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RESEARCH ARTICLE

Challenges and progress in research, diagnostics, and therapeutics in Alzheimer's disease and related dementias

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Abstract

The health, well-being, and financial security of Americans are greatly impacted by Alzheimer's disease. The forecast paints an upward trajectory with the number of Americans suffering from Alzheimer's disease and related dementia. To discuss the Alzheimer's crisis, The Senate Committee on Finance, Subcommittee on Health Care, held a hearing titled, "The Alzheimer's Crisis: Examining, Testing, and Treatment Pipelines and Fiscal Implications," on December 16, 2020. Here, we summarize and expand on the discussion of the panel and its review of recent progress, ongoing challenges associated with Alzheimer's disease, and potential initiatives that promise to speed progress in developing treatments and improving care.

KEYWORDS
ADRD, Alzheimer's disease, dementia, healthcare policy

1 | THE CURRENT STATE OF THE ALZHEIMER'S DISEASE THERAPEUTICS AND DIAGNOSTIC PIPELINES

The Senate Committee on Finance, Subcommittee on Health Care, held a hearing titled, "The Alzheimer's Crisis: Examining, Testing, and Treatment Pipelines and Fiscal Implications," on December 16, 2020.[1] The committee convened this hearing because of growing concern about the impact of Alzheimer's disease (AD) on the health of Americans and the financial impact of this disease on the US health-care system. Recent experience in developing diagnostic tests, treatments, and preventative vaccines for COVID-19 has shown how rapidly and effectively biomedical advances can address a public health crisis under certain circumstances; there is concern that the AD crisis is not being addressed with sufficient speed and success. In this article, we summarize and expand on the discussion of the panel and its review of recent progress, ongoing challenges associated with AD, and potential initiatives that promise to speed progress in developing treatments and improving care.

The speakers at the hearing presented perspectives for the committee on four principal modalities of health care and their relevance to AD: diagnostics, prognostics, therapeutics, and care (preventative, curative, and palliative). All these modalities contribute to the well being of patients and are aimed at maximizing human health and quality of life. Among these modalities, preventative and curative therapeutics would have the most profound impact on eliminating the financial and societal burden associated with the disease, as well as the quality of life of AD patients and their families. The principal challenge in identifying preventative and curative therapeutics is the current gap in scientific knowledge of the early molecular events that are necessary to cause disease—that is, the etiology. Disease-modifying therapeutics targeting disease mechanisms, as opposed to palliative therapeutics that treat symptoms, require an understanding of the mechanisms of disease etiology, which is currently not precise enough on an individual patient

level to determine a curative strategy. Thus, it seems likely that prevention will have a much bigger impact to implement a "cure" within the next several decades.

Speakers presented an overview of some current hypotheses about the pathophysiology of AD and the impact of those hypotheses on development of candidate therapies and diagnostic biomarkers. One of the hallmarks of AD is the accumulation of aberrant protein deposits in patients' brains. These pathological deposits called amyloid plaques and tau tangles contain protein fragments called amyloid beta (Aβ) peptide or tau protein, respectively. The observation of these aggregated proteins, along with genetic variations that increase or decrease Aβ species can cause or protect against AD, has become the central premise for the amyloid cascade hypothesis:[2] that the aggregation process results in a toxic gain of function of the aggregated proteins, ultimately resulting in neuronal death. The amyloid cascade hypothesis has led to molecules in the AD drug pipeline: many drugs that have been developed or are currently in clinical trials target either Aβ production, promote peptide clearance, inhibit aggregation, or promote neuronal resistance to aggregation.[3] More recently, some drugs target tau aggregates and other mechanisms. The only drug programs that have consistently shown some clinical and cognitive benefits are those that substantially remove amyloid plaque by positron emission tomography (PET). Minimal or partial removal do not seem to offer great benefits.

