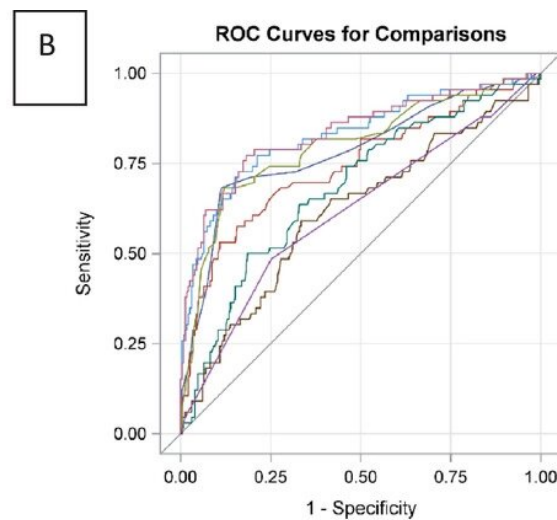
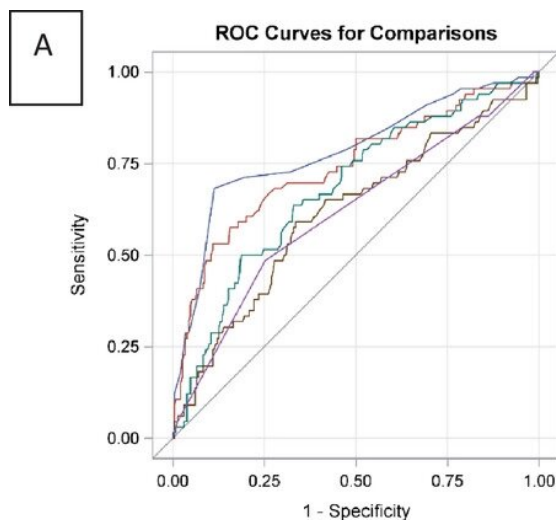


Early Alzheimer's detection up to 17 years in advance

July 21 2022



Predictor	AUC (95% CI)
Aβ misfolding	0.784 (0.713-0.854)
GFAP	0.741 (0.666-0.816)
NfL	0.680 (0.606-0.755)
P-tau181	0.615 (0.534-0.696)
APOE	0.615 (0.541-0.690)

Predictor	AUC (95% CI)
Aβ misfolding	0.784 (0.713-0.854)
GFAP	0.741 (0.666-0.816)
NfL	0.680 (0.606-0.755)
P-tau181	0.615 (0.534-0.696)
APOE	0.615 (0.541-0.690)
Aβ misfolding + APOE	0.798 (0.730-0.865)
Aβ misfolding + GFAP	0.828 (0.764-0.891)
Aβ misfolding + GFAP + APOE	0.835 (0.772-0.897)

Receiver-operating curve (ROC) analyses to determine the discriminative power of all biomarkers to distinguish between patients with Alzheimer's disease (AD) and controls within 17 years. Simoa biomarkers are log-transformed values. Participants with missing apolipoprotein E (APOE) status have been excluded (n = 12). (A) ROC analyses revealed an area under the curve (AUC) for AD versus controls of 0.78 with respect to the degree of amyloid beta (Aβ) misfolding (blue), 0.74 for GFAP (red), 0.68 for NfL (mint), and 0.61 for P-tau181 (brown), underscoring the status of Aβ misfolding as the best performing

solo biomarker. (B) Combined ROC curve analyses showed the highest AUC for the combination of biomarkers A β misfolding, APOE status, and GFAP (AUC 0.83, pink), followed with the same value by A β misfolding and GFAP (AUC 0.83, light blue) and A β misfolding and APOE (AUC 0.80, yellow). The data showed that APOE status did not increase the discriminative power of A β misfolding and GFAP, suggesting that only these two blood-based biomarkers are favored. Note: ROC Contrast Analyses (DeLong test). A β mis. – (A β mis. + GFAP): P = .09. A β mis. – (A β mis. + P-tau181): P = .59. A β mis. – (A β mis. + NfL): P = .34. A β mis. – (A β mis. + APOE): P = .28. Credit: *Alzheimer's & Dementia* (2022). DOI: 10.1002/alz.12745

The dementia disorder Alzheimer's disease has a symptom-free course of 15 to 20 years before the first clinical symptoms emerge. Using an immuno-infrared sensor developed in Bochum, a research team is able to identify signs of Alzheimer's disease in the blood up to 17 years before the first clinical symptoms appear. The sensor detects the misfolding of the protein biomarker amyloid-beta. As the disease progresses, this misfolding causes characteristic deposits in the brain, so-called plaques.

"Our goal is to determine the risk of developing Alzheimer's dementia at a later stage with a [simple blood test](#) even before the toxic plaques can form in the brain, in order to ensure that a therapy can be initiated in time," says Professor Klaus Gerwert, founding director of the Center for Protein Diagnostics (PRODI) at Ruhr-Universität Bochum. His team cooperated for the study with a group at the German Cancer Research Center in Heidelberg (DKFZ) headed by Professor Hermann Brenner.

The team published the results obtained with the immuno-infrared sensor in the journal *Alzheimer's & Dementia* on 19 July 2022. This study is supported by a [comparative study](#) published in the same journal on 2 March 2022, in which the researchers used complementary single-molecule array (SIMOA) technology.

