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# Research Advances Aimed at Prognosis and Treatment of Alzheimers Disease

**Godwin Okoye [a*] and Rachel Vincent [b]**

*[a] Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, USA.*
*[b] Department of Pharmacy, University of Jos, Jos, Plateau, Nigeria.*

***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## ABSTRACT

Alzheimer's disease (AD) continues to remain a public health concern especially for seniors globally. Increased life expectancy owing to improvement in medical advances may have increased AD's prevalence. It remains a matter of concern for stakeholders to look at progress made over the years and to fill the numerous gaps targeted at preventing the onset of AD and/or treating existing condition. In recent times, funding for AD research has increased in the United States (U.S) but the economic burden isn't left out. Controversies on gene modification still exist. The search for a definitive treatment still continues since recently approved drug-Aducanumab still has uncertainty concerning safety and efficacy. Newer therapies hold promise but we are still uncertain as we await their approval and real world evidence for safety and efficacy.

*Keywords: Prognosis; geriatrics neurology; health policy; genetics.*

## GLOSSARY

*AD : Alzheimer's Disease*
*FDA : Food and Drug Administration*

**Corresponding author: E-mail: gokoye8@gmail.com, gokoye@umaryland.edu;*

*CMS : Centers for Medicare and Medicaid Services*
*MCO : Managed Care Organizations*

## 1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with cognitive decline. AD is the most common type of dementia affecting the elderly, with 1 in 9 older adults diagnosed with AD [1]. The disease slowly progresses from disorientation, confusion, and general behavioral changes to difficulty performing essential function like swallowing, speaking, and walking [2]. Prevalence for early-onset AD (AD affecting people <65 years) has been progressively increasing to near 10% of the entire population of people with AD [3]. An estimated 35 million individuals who have AD worldwide is predicted to increase by over 130 million by 2050 [4]. In the United States, AD-related death has increased by more than 16% during COVID-19 pandemic [5]. Furthermore, it has been discovered that AD kills more than breast cancer and prostate cancer combined. Studies have shown that Africans are at high risk of developing AD but are less likely than Whites to get a diagnosis [7]. It has been officially listed as the 5th leading cause of death for those aged 65 and older and the 6th cause of death in the United States [8]. For this paper, we will look at issues surrounding funding, preventive measures, and AD treatment.

## 2. FUNDING FOR RESEARCH ON ALZHEIMER'S DISEASE

In the past, low funding for AD has resulted in a decline in the number of AD researchers [9].

Alzheimer's disease research has received a mere fraction of funding dedicated to cancer, which receives $5.7 billion annually compared to Alzheimer's $550 million in funding [10]. Currently, the rising cost of healthcare could have encouraged Congress to increase funding for Alzheimer's Disease and Related Dementias (ADRD) research in March, 2022 to a whopping $3.5 billion [11]. The estimated medical cost of treating AD in 2020 was about $305 billion. A systematic review conducted by Cummings et al. suggested that since 1995, there has been a total of 1099 clinical trials targeted at finding a cure for AD. This has resulted in about $42.5 billion spent in clinical trials aimed at developing a lasting treatment for this ailment with 50% of this cost being spent in phase III of these clinical trials [12]. Despite these efforts, only five of these drugs (with the exception of Aducanumab) have been able to reach a stage of approval with the FDA [12].

## 3. TRENDS IN ECONOMIC BURDEN OF ALZHEIMER'S DISEASE

Medicare is expected to cover 80% of the medical cost of management of AD however, concerns arise for people with co-morbidities that causes them to pay more than $6,550 per annum prompting the implementation of the Medicare Catastrophic Coverage.

With all the progress made, Medicare covers inpatient hospital visits (Part B) but there has been lapses with covering long term nursing home care (Part A) [13]. The patient's caregivers are now saddled with the responsibility of caring for the patient for as long as these patients are alive except, they can afford to pay for a nursing home. The caregivers are the most impacted and little has been done to recognize and support them.

Research done by Mount Sinai Hospital in New York and other medical centers who studied records from 555 men and women in the Health and Retirement Survey illustrated that medical care for the last five years of life for seniors living with ADRD costs more than for those living with heart disease and cancer. Using 2010-dollar amount, the figures are $287,000 for ADRD, $173,000 for cancer and $175,000 for heart disease [14].

According to AIMS (Alzheimer's Impact Movement), In 2021, about $239 billion is expected to be spent by Medicare and Medicaid in caring for people with Alzheimer's Disease and Related Dementia (ADRD). The direct cost is estimated to be $355 billion. This means that Medicare and Medicaid would cover just about 67% of the direct total cost of this disease. Average annual per person spending for seniors who are Medicare beneficiaries without Alzheimer's versus those with Alzheimer's was estimated to be 3:10. For Medicaid, an estimated ratio of 4:100 was obtained [15].

## 4. COLLABORATION BETWEEN THE GOVERNMENT AND PRIVATE AGENCIES

Of all the risk factors associated with AD; age, environment, and genetics play a huge role in the

propensity to come down with this disease. New findings from high-end research are revealing clues about the molecular mechanisms of AD and new ways to discover potential therapeutic target. Some discoveries were made by six research teams participating in the Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) program [16].