Presently, the diagnosis of AD is based largely upon clinical evidence, although recent advances in imaging, cerebrospinal fluid (CSF), and blood-based biomarkers offer the possibility of a more precise and accessible diagnosis and more effective screening in clinical research and practice. Clinical evidence, such as clinical change over time, family history, assessment of function manifested in activities of daily living, and cognitive tests indicate whether a patient exhibits signs and symptoms of dementia. In some cases, PET, magnetic resonance imaging (MRI), lumbar puncture, and more recently blood tests, aid in confirming or ruling out AD in patients with dementia. Evidence that pathological changes appear many years before clinical symptoms[4] indicates the possibility that pre-symptomatic assessment by biomarkers could enable identification of patients early in the disease course.

2 | GAPS IN DATA OR UNDERSTANDING OF THE DISEASE THAT ARE LIMITING THERAPEUTIC AND DIAGNOSTIC DEVELOPMENT

Alzheimer's disease, similar to many other chronic diseases, has a complex pathophysiology. This complexity makes treatment development more difficult than is the case for some infectious diseases in which the causal agent is well characterized, there are powerful treatments that completely eradicate the cause, and the etiology is an external living agent. Processes that lead to neurodegeneration arise at the molecular level and consequently result in cellular death, but physiological disease onset and consequent cognitive manifestation occurs only after significant and irreversible neuronal loss. As a result, neurodegenerative diseases are age-related and take from years to decades to manifest, by which time, the only treatment available to mitigate the disease is alleviation of symptoms or slowing or stopping progression. The paramount challenge of developing treatments for neurodegenerative diseases lies in identifying the early pathological events that would eventually result in cell death, and targeting those events to rescue the afflicted neurons.

As of now, neurodegenerative diseases have few therapies that would slow progression. Biomarkers that detect early events associated with the neurodegenerative process are in development and have already provided the ability to enhance early detection and enable testing of potential treatments earlier in the disease. To help accelerate progress in developing effective treatments, the field of neurodegeneration needs new and disruptive thoughts and approaches. In a policy context, it is worth noting that advances in the treatment of one neurodegenerative disease could provide lessons for the treatment of others.

The first and most significant barrier to progress in developing new medicines is that we have not yet proven the key biological processes causing AD dementia. As we have learned from experience with COVID-19, once a clear causal agent is identified and characterized biologically, the search for preventative measures and treatments can proceed rationally through the conduct of highly informative basic and clinical research. For a chronic disease such as AD with multiple risk factors and with complex pathology, the path to effective treatments is quite uncertain. In the private sector, there is a high degree of interest and considerable investment in AD drug development, but it is considered higher risk than other therapeutic areas in which the perceived likelihood of clinical and commercial success is seen as higher. This is one reason why we have not seen the number of successful new medicines we have seen in oncology, autoimmune diseases, diabetes, and other conditions. However, it should be noted that for those diseases it also took decades to find effective interventions, and the first drugs had small clinical effects. Today, the largest impacts are realized through public health measures aimed at prevention and in novel medications that slow or stop progression in cancer, diabetes, and cardiovascular and other conditions.

The fundamental challenge of understanding AD etiology is a significant disconnect between times at which pathological processes start and when they manifest in the form of symptoms (Figure 1). With the development of new blood-based biomarkers,[5] we may be able to track processes as they first appear in large numbers of people and before irreversible damage occurs as these changes occur 20+ years before symptom onset.[6]

However, there are challenges in how to implement intervention strategies. Furthermore, we do not know whether Aβ and tau proteins[7] are the sole or most significant early molecular events that lead to downstream processes. Hence, it may be premature to conclude that these deposits are the only or most direct cause of the disease. Yet, while they can serve as biomarkers, little is known about what is triggering these proteins to aggregate, and whether aggregates are the reason why neurons die. Given this uncertainty, it seems scientifically sound to explore other factors that could be involved in starting or promoting neurodegeneration.

