FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2023

SIMPLE FINGER PRICK TEST EXEMPLIFIES
ADVANCES IN ALZHEIMER'S DISEASE BLOOD TESTS

Key Takeaways:
- **Results from a simple, finger prick blood test are promising and may help detect Alzheimer's at home or in the doctor's office.**
- **A blood test was more than 80% accurate in identifying Alzheimer's-related changes — significantly better than doctors in the study who did not have access to the test.**
- **Blood tests for Alzheimer's could improve diagnostic accuracy and treatment of the disease.**

AMSTERDAM, JULY 19, 2023 — A simple, finger prick blood test — not so different from what people with diabetes do every day — shows promise in the ability to detect Alzheimer's disease, according to research reported for the first time today at the Alzheimer's Association International Conference® (AAIC®) 2023, in Amsterdam, Netherlands, and online.

Advancements in technology and practice reported for the first time at AAIC 2023 demonstrate the simplicity, transportability and diagnostic value of blood-based biomarkers for Alzheimer's, including the future potential for at-home testing by a patient or a family member.

"These findings are timely and important with the recent U.S. Food and Drug Administration approvals of Alzheimer's treatments targeting amyloid-beta where confirmation of amyloid buildup and biomarker monitoring are required to receive treatment," said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer. "Blood tests — once verified and approved — would offer a quick, noninvasive and cost-effective option."

Blood tests are already being implemented in Alzheimer's drug trials for further verification of their effectiveness and for screening potential participants, which would be a significant evolution from more expensive and invasive procedures that are currently common practice. In some cases, these blood tests are providing similar information to "gold standard" testing, such as brain imaging scans and cerebrospinal fluid analysis.

"While further standardization and validation are needed, blood tests may soon be an important piece of the diagnostic workup in everyday practice for detecting and monitoring treatment of Alzheimer's disease," Carrillo said.

Finger Prick Blood Sample Detects Alzheimer's Biomarkers; Travels Easily Between Countries

Hanna Huber, Ph.D., of the Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Sweden, and colleagues set out to simplify and increase the accessibility of blood tests by developing a finger prick blood collection to measure key Alzheimer's-related biomarkers neurofilament light (NfL), glial fibrillary acidic protein (GFAP) and phosphorylated tau (p-tau181 and 217).

They collected blood (from both vein and finger prick) from 77 memory clinic patients from the ACE Alzheimer Center, Barcelona. The blood samples were transferred onto dry blood spot cards and shipped

overnight, without temperature control or cooling, to the University of Gothenburg, Sweden. There, the dried blood samples were extracted from the cards, and NfL, GFAP and p-tau181 and 217 were measured. (Note: p-tau217 data is only available in 11 people.) All were detectable in the finger prick samples.

In the vein blood spots, the levels of GFAP, NfL, p-tau217 and p-tau181 associated strongly with standard blood analysis. GFAP, NfL and p-tau217 extracted from finger prick blood also correlated highly with standard blood collection.

"Our pilot study demonstrates the potential of remote collection and measurement of Alzheimer's biomarkers without low-temperature storage or extraordinary preparation or processing," Huber said. "Currently, use of Alzheimer's blood tests is limited by the need to visit a clinic, administration by trained personnel, and strict time-limited and temperature-dependent delivery and storage procedures. A method that allows blood collection at home and that is simple enough to be performed independently, or by caregivers, would increase accessibility of these tests. It would result in improved early diagnosis and better monitoring of patients considered 'at risk' or those who are receiving approved therapies."

Blood Tests May Improve Alzheimer's Diagnosis in Primary Care

Sebastian Palmqvist, M.D., Ph.D., of the Clinical Memory Research Unit at Lund University, Sweden, and colleagues with the BioFINDER-Primary Care study conducted the first study to examine the use of blood-based biomarkers for Alzheimer's in primary care and compare them to the diagnostic accuracy of primary care physicians (PCPs).

The study recruited 307 middle-aged to elderly patients at 17 primary care centers in Sweden (mean age=76, 48% women). After an office visit, cognitive testing and a CT scan or MRI of the brain, the PCPs registered their diagnosis, the likely biological cause(s) and proposed a treatment plan for each study participant.

At the same time, a blood sample was collected and analyzed to determine the concentrations of beta-amyloid and phosphorylated tau using the PrecivityAD2 test by C_2N Diagnostics (USA). Levels of these two markers were combined into a score called the Amyloid Probability Score 2 (APS2). All patients then underwent a thorough clinical examination at a specialized memory clinic, including evaluation by a specialist blinded to the blood sample result.

The PCPs correctly identified the presence of Alzheimer's-related changes or correctly diagnosed Alzheimer's in approximately 55% of the cases, while the blood test did so in more than 85% of the cases. Other findings:
- The PCPs indicated their certainty about the diagnosis was less than 50%.
- The treatment plans revealed that, due to incorrect diagnosis, more than 50% of people who actually had Alzheimer's did not receive symptomatic treatment, and 30% of non-Alzheimer's cases incorrectly received symptomatic treatment.

