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A New Era of Neuroscience

Drill Down and Catch Up: The Role of Biomarkers in Neurodegenerative Disease

November 2024

Lumanity Insight

Transformational, near-term potential across multiple neuroscience areas

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Biomarkers are leading the transformation in neurodegenerative disease

While advances in neuroscience are reducing scientific risks, such as elucidating disease biology and identifying and validating targets, the journey remains fraught with significant clinical, regulatory, and commercial challenges. Neurodegenerative diseases epitomize these difficulties: scientific progress is being made, but issues like patient heterogeneity, inadequate trial design, and the lack of validated diagnostic and therapeutic biomarkers persist. As we transition from symptomatic therapies to the ultimate goal of disease modification—targeting the underlying causes to slow, delay, or even prevent disease progression—these challenges become more pronounced.

The development of disease-modifying therapies (DMTs) is particularly hampered by the insidious onset of symptoms and complex pathological changes occurring long before diagnosis. While several DMTs are approved for multiple sclerosis, only a few exist for other neurodegenerative diseases. A critical barrier has been the lack of reliable biomarkers that objectively identify patients and measure disease progression and therapeutic response. Without these biomarkers, clinical studies may miss relevant patient populations or fail to intervene at effective stages of disease trajectory—issues that plagued early Alzheimer's anti-amyloid therapies. For DMTs that overcome regulatory hurdles, biomarkers may be indispensable in establishing and supporting treatment value in these often slowly progressing conditions.

- The FDA defines **biomarkers** as a "defined characteristic that is measured as an indicator of normal biological processes,pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions", where a **qualified biomarker** "has undergone a formal regulatory process to ensure that we can rely on it to have a specific interpretation and application in medical product development and regulatory review, within the stated context of use"

- The FDA recognizes three types of endpoints that serve as a **surrogate endpoint** – validated surrogate endpoint, reasonably likely surrogate endpoint, and candidate surrogate endpoint

- **Accelerated approval** can be based on demonstration of an effect on a biomarker endpoint that is reasonably likely to predict clinical benefit

https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification

https://www.ncbi.nlm.nih.gov/books/NBK453485/

"Drill Down & Catch Up" segments are not comprehensive but designed to deliver topical information and stimulate thought and discussion. We welcome your comments and opportunities to learn more about your neuroscience programs.

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New biomarker technologies may overcome challenges unique to the brain

Recent advancements in biomarker research have unveiled promising avenues for addressing neurodegenerative diseases like Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS). A few noteworthy advances are highlighted below.

Alzheimer's Disease (AD)

AD studies are pioneering the use of biomarkers to enable and establish disease modification in clinical trials. Biomarkers, particularly amyloid-based brain imaging and cerebrospinal fluid (CSF) assays, played a crucial role in the development and approval of DMT therapies LEQEMBI (lecanemab, Biogen) and Kisunla (donanemab, Lilly) in 2023 and 2024, respectively. These biomarkers helped with accurate patient selection, demonstrated target engagement, and provided evidence of disease modification, supporting both clinical trial design and efficacy claims.