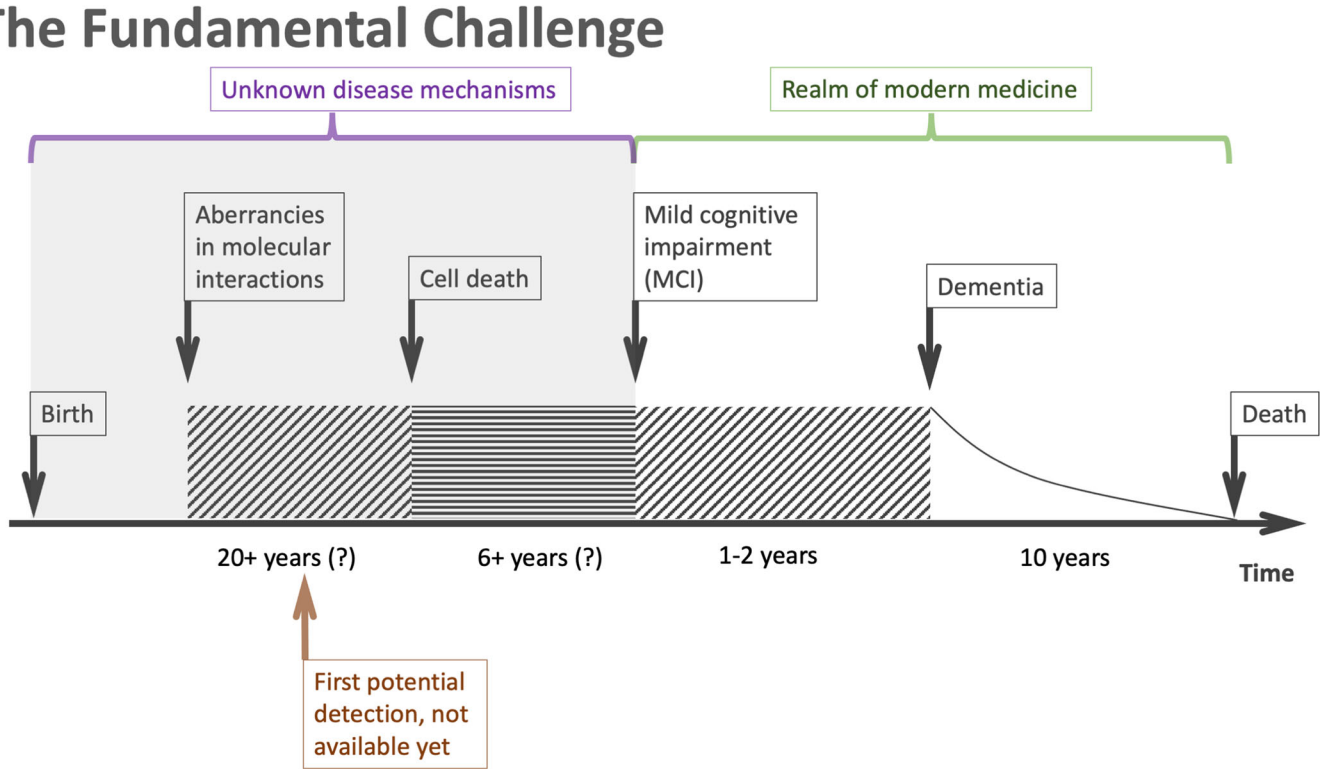

FIGURE 1 Alzheimer's disease timeline. Pathological processes start with abnormal molecular interactions leading eventually to neuronal cell death. However, only when sufficient damage to the brain has occurred do patients exhibit mild cognitive impairment. This critical point defines the realm of modern medicine when the disease is manifested, and patients seek treatment and care strategies. The time preceding this critical point is the prevention period, during which some irreversible tissue damage happens. Even though current advances in biomarkers can detect multiple pathologies in this prevention period, we still do not have direct measures of key Alzheimer's disease processes, which are driven by aberrant molecular interactions.