"Due to the lack of accurate diagnostic tools, it is currently very difficult for primary care doctors to identify Alzheimer's disease, even among patients with cognitive impairment," Palmqvist said. "This too often leads to diagnostic uncertainty and inappropriate treatment. Blood tests for Alzheimer's disease have great potential for improving diagnostic accuracy and proper treatment of people with Alzheimer's. These tests may become even more important in the near future, as new drugs that slow down the disease in its early stages become more widely available."

About the Alzheimer's Association International Conference® (AAIC®)
The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2023 home page: www.alz.org/aaic/

About the Alzheimer's Association®
The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit [alz.org](alz.org) or call 800.272.3900.

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- Hanna Huber, Ph.D., et al. A finger prick collection method for detecting blood biomarkers of neurodegeneration – a pilot study (DROP-AD). (Funder: Alzheimerfonden)
- Sebastian Palmqvist, M.D., Ph.D., et al. Blood Biomarkers Improve The Diagnostic Accuracy Of Alzheimer's Disease As Compared With Current Diagnostic Standard In the Primary Care Setting. (Funders: Alzheimer's Association, Swedish Research Council, Swedish Brain Foundation, Swedish Alzheimer's Foundation)

*** AAIC 2023 news releases may contain updated data that does not match what is reported in the following abstracts.

Proposal ID: 80275 (original submission)
A finger prick collection method for detecting blood biomarkers of neurodegeneration – a pilot study (DROP-AD)

Background: Plasma biomarkers have proven to indicate developing cerebral pathologies and injury that underpin neurodegenerative disorders (ND) in a non-invasive manner. However, the measurement of certain blood biomarkers requires on-site sampling with strict, time-limited and temperature dependent processing protocols. To further facilitate the usefulness of blood biomarkers, methods for remote and/or unsupervised sample collection would greatly increase the utility as a screening and monitoring tool in secondary care and therapeutic trials. This pilot study investigated the capability of capillary dry blood spot (DBS^{capillary}) to measure neurofilament light (NfL), glial fibrillary acidic protein (GFAP) and phosphorylated tau (p-tau). Venous dry blood spot (DBS^{venous}) was also measured after whole blood collection following standard procedures.

Methods: We included 43 memory clinic participants from ACE Alzheimer Center Barcelona. We collected DBS^{capillary} and DBS^{venous}, as well as EDTA plasma and neuropsychological measures from each participant. A subset (n=23) had cerebrospinal fluid (CSF) biomarkers. Capillary whole blood was obtained by a macro lancet needle from the left index finger. A total of 65µL of venous and capillary blood were spotted and dried on Noviplex^R DBS cards, which were shipped overnight, without temperature control or cooling, to Gothenburg, Sweden. Samples were extracted from DBS^{capillary} and DBS^{venous} cards, and NfL, GFAP and p-tau181 were measured by single molecular array (Simoa). Statistical analysis included Pearson correlation between DBS^{capillary}, DBS^{venous} and EDTA plasma.

Results: For DBS^{capillary} GFAP (r=0.6773, p<0.0001) and NfL levels (r=0.4593, p=0.0022), a correlation with their counterparts in EDTA plasma was found. Also DBS^{venous} GFAP (r=0.7624, p<0.0001), NfL (r=0.6798, p<0.0001) and p-tau181 (r=0.5770, p<0.0004) correlated significantly with EDTA plasma. Both, DBS^{capillary} and DBS^{venous} GFAP were correlated with amyloid status (r=0.4305/ r=0.4223, p<0.05), while DBS^{venous} NfL and p-tau181 correlated with MMSE, CDR and amyloid (all p<0.05).

Conclusion: This pilot study demonstrates the potential of remote collection and quantification of GFAP, NfL and p-tau181 without low-temperature storage/transportation or centrifugation (DBS^{venous}). Furthermore, there is potential to quantify capillary blood GFAP and NfL via a finger prick collection. We speculate that this simple, self-executable method of blood collection would facilitate regular monitoring of patients with suspected neurological conditions.

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A finger prick collection method for detecting blood biomarkers of neurodegeneration – a pilot study (DROP-AD)

Introduction: Plasma biomarkers have proven to indicate developing cerebral pathologies and injury that underpin neurodegenerative disorders in a non-invasive manner. However, the measurement of certain blood biomarkers requires on-site sampling with strict, time-limited and temperature dependent processing protocols. To further facilitate the usefulness of blood biomarkers, methods for remote and/or unsupervised sample collection would greatly increase the utility as a screening and monitoring tool in secondary care and therapeutic trials. This pilot study investigated a novel method to quantify neurofilament light (NfL), glial fibrillary acidic protein (GFAP) and phosphorylated tau (p-tau) in capillary dry blood spots (DBScapillary) and venous dry blood spots (DBSvenous).