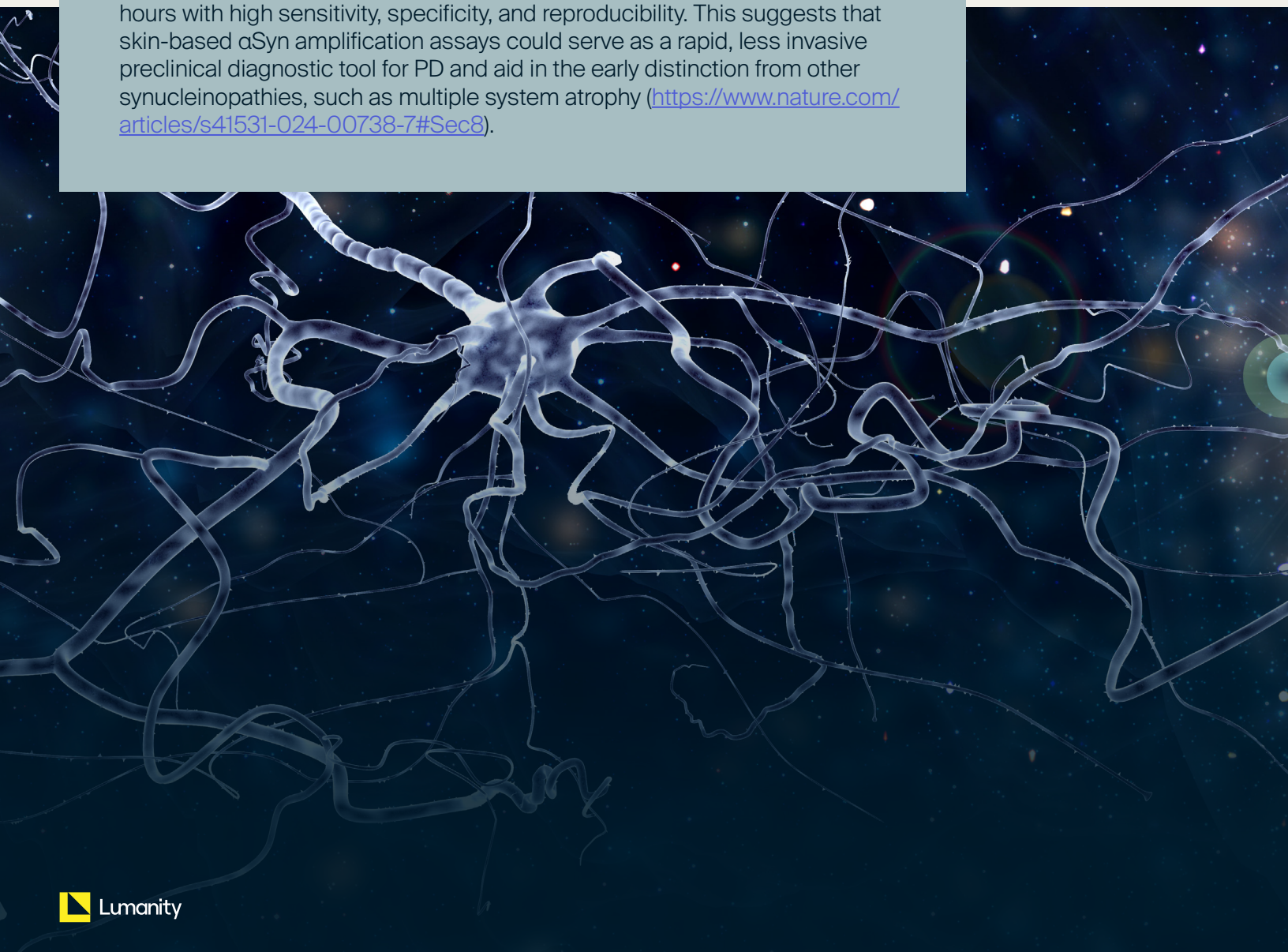
While the decision was not immediate, The Centers for Medicare and Medicaid Services (CMS) have recently agreed to cover amyloid positron emission tomography (PET) and other biomarker tests for confirming therapeutic targets for new anti-amyloid DMTs. This decision removes previous restrictions that limited amyloid PET use to evidence generation contexts, making it more accessible outside clinical trials or registries. Patients undergoing clinical evaluation for anti-amyloid therapies can now access these tests more readily. However, it remains unclear what specific indications or limitations will accompany CMS's coverage decisions, and there are calls for broader coverage beyond this narrow clinical scenario (*JAMA Neurol.* 2024;81(9):903-904. doi:10.1001/jamaneurol.2024.2100).