3 | CHALLENGES TO PRIVATE SECTOR ENGAGEMENT IN THE DEVELOPMENT OF THERAPEUTICS AND DIAGNOSTICS, AND POTENTIAL SOLUTIONS TO THESE CHALLENGES

The for-profit private sector balances knowledge of drug targets against the risks associated with them. Although AD is a potentially profitable area for the pharmaceutical and biotechnological industries, the costs associated with clinical trials and their long duration is a significant deterrent. The pharmaceutical industry is under significant pressure to create novel and innovative solutions and, thus, has one of the highest research and development expenditures among all industries.

While there are clear barriers to developments in the diagnostic, therapeutic, and research pipelines for AD, new federal strategies could enable clinically meaningful advances in the disease's diagnosis and treatment, like what has been accomplished for diagnostics and vaccines for the COVID-19 pandemic. Recent increases in National Institutes of Health (NIH) funding for AD and related dementia research has already realized significant growth in research productivity and capabilities. Novel initiatives, such as Advanced Research Projects Agency for Health, could enable additional transformational changes in implementation of the basic and translational advancements. Summarized below are some of the ongoing challenges, and the associated opportunities that could greatly accelerate the discovery and validation of AD treatments and preventions.

Barriers to therapeutic development include regulatory burden, risk-averse trial designs, and sometimes lack of urgency and not accounting for the costs of inaction, leading to clinical trial delays and higher overall costs. Extensive international regulatory reporting requirements and approval delays contribute to the time and cost of major trials, which can be several hundred million dollars and take 3 to 5 years to complete. Prevention trials are even longer (7 years or more). These trials are too expensive and too long, causing potential treatments to be "left on the shelf" untested, and some drug developers to abandon AD drug development programs. To implement large-scale global trials, the field needs to move quickly and test more drugs in parallel, creating more "shots on goal."[8] Recent efforts to conduct smaller and faster yet informative trials have the potential to increase the probability of success for later phase 3 trials.[9]

How can this be helped? Policy makers and agencies can enable and support standards which: (1) account for the personal and financial cost of AD in terms of the opportunity costs of delays into decision making (i.e., a balanced risk–benefit analysis accounting for time lost on deliberations); (2) enable science and medicine to advance at optimal speed, accounting for potential benefit while managing risk; and

(3) encourage investment in the development of treatments and preventions for AD.

Highly accurate diagnostic measures of AD amyloid plaques and tau tangles have been available for several years, and more recently, simple blood tests have been developed,[10,11] but they are not used in clinics yet for several reasons, including lack of payer support. Symptomatic patients and their doctors have a need for an accurate diagnosis. These tests can accurately identify who has AD, and importantly, who does not have AD. Because ≈50% of AD patients are not accurately diagnosed through a clinical assessment alone, testing for pathology would provide specific and accurate treatment to those with AD, while informing the physician to investigate other causes if problems with memory and thinking are not due to AD. Because some of the causes (e.g., depression, medication side effects, thyroid disorders) are treatable or reversible, it is important to have an accurate diagnosis. We must identify the disease to treat and manage it.

For research purposes, measurable indicators of AD pathology (biomarkers), such as blood and CSF amyloid and tau, offer immense promise. These biomarkers are being used to screen for the disease, track the effects of treatments on AD biological processes, and are also being considered for surrogate biomarker development, which would greatly speed AD trials. When preventions are developed, screening biomarkers will be essential to identify those on the AD path to appropriately treat those with high risk.

There is a disconnect between the way patients with AD are diagnosed in current clinical practice and the way research studies identify study participants. Most practicing physicians wait and make a diagnosis of AD relatively late, when patients manifest clear symptoms and need counseling on how to manage those symptoms after significant functional decline has occurred. We now know that the pathology of AD begins in the brain decades before patients develop symptoms such as memory loss and impairment in activities of daily living. Biomarkers, including PET brain scans, CSF amyloid and tau, and now blood-based measures of amyloid and tau enable the detection of AD pathology well before symptoms of AD are noticeable. Many drugs in development are expected to be most effective by intervening when pathology is just starting rather than when it has advanced enough to cause major impairment. As a result, clinical trial sponsors must evaluate many potential study participants with cognitive tests and expensive, time-consuming PET scans to enroll appropriate trial participants; that is, participants with AD pathology but with only a mild form or no symptoms. This disconnect is one of the reasons AD trials are difficult to conduct even relative to trials in other chronic conditions such as heart disease, cancer, and diabetes.

