Transcript Details
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Beyond Amyloid and Tau: A Multimarker Approach to Alzheimer's Detection

Announcer:
Welcome to *NeuroFrontiers* on ReachMD. On this episode, we'll hear from Dr. Thomas Karikari, who's the Director of the Biofluid Biomarker Laboratory at the University of Pittsburgh and an Assistant Professor of Psychiatry at the University of Pittsburg. He'll be discussing a study that examined a new blood test that can detect early signs of Alzheimer's disease by measuring markers related to brain inflammation, blood vessel health, and nerve connections. Here's Dr. Karikari now.

Dr. Karikari:
So this study was performed to answer some very simple questions, and those questions have been lingering in the field for quite some time. For example, when it comes to the very preclinical stages—so in individuals over 65 years old who do not have any clear signs of cognitive decline—what are some of the clear signs or some of the incipient signs that we could see to tell us about what is coming up about Alzheimer's? And that was the main thing we did. And oftentimes, we look at amyloid; we look at tau. Those are the key ones that we have in the clinic. But probably, the signs are not going to come from there. Probably, the other pathologies or other processes that interface with these ones would give what is actually happening, and that links to more recently what the two different criteria in the field have come up with. So in this very setting, we use a new method—they call it NULISA. Just to go a little bit into the biochemistry of it, proximity ligation assay, what it means in a simple sense is a NULISA is an immunoassay, but with amplifications that happen by PCR, or polymerase chain reaction.

So with that method, they selected up to about 10,000, so about 120 markers that you have in that very panel that we tested, and that has a mix of proteins selected from different pathways and processes; that includes the classical amyloid tau neurodegeneration markers that you have for Alzheimer's, but they also include some inflammation markers, including some cytokines but also some astroglia and microglia, so broadly glial markers, and then looking at some vascular dysfunction markers as well. They also do include some co-pathology markers, so those are looking at, for example, TDP-43, and at alpha-synuclein as what you would see in Parkinson's where you may have some individuals who have Alzheimer's and also have Parkinson's and things of that kind. But this has not been tested in an independent way, and at the time that we run the study, we wanted to evaluate the capacity of this platform in a very preclinical setting, so we chose a cohort that has very early disease. So over 95 percent of the individuals were cognitively normal, so they had no clinical signs of memory changes or broadly cognitive changes that could trigger that they needed any attention.

And then what we also did was these individuals had the ground truth markers or ground truth diagnostic data. So they had neuroimaging data for amyloid PET, so positron emission tomography; they also had tau PET; and then they had MRI focused on cortical thickness, in this sense for neurodegeneration; so these being the classical amyloid tau neurodegeneration that's well accepted by the field. In addition, the individuals had data for other blood tests in the field. Those include phospho-tau data, amyloid peptide data, and some neurodegeneration ones like neurofilament and also GFAP glial fibrillary acidic protein that were generated using a different platform, which in this case happened to be the Simoa platform, which is arguably the most widely used platform in the field when it comes to blood markers. So what we wanted to do was to benchmark this new platform from NULISA against these established imaging and blood-based marker methods.

So the results that we found were quite exciting. Number one, when we focus on markers where you also had data from Simoa, for example, for blood tests, we have very good correlations, which meant that for results for phospho-tau or phosphorylated tau markers like 217, phosphorylated tau 231, and phosphorylated tau 181, they're very good correlations. And same also for neurofilament light and also for glial fibrillary acidic protein, and moderate correlations for amyloid beta 40 and amyloid beta 42 peptides, which those ones in

the field understand that it's quite tricky with the handling of blood for amyloid beta. But at least when we look at these other markers, these correlations are pretty good, which would mean that as opposed to using other platforms that give you same relative comparable results like we showed here, let's say, if you used the Simoa platform where sometimes you have to use a single measure as a single marker assays or very few marker assays as opposed to when you compare with this one where you have a large set of markers in a very selected way, you get almost the same results, but you have the advantage of being able to measure them at the same time and being able to also get the results at the same time. So instead of looking at things from a narrow single lens, now you can look at multiple lens, and you can start to really build a hypothesis as to what might be happening in tandem.

Another set of the results that we can say is that in individuals who had amyloid pathology, so who had abnormal pathology—in other words, amyloid positive individuals based on PET—what we did see was that there were some differences in terms of some of the proteins, especially from an inflammation sense, some of the proteins that were also from the vascular sense and from even some other processes in those individuals as opposed to those who were amyloid negative, which would suggest that in the early stages when individuals become amyloid positive or when they develop abnormal amyloid pathology, there are other inflammation, vascular, and even mitochondria processes that you change in response to this, so which would mean that in situations where you may not have a clear-cut blood test, we can look at these other processes to tell us what is going on. And at the same time, we can also tell that when amyloid changes are happening, these other processes are also happening, which are definitely going to be either one triggering the other in a sense that tell us more about the brother pathophysiological framework that you do see as Alzheimer's disease.

Announcer:
That was Dr. Thomas Karikari talking about a new blood test that can detect early signs of Alzheimer's disease. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!