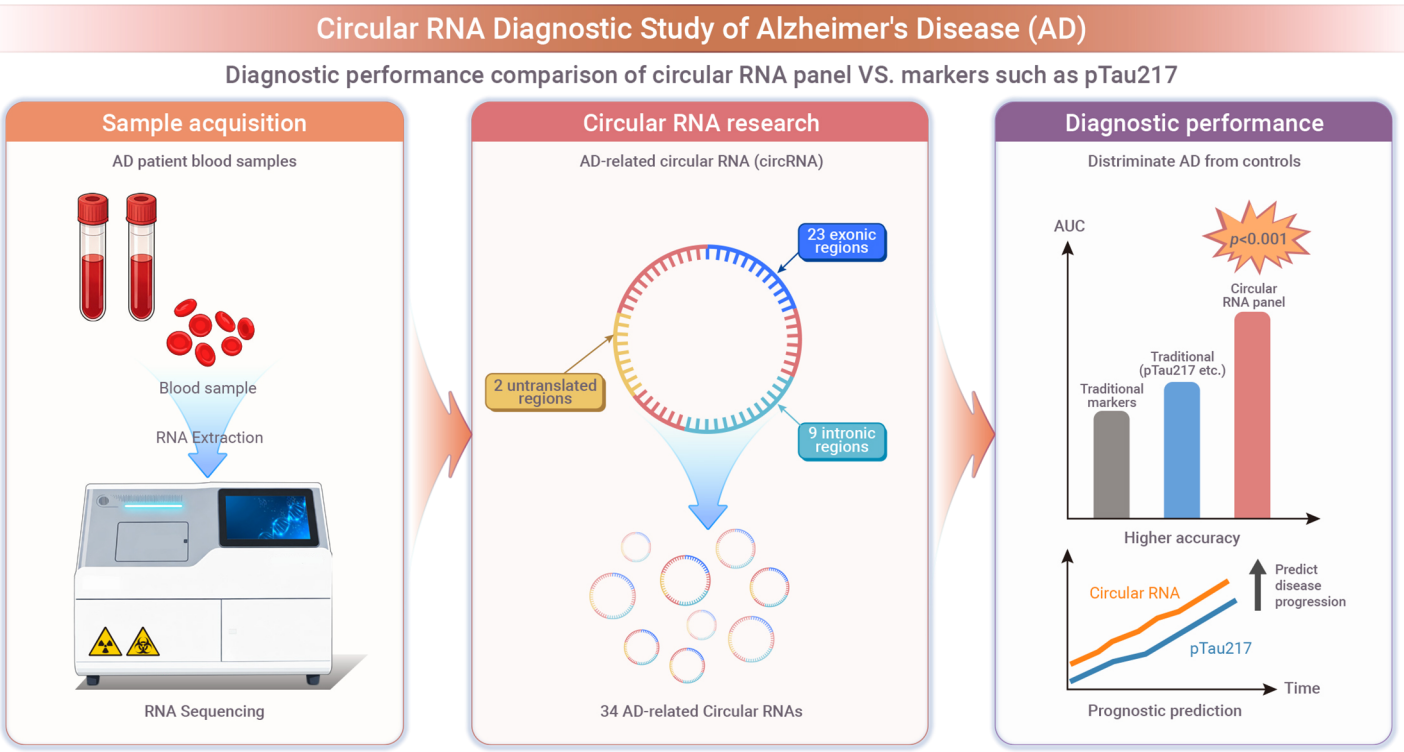

Figure 1. Schematic illustrations of the Blood-Based Circular RNAs acted as an Early Diagnostic Tool for Alzheimer' s Disease.

2.92 for predicting which CU individuals would later progress to symptomatic AD, significantly outperforming plasma pTau217 which only reached a hazard ratio of 1.81 in the same cohort. For predicting progression to dementia within 5 years, the circRNA panel delivered an AUC of 0.870, far exceeding the 0.676 AUC of pTau217 alone.

Stratifying participants by combined biomarker status created a clear four-tier risk stratification system with striking clinical utility:

(1) Individuals negative for both circRNA and pTau217 had only a 15% chance of progressing to symptomatic AD.

(2) Individuals positive only for pTau217 had a 41% progression rate (hazard ratio 3.25).

(3) Individuals positive only for the circRNA panel had a 74% progression rate (hazard ratio 3.96).

(4) Individuals positive for both biomarkers had an 84% progression rate (hazard ratio 4.83).

This risk stratification capacity is a game-changer for the design of preventive AD clinical trials, which currently struggle to efficiently identify high-risk preclinical participants most likely to benefit from investigational interventions. The researchers successfully replicated all key findings in the independent Knight-ADRC replication cohort and the large A4 cohort, confirming the results are not limited to a single study population.

IMPLICATIONS for CLINICAL PRACTICE and PUBLIC HEALTH

As the global population ages, the number of people living with Alzheimer's disease is projected to triple by 2050, creating an unsustainable burden on healthcare systems worldwide. The availability of a low-cost, widely accessible blood test that can detect AD pathology before symptoms appear, accurately predict dementia onset, and monitor disease progression will fundamentally shift how clinicians approach dementia care.

The research team notes that additional multi-site validation in broader community cohorts is still required before the assay can be cleared for routine clinical use, but the existing data already position blood circRNAs as one of the most promising AD biomarker discoveries of the past decade. When combined with the ongoing rollout of anti-amyloid therapies that can slow disease progression if administered in early preclinical stages, this new test creates a fully functional early detection pathway that was not possible just five years ago.

This study represents a major proof of concept for leveraging brain-enriched, blood-detectable circular RNAs as diagnostic windows into central nervous system disease-a framework that researchers say could eventually be adapted for early detection of other currently hard-to-diagnose neurological conditions.[5]

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AUTHOR CONTRIBUTIONS

L.C. conceptualized the study, performed the investigation, and wrote the original draft. F.S. and E.X. contributed to conceptualization and provided writing-review. N.G. supervised the work, reviewed and edited the manuscript, and acquired funding. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.