The Global Alzheimer's Platform (GAP) foundation is in the process of standing up a platform study that will test the efficacy of more than a dozen promising blood biomarkers and digital cognitive assessments as prognostic or diagnostic indicators for AD. Known as the Bio-Hermes study,[12] it will generate biological samples and digital biomarker data from 1000 participants; the study will also enable development of a data algorithm to produce next-generation clinical trial enrollment solutions. The Bio-Hermes study will include racially and ethnically diverse participants to assess whether biomarker risk factors vary by race and ethnicity.

Recruiting a diverse group of informed and willing participants for an AD clinical trial is both extremely important and challenging. Despite making up about 30% of the US population, Black and Latino people usually make up only about 3% to 8% of clinical trial participants. To help address this issue, GAP has committed to recruiting at least 20% Black or Latino volunteers for the upcoming Bio-Hermes study and will not close recruitment for this trial until it has a group of study participants that accurately reflects the community of people living with AD. GAP's intention is for the Bio-Hermes study to be a model for building back a clinical trial infrastructure that is more efficient and gets us to better diagnostics and medicines faster.

4 | OTHER BARRIERS THROUGHOUT THE RESEARCH AND DEVELOPMENT PROCESS AND APPROVAL PROCESS FOR ALZHEIMER'S DISEASE AND POTENTIAL SOLUTIONS TO THESE BARRIERS

Federal grant programs, specifically those sponsored by the NIH, offer support for both fundamental and translational biomedical research. At the NIH, scientific merit reviews are performed by scientists, and, therefore, offer a broad and fair coverage of research directions. These grant programs are highly competitive, and thus proposals that offer something radically different and risky ("high risk, high reward") tend to fare worse than risk-averse proposals that continue established lines of research. While the NIH has provided venues for high-risk high-return projects, they remain extremely competitive, especially for younger scientists and those with new ideas who come from outside of a traditional neuroscience background.

Protein aggregation is a hallmark of neurodegenerative diseases, including AD. The mechanisms of protein aggregation are understood from a biophysical perspective, but how this molecular knowledge relates to physiology remains unknown. Thus, translational science programs aimed at marrying disparate scientific fields with clinical research are critical to establish a working model of disease. The success of translational science relies on attracting scientists with backgrounds in diverse fields to build inter-disciplinary programs. In addition, attracting industrial partners to these inter-disciplinary consortiums will facilitate their progress.

The dominant cost associated with caring for AD patients stems from the extensive care required in later stages of the disease. Reducing the cost of care is mostly an untapped direction in mitigating the growing cost of the disease in the United States. Recent scientific and engineering innovations, especially in machine learning and artificial intelligence, wireless solutions, and miniature devices, may offer new and unparalleled means of caring for patients, especially in the advanced stages of the disease. For example, wearable devices with geofencing abilities may allow automated remote monitoring of a patient's health state, while location services may significantly reduce the risk of a patient with dementia wandering from home, thus allowing those with AD to remain at home and out of care homes for

longer. Facilitating such innovations through federal and private sector programs will have a major impact on improving the quality of care and reduce financial burden on both government programs and on individuals.

The Food and Drug Administration (FDA) is an essential partner to the efforts of the pharmaceutical industry and academic researchers when it comes to the search for better diagnostics and treatments for AD. We applaud the agency's approach to public engagement around their evaluations. We appreciate that the FDA has been transparent and energetic in its engagement with a broad range of stakeholders, including patient advocates, researchers, and pharmaceutical companies. Given the need for greater diversity in clinical trials, Congress could use the Prescription Drug User Fee Act renewal process to encourage the FDA to develop clear guidance on minimum standards for diversity in clinical trials.

