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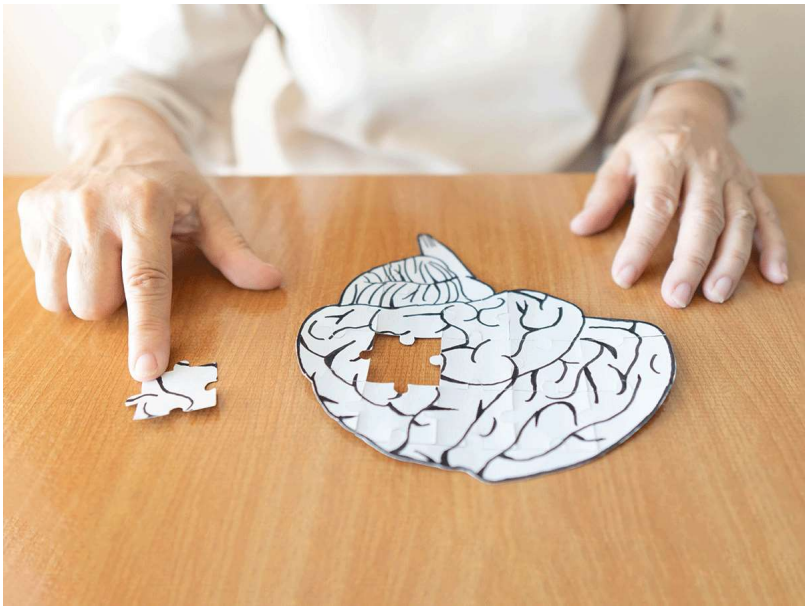

FDA approval of aducanumab paves way for Alzheimer's blood tests

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Developers of blood tests for the early diagnosis of Alzheimer's disease (AD) are poised to see a spike in demand, following the FDA's accelerated approval on Tuesday of Cambridge, Mass.-based Biogen Inc.'s AD drug treatment Aduhelm (aducanumab). The FDA's decision paves the way for AD assays to move beyond aiding in drug development toward addressing ongoing issues with undiagnosed cases.

The move (https://www.bioworld.com/articles/507901-all-said-and-dunn-aduhelm-overwhelms-negative-panel-vote-to-win-fda-go-ahead-in-ad) makes aducanumab the first and only approved therapy addressing a defining pathology of AD, representing a significant long-term growth opportunity. However, because Alzheimer's dementia is often underdiagnosed and people are often unaware of their diagnosis by a clinician a large portion of Americans with Alzheimer's may not even know they have it.

Blood tests for the proteins tau and amyloid are already in demand, with companies like St. Louis-based C2N LLC, Indianapolis-based Eli Lily & Co., Billerica, Mass.-based Quanterix Corp. and more developing assays for this and other Alzheimer's biomarkers for use in clinical trial enrichment. Yet they have the potential to be used to diagnose AD, also.

The industry touted the FDA's approval of the drug on the basis of amyloid plaque reduction for Alzheimer's treatment as an important step in the ongoing fight against the disease. "The FDA's decision is consistent with C2N's focus on the development and commercialization of impactful diagnostic tests that track the

most important biological features of the disease," said Joel Braunstein, CEO of C2N, the developer of the commercially available PrecivityAD blood test.

The burden with underdiagnosis of Alzheimer's

AD is the most common cause of dementia and the only one of the 10 top causes of death that can be prevented or slowed. The associated costs are projected (https://healthpolicy.usc.edu/article/research-spotlight-alzheimers-disease/#:~:text=Annual%20per%2Dperson%20costs%20of,to%20%241.5%20trillion%20by%202050.) to reach $1.5 trillion by 2050.

Yet underdiagnosis of Alzheimer's and other dementias in the primary care setting is such an issue that an estimated 6.2 million Americans age 65 and older are living with Alzheimer's dementia, about half of whom have not yet been diagnosed by a clinician, the Alzheimer's Association reports (https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf). Only about half of Medicare beneficiaries diagnosed with Alzheimer's or another dementia in their Medicare billing records report being told of their diagnosis, also.

Several groups of researchers, however, have reportedly found that both health care as well as prescription drug spending are significantly higher in the one to two years prior to diagnosis, and one year after diagnosis compared with otherwise similar people who have not been diagnosed.

Blood tests and PET scans can help identify and track the disease, and help to accurately define who is on the continuum such that drug trials can be conducted at the earliest stage of the disease, thus preventing irreversible damage to the diagnosed patient's "normal" brain.

Some progress has been made in understanding the disease in the past few years, including how the disease progresses over time. Panelists on a Schaeffer Initiative for Health Policy webinar last September discussed the hope and possibilities that the approval of aducanumab could bring. They have come to recognize the disease as a continuum of 25 years or more, an accumulation of amyloid in the brain. "Very early intervention targeting this will be effective in slowing the disease," said Alzheimer's Therapeutic Research Institute Director Paul Aisen.