Early detection of symptom-free people with a high risk of Alzheimer's disease

The researchers analyzed [blood plasma](#) from participants in the ESTHER study conducted in Saarland for potential Alzheimer's biomarkers. The blood samples had been taken between 2000 and 2002 and then frozen. At that time, the test participants were between 50 and 75 years old and hadn't yet been diagnosed with Alzheimer's [disease](#). For the current study, 68 participants were selected who had been diagnosed with Alzheimer's disease during the 17-year follow-up and compared with 240 control subjects without such a diagnosis. The team headed by Klaus Gerwert and Hermann Brenner aimed to find out whether signs of Alzheimer's disease could already be found in the blood samples at the beginning of the study.

The immuno-infrared sensor was able to identify the 68 [test subjects](#) who later developed Alzheimer's disease with a high degree of test accuracy. For comparison, the researchers examined other biomarkers with the complementary, highly sensitive SIMOA technology—specifically the P-tau181 biomarker, which is currently being proposed as a promising biomarker candidate in various studies.

"Unlike in the clinical phase, however, this marker is not suitable for the early symptom-free phase of Alzheimer's disease," says Klaus Gerwert. "Surprisingly, we found that the concentration of glial fiber protein (GFAP) can indicate the disease up to 17 years before the clinical phase, even though it does so much less precisely than the immuno-infrared sensor." Still, by combining amyloid-beta misfolding and GFAP concentration, the researchers were able to further increase the accuracy of the test in the symptom-free stage.

Start-up aims to bring immuno-infrared sensor to

market maturity

The Bochum researchers hope that an [early diagnosis](#) based on the amyloid-beta misfolding could help to apply Alzheimer's drugs at such an early stage that they have a significantly better effect—for example, the drug Aduhelm, which was recently approved in the U.S. "We plan to use the misfolding test to establish a screening method for older people and determine their risk of developing Alzheimer's dementia," says Klaus Gerwert.

"The vision of our newly founded start-up betaSENSE is that the disease can be stopped in a symptom-free stage before irreversible damage occurs." Even though the sensor is still in the development phase, the invention has already been patented worldwide. BetaSENSE aims to bring the immuno-infrared sensor to market and have it approved as a diagnostic device so that it can be used in clinical labs.

Clinical trials with Alzheimer's drugs often fail

Approved by the FDA in the U.S. in spring 2021, the drug Aduhelm has been shown to clear amyloid-beta plaques from the brain. However, previous studies showed it had only a minor effect on clinical symptoms such as memory loss and disorientation. Consequently, the European Medicines Agency decided in winter 2021 not to approve the drug in Europe.

"Up to now, [clinical trials](#) for Alzheimer's drugs have been failing by the dozen, apparently because the established plaque tests used in the trials don't flag up the disease in time," says Gerwert. "It seems that once plaques are deposited, they induce irreversible damage in the brain." In the tests used to date, the plaques are either detected directly in the brain with the complex and expensive PET scan technology or indirectly

determined in a less complex way using protein biomarker concentrations in invasively obtained cerebrospinal fluid with ELISA or mass spectrometry technology. In contrast to established plaque diagnostics, the immuno-infrared sensor indicates the earlier misfolding of amyloid-beta, which causes the later plaque deposition.

"However, it is still controversially discussed whether this misfolding is the cause of Alzheimer's disease or if it's just an accompanying factor," says Gerwert. "For the therapeutic approach, this question is crucial, but it is irrelevant for the diagnosis. The misfolding indicates the onset of Alzheimer's disease."

"The exact timing of therapeutic intervention will become even more important in the future," says Léon Beyer, first author and Ph.D. student in Klaus Gerwert's team. "The success of future drug trials will depend on the study participants being correctly characterized and not yet showing irreversible damage at study entry."

Biomarkers for Parkinson's and ALS

Misfolded proteins play a central role in many neurodegenerative diseases, such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (ALS). As the researchers have showed, the immuno-infrared sensor can in principle also be used to detect other misfolded proteins, such as TDP-43, which is characteristic of ALS. They don't measure the concentration of a specific protein, but detect its misfolding using disease-specific antibodies.

"Most importantly, this platform technology enables us to make a differential, precise biomarker-based diagnosis in the early stages of neurodegenerative diseases, in which the currently applied symptom-based diagnosis is very difficult and prone to errors," says Gerwert.

More information: Léon Beyer et al, Amyloid-beta misfolding and GFAP predict risk of clinical Alzheimer's disease diagnosis within 17 years, *Alzheimer's & Dementia* (2022). [DOI: 10.1002/alz.12745](https://doi.org/10.1002/alz.12745)

Hannah Stocker et al, Association of plasma biomarkers, p-tau181, glial fibrillary acidic protein, and neurofilament light, with intermediate and long-term clinical Alzheimer's disease risk: Results from a prospective cohort followed over 17 years, *Alzheimer's & Dementia* (2022). [DOI: 10.1002/alz.12614](https://doi.org/10.1002/alz.12614)

Provided by Ruhr-Universitaet-Bochum

Citation: Early Alzheimer's detection up to 17 years in advance (2022, July 21) retrieved 24 June 2024 from <https://medicalxpress.com/news/2022-07-early-alzheimer-years-advance.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.