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Norwegian Startup Pre Diagnostics Developing Monocyte Test for Presymptomatic Alzheimer's Disease

By Leo O'Connor

NEW YORK — Norwegian firm Pre Diagnostics is preparing to enter the market for Alzheimer's disease testing using a monocyte blood immunoassay that analyzes the inside of innate immune cells to detect disease before there are symptoms.

The assay, called PreADx, uses intracellular measurements to monitor the ongoing clearance from the brain of amyloid-beta (Aβ) plaque, a hallmark of Alzheimer's disease pathology.

The analysis of monocytes in the Pre Diagnostics assay represents a detection method unlike others used in blood-based biomarker tests, most of which employ plasma or serum as a sample, Charlotte Berg-Svendsen, the company's chief commercial officer, said in an interview.

Unlike other blood-based tests, PreADx provides a direct indication of how a dysfunctional immune system could lead to Alzheimer's disease, she said.

Blood-based diagnostic tests are already being developed to detect Alzheimer's disease before symptoms show up, with the aim of enabling early intervention to improve patient outcomes. Because their assays have the potential to be more affordable than brain imaging and less invasive than assays that require a spinal tap, developers believe their blood-based tests could become part of the overall clinician toolbox for the early diagnosis of Alzheimer's disease.

"[In the Pre Diagnostics test] monocytes do the job of clearing amyloid-beta plaques that build up in the brain," Berg-Svendsen said.

The monocytes are from the same cell lines as microglia and macrophages found in the central nervous system and used to remove damaged neurons and infections. "All of these cells are part of the innate immune system," Berg-Svendsen said, adding, "For these reasons, we believe that our scientific approach is more disease-relevant" than measuring biomarkers in plasma or serum.

Additionally, because the test measures the clearance of amyloid-beta plaque, it is well suited to continuously monitoring the progression of Alzheimer's disease in patients, she said.

The PreADx test detects amyloid-beta peptides using a pair of monoclonal antibodies as part of an assay that currently runs on the Simoa immunoassay platform developed by Billerica, Massachusetts-based Quanterix. The test first isolates monocytes from a whole-blood sample and then uses the specially designed monoclonal antibodies to quantify the degradation of amyloid-beta peptides. After isolation, the monocyte cells are lysed to reveal amyloid-beta peptides, and then the Simoa immunoassay platform uses paramagnetic beads that bind to the PreDx monoclonal antibodies that are tailored to detect amyloid-beta peptides. Detection antibodies that fluoresce in the presence of target analytes are added to the mix, forming an immunocomplex consisting of the paramagnetic beads, target peptides, and the detection antibodies.

When the isolated monocytes are loaded into arrays in a Simoa disc consisting of more than 200,000 microwells – each large enough to hold one bead — the immunoassay system reads the signal intensity on each bead and determines the biomarker concentration based on a calibration curve.

The startup said that a recent clinical study involving 62 patient samples showed that the test demonstrated clinically relevant performance with an area under the curve of .81.

Operating with the AUC of .81, the firm established sensitivity and specificity levels that are aligned with the requirements of different clinical settings, Pre Diagnostics' Chief Medical Officer and Cofounder Erik Christensen said in an interview.

In memory clinics where, according to some estimates, about 60 percent of all patients have Alzheimer's disease, the test's positive predictive value is 84 percent. For testing by neurology specialists, the firm has established a positive predictive value of 77 percent and a negative predictive value of 73 percent. For the screening of healthy people aged 50 and older, the negative predictive value is 100 percent, the firm said.

The variation in sensitivity and specificity levels enables flexibility in managing different populations of patients and their varying testing needs, Christensen said.

The results of Pre Diagnostics' clinical study represent "a good start and this technique clearly has great potential," Dag Aarsland, chair of old age psychiatry at Kings College London, said in an interview.

A blood test that shows an AUC of .8, or above, is what clinicians operating in the field require and is seen as "very promising," said Aarsland, a long-time clinician and researcher with an interest in Alzheimer's disease and dementia who is not affiliated with Pre Diagnostics or the development of its test.

