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Biomarkers could predict Alzheimer's before it starts

Study identifies potential blood test for cognitive decline.

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Howard Federoff on diagnosing Alzheimer's early

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A simple blood test has the potential to predict whether a healthy person will develop symptoms of dementia within two or three years. If larger studies uphold the results, the test could fill a major gap in strategies to combat brain degeneration, which is thought to show symptoms only at a stage when it too late to treat effectively.

The test was identified in a preliminary study involving 525 people aged over 70. The work identified a set of ten lipid metabolites in blood plasma that distinguished with 90% accuracy between people who would remain cognitively healthy from those who would go on to show signs of cognitive impairment.

“These findings are potentially very exciting,” says Simon Lovestone, a neuroscientist at the University of Oxford, UK, and a coordinator of a major European public-private partnership seeking biomarkers for Alzheimer's. But he points out that only 28 participants developed symptoms similar to those of Alzheimer's disease during the latest work. “So the findings need to be confirmed in independent and larger studies.”

There is not yet a good treatment for Alzheimer’s disease, which affects 35 million people worldwide. Several promising therapies have been tested in clinical trials over the last few years, but all have failed. However, those trials involved people who had already developed symptoms. Many neuroscientists fear that any benefits of a treatment would be missed in such a study, because it could be impossible to halt the disease once it has manifested. “We desperately need biomarkers which would allow patients to be identified — and recruited into trials — before their symptoms begin,” says Lovestone.

In the blood

The latest study, which is published today in *Nature Medicine*[1], was led by neurologist Howard Federoff of Georgetown University Medical Center in Washington DC. He and his colleagues tested the participants' cognitive and memory skills, and took blood samples from them, around once a year for five years. They used mass spectrometry to analyse the blood plasma of 53 participants with mild

cognitive impairment or Alzheimer's disease, including 18 who developed symptoms during the study, and 53 who remained cognitively healthy. They found ten phospholipids that were present at consistently lower levels in the blood of most people who had, or went on to develop, cognitive impairment. The team validated the results in a set of 41 further participants.

"We don't really know the source of the ten molecules, though we know they are generally present in cell membranes," says Federoff. But he proposes that concentrations of the phospholipids might somehow reflect the breakdown of neural-cell membranes.

Federoff emphasizes that his results will have to be validated in independent labs, and in much larger studies: "We also have to look at different age groups and a more diverse racial mix, and we need longer study periods."

Ease of use

Monique Breteler, head of epidemiology at the German Centre for Neurodegenerative Diseases in Bonn, says that a test based on Federoff's biomarker set would be advantageously simple. "If you are to screen the population for those destined to get Alzheimer's, and who may therefore benefit from any treatment that is developed," she says, "then you need to use material you can access easily, like blood."

Some groups are looking for molecules present in spinal fluid or biomarkers based on brain imaging — procedures that are not practical for large-scale use, she adds.

Other research has found differences in patterns of other molecules in the blood of people with Alzheimer's and healthy controls. But such case–control studies fail to take into account normal variation between individuals, says Breteler. "In general it is better to do a prospective study, like this one, so you can follow how measurements in each individual change as their life progresses."

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References

1. Mapstone, M. *et al. Nature Med.* http://dx.doi.org/10.1038/nm.3466 (2014).