While amyloid PET scans and CSF biomarkers are essential for developing and utilizing new AD disease-modifying therapies (DMTs), they come with limitations and capacity constraints. Blood-based biomarkers are likely the only practical method that can be scaled to test everyone who might benefit from early and accurate diagnosis and potential DMT use. The advent of ultrasensitive assays for measuring blood biomarkers, such as pTau217, holds significant promise for revolutionizing clinical practice and research.

Parkinson's Disease (PD)

In Parkinson's, disease-modifying therapies aim to target alpha-synuclein aggregation, mitochondrial dysfunction, or other disease mechanisms, but most available treatments are symptomatic rather than truly disease-modifying. However, ongoing research is yielding potential candidates.

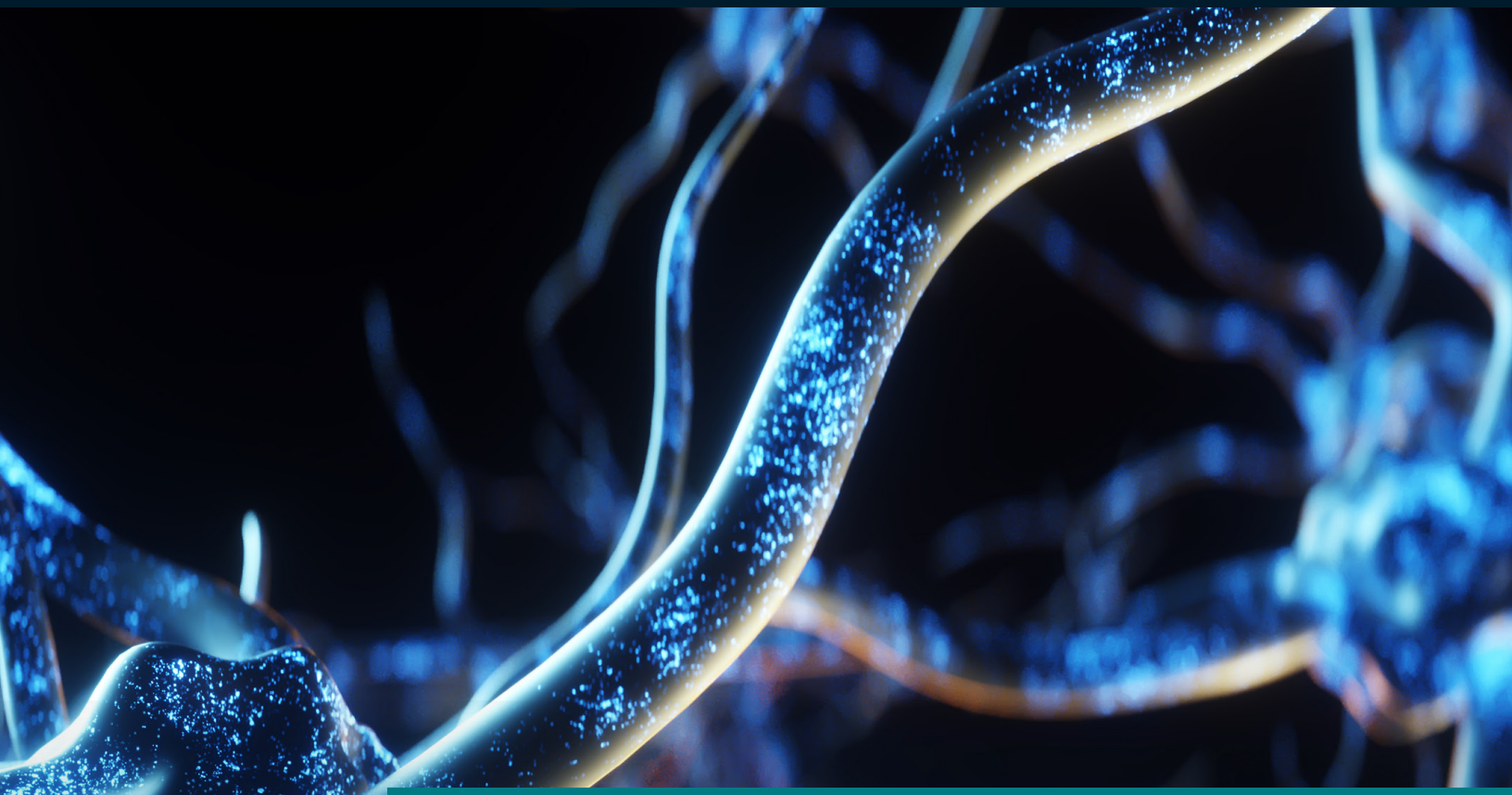
The seeding amplification assay (SAA) has recently emerged as a valuable tool for detecting α-synuclein (αSyn) aggregates that are hallmark pathologies of PD and other synucleinopathies. Various research groups have applied this assay using samples from brain homogenates, olfactory mucosa, saliva, and skin to detect the seeding activity of αSyn. Despite differences in current SAA protocols, researchers have optimized these conditions to enhance detection sensitivity and reduce assay duration. A 2024 study published in Nature customized the factors governing αSyn amplification, creating a streamlined SAA assay capable of detecting αSynD from skin samples in less than 24 hours with high sensitivity, specificity, and reproducibility. This suggests that skin-based αSyn amplification assays could serve as a rapid, less invasive preclinical diagnostic tool for PD and aid in the early distinction from other synucleinopathies, such as multiple system atrophy (https://www.nature.com/articles/s41531-024-00738-7#Sec8).