He noted that the firm's approach involving intracellular detection is "very different from other test procedures used to measure proteins and peptides" for Alzheimer's disease diagnosis and may provide better performance than other blood-based tests. Nonetheless, the test will require further clinical validation to prove that it can perform better than others, he added.

Oslo-based Pre Diagnostics said it is scheduled to present the data from its multicenter study at the Alzheimer's Association International Conference (AAIC) conference in Amsterdam in July. It has also embarked on a follow-up study that it plans to complete in about one year and is aimed at further validating the clinical utility of its test using about 300 clinical samples.

The company is also developing an assay for Parkinson's disease diagnosis, using its monocyte detection technology. The test could be used to differentiate patients with Parkinson's disease from those with Alzheimer's disease because it uses alpha-synuclein peptides instead of beta amyloid-beta peptides as disease biomarkers.

"We believe that the clinical utility of our tests includes finding and diagnosing patients with a disease and also monitoring patients in clinical studies," Berg-Svendsen said. "These are dynamic markers and they show you how the disease pathology changes."

Pre Diagnostics anticipates obtaining CE marking for its assay in the second quarter of this year, which would enable it to begin offering a kit for sale in the European Union and other regions that accept the designation.

Following CE marking, the firm plans to target clinicians and researchers in Norway and the Nordic region — first using a testing service in its own laboratory and later selling an IVD kit and testing service throughout Europe through distributors. The company said it has a long-term plan to enter the US market with a diagnostic industry partner.

Pre Diagnostics is further developing its PreADx assay with the aim of broader use of the test, by making it compatible with high-throughput immunoassay instruments used for routine IVD testing.

The firm is in discussions with pharma and biotech companies developing Alzheimer's disease therapies, which would enable it to continue building evidence and documentation that supports the test's validity and clinical utility, Berg-Svendsen said.

Håkon Saeterøy, the firm's CEO, noted that it has thus far raised €6 million ($7.2 million), which includes €2.4 million in funding from a European Union Horizon 2020 research and innovation program that ends later this year, and it has opened a new funding round, expecting to raise between €5 and €10 million, that it anticipates closing this summer.

Saeterøy and Christensen founded Pre Diagnostics in 2013 by acquiring the rights to develop and commercialize technology discovered at Akershus University Hospital that became the basis of its current tests.

The new financing would support the launch of its test as a laboratory service for the Nordic markets, and provide funding for the firm's continuing clinical validation initiatives as well as the development of its next assay for Parkinson's disease, Saeterøy said. He added that the firm also has its eye on developing an over-the-counter kit that could be purchased without a prescription to detect neurological conditions.

As they await the potential approval of drugs that can help patients with Alzheimer's disease, clinicians currently prescribe cholinesterase inhibitors that can temporarily alleviate symptoms, and they make recommendations about lifestyle interventions, diet, sleep, exercise, and management of vascular risk factors. Though the clinical diagnosis of Alzheimer's disease in its moderate to late progression is about 80 to 90 percent accurate, a diagnosis based on earlier symptoms, such as mild cognitive impairment, is more challenging and creates a need for testing, including in vitro diagnostic tests and imaging.

A number of IVD diagnostic tests are in development or on the cusp of market entry.

In January, Fujirebio Diagnostics said it soon expects a decision about a submission to the FDA for clearance of its CSF-based Lumipulse G β-Amyloid Ratio (1-42/1-40) diagnostic test. The company is also developing blood-based Alzheimer's disease assays, exploring the detection of amyloid-beta, neurofilament light, and phosphorylated tau biomarkers.

The barrier to collecting blood is far lower than for CSF, and industry observers believe that blood-based assays could be made available to screen patients for Alzheimer's during annual exams.

Last November, St. Louis-based C2N Diagnostics became the first company to bring a blood-based test for Alzheimer's to market and subsequently announced approval from the state of California to test patients samples in a CLIA-certified facility. Its test uses mass spectrometry to measure levels of amyloid-beta and apolipoprotein E in patient blood. Further, Milan-based Diadem is developing a blood-based test, AlzoSure Predict, that uses an antibody to target changes in the p53 protein.