Alzheimer's Disease (AD): Pathophysiology

Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disorder that gradually impairs and destroys cognitive functioning (e.g., memory and thinking) and impacts behavioral abilities. This affects one's capacity to carry out straightforward of tasks. Symptoms generally first materialize in individuals in their mid-60s, but the disease is also known to affect younger individuals, so-called early-onset AD. AD is the most frequent cause of dementia among older adults.

Although the exact cause of AD is still unknown, a genetic component is suspected in some patients (e.g., apolipoprotein E (*APOE* gene) and a lengthy period of brain deterioration is believed to trigger late-onset AD. Adverse changes in the brain are thought to result predominantly from brain deposition of irregular clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary, or tau, tangles). Pursuant to these symptoms is a crucial loss of connections between nerve cells (or neurons) in the brain.

Beta-amyloid peptide (Aβ) is the main constituent of amyloid plaques. It is derived from the proteolytic processing of the amyloid precursor protein (APP) and accumulates in the extracellular region, where it forms plaques together with fragments of additional proteins and snippets of neurons. Neurofibrillary tangles are irregular agglomerations of tau, a protein essential for healthy neurons. In AD, tau molecules hyperphosphorylate and clump together, impairing the function of neurons.

When neurons lose their connections to other neurons they die, and the area of the brain in which they reside atrophies. Two particular protein kinases are believed to be involved in abnormal tau phosphorylation: the cyclin-dependent kinase Cdk5 and the glycogen synthase kinase GSK3β. Cdk5 is crucial for brain development and plays a part in neurogenesis

Opportunities and challenges in an evolving market

Millions of Americans could benefit from blood tests that can identify people at risk years before symptoms occur. Reducing the risk reduces the number of people who develop dementia, and delaying symptoms by up to five years could have a major impact on the financial burden of AD.

Biogen anticipates an uptick in demand in testing because of the approval of aducanumab. "We expect revenue to start ramping up in 2022 and beyond as we believe that detection and diagnosis of early AD will increase, system capacity will increase due to greater physician focus on training dementia, site infrastructure will continue to scale and availability of amyloid testing and reimbursement will increase for both PET and CSF," Biogen' executive vice president and chief financial officer, Michael McDonnell, said during a conference call discussing (https://www.bioworld.com/articles/507901-all-said-and-dunn-aduhelm-overwhelms-negative-panel-vote-to-win-fda-go-ahead-in-ad) the approval.

But the problem has been the lack of early diagnosis of the disease before dementia symptoms emerge and the brain suffers irreparable damage. There has not been much of an incentive to develop diagnostics that could detect the disease early on because there were no approved therapeutic solutions for early-stage AD,

otherwise known as Alzheimer's dementia. This was anticipated to change once drugs such as aducanumab were approved and reached the market.

"It's possible to identify brain amyloid plaques from a single sample of blood and to aid in the early diagnosis of Alzheimer's disease," Braunstein said reacting to the approval. "Early intervention represents our greatest chance for delaying or halting future progression."

C2N's test is available in 48 states, Washington and Puerto Rico, though it cannot be purchased directly by the consumer. Fujirebio Diagnostics Inc.'s Innotest immunoassays, which is seeking (https://www.bioworld.com/articles/500865-fujirebio-diagnostics-seeks-fda-clearance-of-alzheimers-disease-test) FDA clearance, Quanterix's tau assay, Lilly's FDA-approved tau imaging agent, among others, have entered the space, too.

Industry trade association Medical Imaging and Technology Alliance (MITA) commended the FDA's decision while urging updates to Medicare coverage for diagnostic tools. The CMS "needs to act to update its outdated coverage and payment policies and provide patients with access to amyloid PET diagnostic drugs," said Patrick Hope, executive director at MITA. "CMS should revise the legacy coverage and payment policies that will hinder access to this life-changing treatment," he said. MITA specifically calls on CMS to expedite reconsidering of the amyloid PET reconsideration request that has been pending since September 2020.

The implications for the diagnostics industry are still relatively fluid, particularly for amyloid PET diagnostic drug manufacturers. "But PET imaging remains the most accurate and least invasive way to detect the amyloid plaques which are targeted by this treatment," Hope told *BioWorld.*

When it comes to Medicare coverage, Hope explained that the issue is the fact that amyloid PET tracers are rarely covered by CMS as the current policy is over 20 years old and only covers amyloid PET scans as part of CMS's limited Coverage with Evidence Development program in CMS-approved clinical trials. "To help patients access AD diagnostics and therapies, MITA, Biogen, Lilly, GE, and Life Molecular Imaging made a formal request to CMS in September 2020 to reconsider its limited coverage policy on amyloid PET scans for AD," he said. "If CMS opens this reconsideration, the process can take up to nine months or more."