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ADDF Leaders Discuss Future Strategies In Alzheimer's Research And Crucial Role Of Diagnostic Markers

by Marion Webb

Medtech Insight talked to two leaders at the Alzheimer's Drug Discovery Foundation about current therapies and the role of biomarkers and digital tools to build on recent advancements in the space and accelerate progress to identify the disease early and slow cognitive decline.

Over the last three years, researchers have made significant progress in defining key drivers of Alzheimer's disease, which affects more than 50 million people worldwide.

Tests such as a PET scan, MRI or spinal tap can now be used to detect amyloid plaques and tau tangles in the brain, both proteins are linked to Alzheimer's disease. And Eli Shobin, who is head of the Diagnostics Accelerator at the Alzheimer's Drug Discovery Foundation (ADDF), noted significant advancements in fluid biomarkers-and cognitive testing. These developments are critical for early diagnosis of Alzheimer's disease and can help slow the decline in Alzheimer's patients.

"Looking at the broader mission of the ADDF, we really see Alzheimer's as part of a larger picture within the biology of aging," Shobin told *Medtech Insight* during the BIO 2024 conference, held from 3-6 June in San Diego.

He explained, "Aging is the leading risk factor for Alzheimer's disease. So what are the other pathologies that are associated with aging that may be feeding into Alzheimer's or other related dementia – things like inflammation, metabolic disturbances, vascular dysfunction … and beyond understanding amyloid and tau, what are the other measures that we need to enable a world of precision medicine and combination therapy in the future?"

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ELI SHOBIN, HEAD OF ADDF'S DIAGNOSTICS ACCELERATOR *Source: ADDF*

based on the stage and scope of work. In diagnostics, investments typically range from between $200,000 and $1.5-$2m on the higher end, Harris said.

ADDF Diagnostics Accelerator Supports Broad Portfolio

Last April, the ADDF received a $200m gift from the Lauder family to accelerate the discovery and development of drugs to prevent and treat Alzheimer's disease.

The Diagnostics Accelerator launched in July 2018 with $100m in financial support from tech titans Bill Gates and Jeff Bezos, Leonard Lauder, MacKenzie Scott, the NFL Players Association, *Eli Lilly and Company*, *Biogen, Inc.*, the Shanahan Family Foundation, the Dolby family, the Charles and Helen Schwab Foundation, the Association for Frontotemporal Degeneration, and others. This year, about $15m of the $100m in financial support will be invested in diagnostics,

These are some of the complexities that the ADDF and other researchers still hope to unravel.

Medtech Insight also spoke with Karen Harris, chief financial officer at the ADDF, to learn more about the nonprofit, which is dedicated to accelerating the discovery and development of drugs to prevent and treat Alzheimer's.

Founded in 1998 by Leonard and Ronald Lauder and Howard Fillit, ADDF's chief science officer, the group employs a venture philanthropy model to support research in academia and in the biotech industry. It has been awarded more than $250m to fund over 720 Alzheimer's drug discovery programs, diverse biomarker programs and clinical trials in 19 countries. ADDF investments range from about $100,000 to $3m,

Key Takeaways

- The ADDF's Diagnostics accelerator launched in 2018 with $100m in funding from tech giants Bill Gates and Jeff Bezos, Leonard Lauder, the NFL Players Association, Eli Lilly & Co., Biogen
- Eli Shobin, head of the Diagnostics Accelerator, researchers will be able to make significant strides in dementia and target specific subsets of patients with combined pathologies such as amyloid, alpha-synuclein and TDP-43, another hallmark of several neurodegenerative diseases including ALS patients.
- "Ultimately the goal of all of these is that we won't be targeting patients who already have full-blown mild dementia, but that we can get them even in the pre-

Harris said.

> clinical stages of disease," he said. In the next 5-10 years, "I'm very hopeful that we will see some of the progress there, but when it comes to sub-typing patients, I think we still have a ways to go [at least 15 years]."

"We have a pretty broad portfolio," Shobin noted. It includes peripheral blood biomarkers, nucleic acids as potential biomarkers, retinal imaging and other ocular tests and cognitive tools, mostly digital, to detect cognitive decline.

"Our goal is to have as many different types of tests out there as possible that are well validated, because we know that no single test will work for any one use case," Shobin explained.

Among the ADDF's investments are the Amyvid PET scan (now part of Eli Lilly), blood tests such as *C2N Diagnostics, LLC*'s PrecivityAD and PrecivityAD2 to determine the presence of amyloid plaques in the brain, *Optina Diagnostics*' Optina-4C for retinal imaging, C. Light Technologies' FDA-cleared retinal eye-tracker, *Neurotrack Technologies, Inc.*' three-minute digital screening to detect cognitive impairment in annual wellness tests, and speech-based biomarkers. (Also see "*Neurotrack Rethinks 'Cognitive Health Program' Website Following Ad Claims Challenge*" - Medtech Insight, 5 Apr, 2023.)

Amyvid PET uses the imaging agent Amyvid with a positron emission tomography (PET) scanner to assess if an adult has an abnormal buildup of beta-amyloid. The diagnostic imaging test can visualize amyloid plaques, the hallmark of the disease, which, prior to amyloid PET scans, could only be detected by examining a brain at autopsy.

Amyvid PET was used in Eli Lilly's *TRAILblazer-alz2* donanameb drug trial. Donanameb has been shown to modestly slow cognitive decline in patients with early Alzheimer's disease, but poses significant risks, including swelling and bleeding in the brain. (Also see "*Addition to Quest Alzheimer's Suite Looks For Biomarker P-Tau217*" - Medtech Insight, 22 Apr, 2024.)