We hope that Congress will take lessons learned from COVID-19 and apply them to the AD crisis. For example, the Federal government should establish a task force with authority to evaluate the barriers to progress and move with great urgency to deliver on the National Alzheimer's Project Act promise for effective therapeutics by 2025. Federal agencies should have increasing support for greater involvement and coordination to address the AD challenge. For example, increased collaboration between the FDA and the Centers for Medicare and Medicaid Services could accelerate future reviews regarding efficacy of new diagnostics and medicines and consideration of their merits for reimbursement can occur concurrently, more efficiently, and in less time. This would help speed the delivery of innovative diagnostics and medicines to patients and clinicians.

CONFLICTS OF INTEREST

N.V.D. is the President of the Molecules in Action LLC. He also serves on the advisory board at Atom Bioworks. He also serves as the Editor-in-Chief of *Proteins*. R.C.M. is the Chief Science Officer for the Global Alzheimer's Platform (GAP) Foundation and Vice President for Clinical Development at Agenebio, Inc. a Baltimore-based biotechnology company; he is PI for NIA Grant R01AG061091 "A Phase 3 Pivotal Trial of AGB101 to Slow Progression in MCI due to Alzheimer's Disease" awarded to AgeneBio. He is member of the Board of Governors for the Alzheimer's Drug Discovery Foundation (ADDF), and a member of the Board of Directors for CogState, Ltd. He has received consulting fees from Vaxxinity, Inc., Amyriad Therapeutics, and the MD Anderson Cancer Center, Center for Neurodegeneration. R.J.B. has received research funding from Avid Radiopharmaceuticals, Janssen, Roche/Genentech, Eli Lilly, Eisai, Biogen, AbbVie, Bristol Myers Squibb, and Novartis. Washington University and RJB have equity ownership interest in C2N Diagnostics and receive royalty income based on technology (stable isotope labeling kinetics and blood plasma assay) licensed by Washington University to C2N Diagnostics. RJB receives income from C2N Diagnostics for serving on the scientific advisory board. R.J.B. has received honoraria as a speaker, consultant, or advisory board member from Amgen and Roche.

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REFERENCES

1. Dokholyan N, Bateman RJ, Mohs R & Carrillo M. The Alzheimer's Crisis: Examining Testing and Treatment Pipelines and Fiscal Implications. Hearing Before The Subcommittee On Health Care Of The Committee On Finance United States Senate One Hundred Sixteenth Congress Second Session. (2020).
2. Hardy JA & Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256:184–185.
3. Udeh-Momoh CT, de Jager-Loots CA, Price G & Middleton LT. Transition from physical to virtual visit format for a longitudinal brain aging study, in response to the Covid-19 pandemic. Operationalizing adaptive methods and challenges. *Alzheimer's Dement (N Y)*. 2020;6:e12055.
4. McDade E, Wang G, Gordon BA, et al. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. *Neurology*. 2018;91:e1295–e1306 .
5. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol*. 2022;21:66-77.
6. Schindler SE, Bollinger JG, Ovod V, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology*. 2019;93:e1647–e1659.
7. Barthélemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat. Med*. 2020;26:398-407.
8. Bateman RJ, Benzinger TL,Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimer's Dement*. 2017;13:8-19.
9. Friedman LG, McKeehan N, Hara Y, et al. Value-generating exploratory trials in neurodegenerative dementias. *Neurology*. 2021;96:944-954.
10. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimer's Dement*. 2017;13:841-849.
11. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324:772-781.
12. Bork J et al. The global Alzheimer's Platform Foundation®: Delivering new medicines faster by accelerating clinical trials. *Alzheimer's Dis. Drug Dev. Res. Dev. Ecosyst*. 2022;207.

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