Methods: We included 77 memory clinic participants from ACE Alzheimer Center Barcelona. DBScapillary , DBSvenous , and EDTA plasma as well as neuropsychological measures were obtained from each participant. A subset (n=23) had cerebrospinal fluid (CSF) biomarkers. Capillary whole blood was obtained by a macro lancet needle from the left index finger. A total of 65μL of capillary and venous blood were spotted and dried on Noviplex DBS cards, which were shipped overnight without temperature control or cooling to Gothenburg, Sweden. Samples were extracted from DBScapillary and DBSvenous cards, and NfL, GFAP, p-tau181, and, in a subset (n=11), p-tau217 were measured by single molecular array (Simoa). Statistical analysis included Pearson correlation between DBS and EDTA plasma.

Results: DBScapillary GFAP (r=0.7180, p<0.0001), and NfL (r=0.6967, p<0.0001) correlated highly with their counterparts in EDTA plasma. We also demonstrated that DBScapillary p-tau217 (r=0.8955, p=0.0002) but not DBScapillary p-tau181 (r=0.0132, p=0.9447) correlated with the same measures in EDTA plasma, likewise DBSvenous GFAP (r=0.7614, p<0.0001), NfL (r=0.7701, p<0.0001), p-tau217 (r=0.9625, p<0.0001) and p-tau181 (r=0.6619, p<0.0001). Moreover, DBScapillary GFAP and DBSvenous GFAP, NfL and p-tau181 correlated with MMSE, CDR and amyloid status (all p<0.05).

Conclusion: This pilot study demonstrates the potential of remote collection and quantification of GFAP, NfL, p-tau217 and p-tau181 without low-temperature storage/transportation or centrifugation (DBSvenous). Our data also suggests that this may be possible from a simple finger prick collection, including p-tau217. We speculate that this simple, self-executable method of blood collection would facilitate regular monitoring of patients with suspected neurological conditions.

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Proposal ID: 78819

Blood Biomarkers Improve The Diagnostic Accuracy Of Alzheimer's Disease As Compared With Current Diagnostic Standard In the Primary Care Setting

Background: The first and final level of care for most individuals with cognitive impairment is primary care. The aim was to examine the diagnostic accuracy of plasma phospho-tau217/non-phospho-tau217 (p-tau217 Ratio) and Aβ42/40 Ratio for Alzheimer's disease (AD) as compared to usual care by primary care physicians (PCPs).

Method: In the BioFINDER-Primary Care study, we recruited patients examined due to cognitive complaints at 25 primary care centers in Sweden (n=307). After care-as-usual (CT/MRI, cognitive testing, and clinical assessment), the PCPs documented the most likely underlying etiology and proposed a treatment plan. Plasma biomarkers included p-tau217 Ratio, Aβ42/Aβ40 Ratio, and a predefined algorithm combining both (C_2N mass-spectrometry). The outcome was AD pathology defined using FDA-approved cerebrospinal fluid Aβ42/p-tau181 (Lumipulse®) or visual read of 18F-Flutemetamol Aβ-PET.

Result: The mean age was 76±6.3 years, 48% were women, and 49% had AD pathology. Twenty-five percent had subjective cognitive decline, 47% mild cognitive impairment, and 28% dementia. Using AD pathology as the outcome, the AUCs were 0.80 (95%CI 0.75-0.86) for Aβ42/Aβ40 Ratio, 0.91 (0.88-0.94) for pTau217 Ratio, and 0.94 (0.92-0.97) for the algorithm. In those with available PCP questionnaires (n=265), the PCPs correctly classified AD in 54% (50-59%) of the cases, compared with 77% (73-81%) for Aβ42/40 Ratio, 85% (82-88%) for p-tau217 Ratio, and 87% (84-90%) for the algorithm. The mean certainty of the PCPs' diagnosis (1-10, not at all to completely certain) was 4.7 (5.1 in those with AD pathology who were correctly diagnosed as AD and 4.6 in the missed AD cases). The PCPs' proposed treatment, which in 87% followed the treatment guidelines, led to 50% of true AD cases not receiving symptomatic treatment and 30% of non-AD cases incorrectly receiving symptomatic AD treatment (DLB patients excluded).

Conclusion: We found that it is difficult for PCPs to identify AD among patients with cognitive impairment in primary care, which leads to diagnostic uncertainty and incorrect treatment. The use of a blood test for AD pathology has great potential for improving the diagnostic accuracy and treatment of AD in primary care. At AAIC, a larger dataset will be presented including the effects of co-morbidities and medications.

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Accuracy for AD pathology in BioFINDER–Primary Care
n=307