Donanameb was expected to be approved earlier this year in the US. After several regulatory delays, Eli Lilly celebrated a major win when on 10 June a panel of experts advised the US Food and Drug Administration to approve the drug. If approved, donanameb would become only the second Alzheimer's drug authorized for marketing in the US. (Also see "*Anti-Amyloid Class Labeling Could See Changes With Lilly's Donanemab Approval*" - Pink Sheet, 11 Jun, 2024.)

To date, *lecanemab* (Leqembi), made by Eisai and Biogen, is the first and only authorized treatment for Alzheimer's. Before joining the Diagnostics Accelerator in March, Shobin was Biogen's Alzheimer's Diagnostic Head and worked on lecanemab's development.

Based on data he has seen, Leqembi, donanameb, and to an extent Biogen's controversial drug aducanumab [Aduhelm] "all perform fairly similarly. They show a slowing of decline to a certain extent," Shobin said. Aducanumab received accelerated FDA approval for treating Alzheimer's in 2021, but was later discontinued because it didn't show sufficient evidence to benefit patients. Its development and approval process were highly controversial and fraught with debates over its efficacy and significant challenges in clinical trials.

"[Now] the conversation has become very focused on what is clinically meaningful. If we can slow cognitive decline by about 30% – which is what we've seen from all of them – is that clinically meaningful? … You hear from patients and patients' families, of course, that it is clinically meaningful … Is it a cure? Absolutely not," Shobin said.

Some researchers have criticized the notion that removing amyloid plaques from the brain actually improves cognitive function. Mike Greicius, former director of the Stanford Center for Memory Disorders, stated in *Stanford Medicine* that all three plaque-attack drugs are "decidedly underwhelming." While the drugs effectively remove amyloid plaques from the brain, none have shown a meaningful impact on the patient's well-being, he said.

Another concern is affordability of the drugs. Aduhelm cost $56,000 per year, and neither Medicare nor private insurance companies would cover it. Similarly prohibitive, Leqembi costs $26,000 a year. (Also see "*Leqembi's EU Approval Process Delayed Over Advisory Group COI Considerations*" - Pink Sheet, 25 Mar, 2024.)

A Lot Of Unknowns Remain

Diagnosing Alzheimer's before symptoms occur is crucial for developing treatments that can help prevent memory loss, but that is a tall order due to the many unknowns surrounding Alzheimer's, Shobin said.

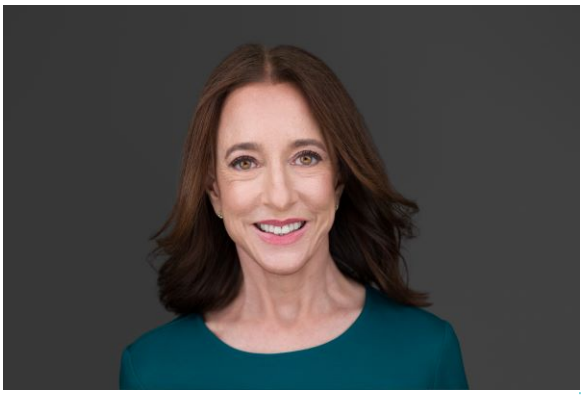
"We have seen some success with the initial anti-amyloid therapies, and there is a lot of rejuvenated excitement in the field, but there is still a long way to go – these are not cures," he said. "Part of that has to do with just how heterogeneous Alzheimer's disease and aging in general are. Trying to understand more about the different subsets of biology is going to be critical for the next stage of how we treat patients."

Shobin noted that people progress through the disease differently, but researchers have yet to fully understand why. Recent trials have revealed underlying biological differences. For instance, the donanameb trial demonstrated that both tau and amyloid statuses impact responses to therapy.

Further complicating matters are biomarkers linked to multiple synucleinopathies. Shobin gave the example of alpha-synuclein, a small protein found in Alzheimer's patients, but also those

with Parkinson's disease.

He believes that investing in the development of more biomarkers will be crucial to "moving the needle on therapeutics." Just as biomarkers are driving breakthroughs in cancer treatments, their delineation promises to deliver important insights into Alzheimer's disease, diagnosis and potential therapies.



KAREN HARRIS, CFO ADDF *ADDF*

"They [cancer researchers] were very forward-thinking by marrying biomarkers to the types of targeting agents that they were putting out there and developing them in tandem, making sure that they had the appropriate way to test their patients while they were looking at [how they could treat them with a therapeutic]."

Harris said securing venture capital investment in Alzheimer's disease has been particularly challenging because of the many failures in developing therapies and high regulatory hurdles. Whereas venture capitalists typically look for opportunities with potential for high returns within a relatively short time frame, diagnostics and Alzheimer's disease research often require long-term investments with high levels of uncertainty. Now that one drug is on the market and Eli Lilly's drug could be next, Harris said she is seeing more interest among VCs in trying to understand the space.

"Typically it was much safer to invest in cancer, so why would you invest in Alzheimer's?," she said. "It was just so risky and it's expensive, but I think that now that they see drugs getting approved, they don't want to miss the train," Harris said, adding, "We work very hard to get to know the VCs and to encourage investments."

Shobin said that while there is reason for optimism, he does not expect to see major breakthroughs any time soon.

Looking ahead, he expects that researchers will be able to make significant strides in dementia and target specific subsets of patients with combined pathologies such as amyloid, alpha-synuclein and TDP-43, another hallmark of several neurodegenerative diseases including ALS patients.

"Ultimately the goal of all of these is that we won't be targeting patients who already have full-blown mild dementia, but that we can get them even in the pre-clinical stages of disease," he said. In the next 5-10 years, "I'm very hopeful that we will see some of the progress there, but

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