Amyotrophic Lateral Sclerosis (ALS)

ALS is characterized by significant heterogeneity, making the traditional division into familial and sporadic forms increasingly inadequate. Progression rates vary greatly between patients and even within the same patient, complicating comparisons with historical data. Without a validated biomarker to predict the rate of decline, assessing the effectiveness of treatments on disease progression remains challenging for individual ALS patients.

Of recent note, Biogen gained FDA accelerated approval for QALSODY (tofersen) in April 2023. This antisense oligonucleotide (ASO) was approved for treating a small subset of ALS patients with a mutation in the superoxide dismutase 1 (SOD1) gene, based on reductions in neurofilament, a blood-based biomarker of axonal damage and/or neuronal degeneration (not necessarily specific to ALS) despite not meeting expectations for functional outcomes. The ongoing Phase 3 ATLAS study of tofersen in presymptomatic SOD1-ALS patients will serve as the confirmatory trial, expected to be completed in 2027. The primary efficacy endpoint is the proportion of participants who develop clinically manifest ALS (https://investors.biogen.com/news-releases/news-release-details/biogens-qalsodyr-tofersen-first-therapy-treat-rare-genetic-form).



Early development of biomarker strategies is imperative in the development and commercialization of DMTs for neurodegenerative disease.

Biopharmaceutical companies must develop clear biomarker strategies to effectively advance and commercialize disease-modifying therapies (DMTs) for neurodegenerative diseases. Incorporating biomarkers into clinical trial designs can accelerate development milestones by aiding in accurate patient selection, demonstrating target engagement, and providing evidence of disease modification. Biomarkers are essential for identifying appropriate patients, driving therapy choices, monitoring treatment effects, and guiding the duration of therapy. Moreover, they help define and support the utility of new treatments for clinicians, patients, and payers, bolstering the overall value proposition. This, in turn, is crucial for securing access and reimbursement to ensure that innovative therapies reach those in need.

Look for our next installment in the series that will wrap up 2024 and peek at a few exciting advancements expected in 2025!

Contact us

Lumanity offers extensive experience-based strategic guidance and insights in the field of neuroscience. Our goal is to provide our clients with actionable solutions that de-risk and optimize the development and commercialization of therapies, ultimately improving the lives of patients who are impacted across a range of conditions.

Contact us to learn more about how Lumanity can support your unique challenge today.