A two-minute digital cognitive task as a pre-enrichment screening method for Alzheimer's disease trials

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What is the Methodological Issue Being Addressed? Enrolment in Alzheimer's disease (AD) trials is slow and costly, and many candidates do not pass screening. Failure rates can exceed 40% in mild dementia, rise above 75% in prodromal and 85% in preclinical cohorts, and may be higher still in rare phenotypes. Eligibility rests on two burdensome and resource-intensive steps: pathology confirmation by PET, lumbar puncture or plasma; and in-person assessment by a clinical professional. Pathology status is difficult to predict based on clinical presentation or self-report, and subtle cognitive decline is challenging to detect with interview or standardised clinical tools. Depending on logistical constraints, automated in-clinic or at-home assessment may be an effective way of pre-identifying likely suitable candidates. The methodological question here is whether a brief digital task can identify individuals most likely to have early AD pathology or subtle cognitive decline.

Introduction We quantified how well a brief tablet-based symbol-coding task (an engaging reimplementation of the Digit Symbol Substitution Test, made available in multiple languages including English, Spanish and French) discriminates clinical status and AD pathology, and how it compares with the paper-and-pen instruments currently used to make these decisions. The task is deliberately short, about two minutes, and designed for at-home and in-clinic use, minimizing patient and operational burden.

Methods The ROC-AUC rank discrimination measure was calculated against two reference standards: clinician-determined diagnosis for clinical status; and plasma p-tau217 positivity (ALZpath; single threshold from Ashton 2024) for pathology. The task was administered across one completed at-home study and two ongoing in-clinic studies: Study 1 (CNS-101, at-home; 46 dementia, 54 controls; benchmark ADAS-Cog 13, ~45 min); Study 2 (Fastball i4i, ongoing; target N=1000; n≈565; in-clinic; MoCA, ~20 min); and Study 3 (BioHermes-2, ongoing; target N=1000; n≈619; in-clinic; MMSE excluded as it defined the groups).

Results As can be seen in Table 1, the task discriminated at AUC 0.69–0.93, comparable to conventional assessments needing 20–45 min of clinician time, across several cohort contrasts. Crucially, this digital cognitive assessment was substantially sensitive to p-tau217 pathology, both in patients, and in clinically normal controls.

For comparison, we considered additional cognitive outcomes from Study 1, which showed promise but did not match the performance of the symbol coding task in discriminating clinical status and

pathology respectively: episodic memory (visual associative) AUC of 0.87 and 0.67; language (picture-description speech rate) AUC of 0.76 and 0.62; and working memory (n-back) AUC of 0.66 and 0.53 (status / p-tau217).

Conclusion In a post-hoc analysis of screening performance in dementia, MCI and control participants, a two-minute digital task discriminated clinical status and AD pathology comparably to longer clinician assessments. Notably it detected pathology in unimpaired individuals where in some cases the benchmark was near chance. These patterns were confirmed broadly with N≈1,280 participants across several studies, conducted at >25 sites in three countries and three languages – and using both autonomous at-home and assisted in-clinic assessment.

The results support digital cognitive endpoints as a scalable enrichment step to reduce screen failure – with downstream efficiencies in patient burden, recruitment timelines and study costs. In the Alzheimer's space, this could precede the use of plasma biomarkers, or be combined in a multimodal composite including further cognitive and speech endpoints. In psychiatry, the same principles may hold where cognition is impaired (e.g. in MDD or Schizophrenia) and where novel treatments may have benefits beyond core mood symptoms.

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Guidelines I have read and understand the Poster Guidelines

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Related Tables and Supporting Materials Table_1_Figure_1.png