A new diagnostic model offers hope for Alzheimer's

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A new mathematical model offers hope for better prediction and treatment of Alzheimer's disease. Most mathematical models of Alzheimer's are theoretical, focusing on short term molecular and

cellular-level changes that cannot be measured in patients.

However, researchers at Duke University School of Medicine and Pennsylvania State University have used real-world data from over 800 people with varying cognitive abilities, to develop the Alzheimer's Disease Biomarker Cascade (ADBC) model.

This personalized approach, published in the *Journal of the Prevention of Alzheimer's Disease*, goes beyond traditional diagnostic methods by incorporating an individual's own biological markers to predict their disease progression.

Subjects were enrolled in the Alzheimer Disease Neuroimaging Initiative (ADNI), a multinational longitudinal study following subjects from normal cognition to mild cognitive impairment, to dementia, with serial cognitive testing, imaging and fluid biomarker data over a period up to two decades.

The ADBC model analyzes participants' cerebrospinal fluid, brain scans and memory tests to find unique patterns, or clues, about each person's condition.

The model combines both theory and individual biomarker data to predict how Alzheimer's might evolve and respond to treatment in individual patients. By analyzing current biological markers, it was able to predict with surprising accuracy how these markers might change in the future for a particular patient.

Researchers say the model opens doors for reclassifying individuals along the Alzheimer's clinical spectrum and tailoring treatment strategies.

"Alzheimer's disease has long been viewed as a single disorder," said

Jeffrey R. Petrella, MD, a neuroradiologist and director of the Alzheimer's Imaging Research Laboratory at the Duke University School of Medicine. "This research shows that the disease progresses differently in each person, with unique patterns of biomarker changes."

Petrella led the team of Duke researchers including Juliet Jiang, Kashyap Sreeram, Sophia Dalziel and Murali Doraiswamy MD, alongside senior study author Wenrui Hao, Ph.D., professor of mathematics at Penn State, in investigating the feasibility of customizing a causal model of Alzheimer's disease.

Alzheimer's disease is characterized by changes in the brain including amyloid plaques and neurofibrillary tangles that may harm neurons and affect other types of brain cells. New medications have been successful at reducing amyloid-beta proteins in the brain and slowing memory and thinking decline from Alzheimer's.

"I would envision using this model in clinical care as part of a precision medicine approach to treatment," said Petrella. "The model could develop a recommendation of the optimal therapeutic regimen needed to help a patient achieve the best possible result over time while minimizing exposure to side-effects." Treatment may be one medication or a combination of therapies.

The model identified 14 personalized parameters for each patient. These parameters reflected the growth rates, starting points (latency values), and maximum levels (carrying capacities) of various biomarkers associated with Alzheimer's. Importantly, these parameters differed significantly between individuals categorized by their clinical diagnosis, suggesting they reflect clinically meaningful aspects of the disease process.

When tested against existing data, the ADBC model predicted future

biomarker levels with a high degree of accuracy, with an average error rate of just 9% across the entire study group. This accuracy remained strong even when applied to individual patients, with over 80% showing a low error rate in predicting future biomarker points.

The research also revealed a potentially crucial finding. By analyzing the personalized parameters, researchers identified two distinct clusters of patients. These clusters seemed to represent different "endophenotypes," meaning different underlying biological profiles that influence disease progression.

The researchers emphasize the need for further studies to validate these findings in larger and more diverse community-based patient populations.

More information: J.R. Petrella et al, Personalized Computational Causal Modeling of the Alzheimer Disease Biomarker Cascade, *The Journal of Prevention of Alzheimer's Disease* (2024). DOI: 10.14283/jpad.2023.134

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