A collaboration between NIA and non-profit organizations like the Sage Bionetworks in Seattle used innovative computational approaches to predict the sequence of molecular changes that lead to AD. In 2014, $34 Million was invested. This has been increased over the years to about $400 million dollars in 2020. Even though the failure rate has been estimated to be around 99%, One breakthrough is all that is needed for sustained improvement in cognition of AD patients. The research teams has successfully determined molecular subtypes for late-onset Alzheimer's disease [17]. Some notable discoveries have been on tau phosphorylation and amyloid plaques. This has served as the basis for current longitudinal studies that are ongoing to discover potential drug targets at different stages of the disease. However, the drawback of this collaboration is the time required to achieve a breakthrough and the constant dessert of researchers to other rewarding disciplines that provide better results.

## 5. PREDICTIVE GENE TESTING- A WAY FORWARD?

FDA regulates medical devices used for testing for the presence of gene-related Alzheimer's disease and has approved the kits from 23andme® [18].

A predictive genetic test aims to see whether there is an inheritance of the genetic mutation associated with AD development. This gene is inherited in an autosomal dominant pattern and can be detected easily. Now, one important pro of genetic testing is that it has helped in selecting participants for clinical trials as cases for those who show a positive test and as controls for those whose outcome is a negative test. As with any other screening tests, The NIA has advised against people routinely requesting to know if they have this gene. This is because there are no available treatments. But this has been a tool of controversy between the NIA and various Patient Advocacy Groups. The cons of genetic testing are that insurance companies do not cover it, and it is expensive. Some insurance companies may choose not to cover people who have a positive test to APOE-e4 [19] (Gene responsible for early-onset AD) because of a perceived liability.

## 6. CURRENT RESEARCH ONGOING FOR THE PREVENTION/DELAYED ONSET OF ALZHEIMER'S DISEASE

The government can reduce the incidence of early-onset Alzheimer's by funding research that seeks to tackle AD at the genome level. This would correct genetic mutation to one that is not associated with the disease. The modified genes can be passed down through generations. CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) has been one such technique developed for gene editing. It allows for precise and relatively straightforward DNA editing; it has transformed every disease for which we know the underlying mutation(s)—into a potentially treatable target [20].

The potential role of gene-editing tools in advancing precision medicine for Alzheimer's disease could improve the accuracy of dementia diagnosis, thus enabling more personalized treatment strategies and speeding up the discovery of new drugs and interventions [21]. Bayer, Merck, and Curevac have invested more than $400 million in Crispr technology [22]. Stakeholders' regulatory concerns have been an issue because it is presumed that the edited gene would be passed down to offspring. In this context, it is believed that this is an advantage because it can eradicate AD linked to genetics. International agencies concerned with HGGE (Human Germline Genome Editing) are reluctant to give their absolute approval because of unanswered ethical, legal, and social questions [23]. A major concern has been on off target mutations [23].

## 7. USE OF BIOMARKERS AND SURROGATE ENDPOINTS TO EXPEDITE DRUG APPROVAL

Developing new drugs is a slow and painstaking process. For over 18 years, more than 400 drug trials for AD have been done but with no definitive success [24]. As soon as a helm of hope was seen with Aduhelm®, an accelerated approval was granted by the FDA.

Biogen developed Aducanumab (Aduhelm®). In the case of Aducanumab, the surrogate endpoint

is the removal of the beta-amyloid plaques that are presumed to be a causative agent of AD by creating a protective anti-amyloid antibody [25]. FDA granted Aducanumab an accelerated approval based on clearance of the beta-amyloid plaques with the hope that it will slow cognitive decline in patients suffering from AD. Studies have shown that there is no meaningful sign of clinical benefit with aducanumab except for plaque clearance. In addition, safety concerns for microhemorrhage and hemosiderosis have been discovered.

FDA's approval does not mandate Medicare coverage of Aducanumab. Instead, CMS decides based on facts available about which treatment is reasonable and necessary. 80% of those eligible for this drug are Medicare beneficiaries [26]. This is bound to have a severe economic impact on both the program and out-of-pocket medication costs because of the price. For this reason, a national coverage determination might be used to determine who gets the drug and who does not. So far, criteria for eligibility include those less than 85 years, must have a mild cognitive impairment, presence of beta-amyloid plaques determined using recent MRI scans/Lumbar puncture [26]. An expansion of these criteria might be reached for all inclusion criteria used in phase 3 of the clinical trial [27]. Also, paying for the drugs based on an expected outcome would go a long way to save costs (Value based payment). If a consensus is reached not to adopt this drug, Biogen would be adversely affected, including its stakeholders.

Some monoclonal antibodies are still undergoing clinical trials for their capacity to clear beta amyloid plaques or prevent these plaques from clustering. An example is Lecanemab which has moved to phase 3 clinical trials. Donanemab is another one that has shown promise in phase 2 trials and is moving into phase 3. Solanezumab holds promise for being effective in the preclinical stage of the disease [28 29].

## 8. CONCLUSION

Progress has been made in developing prognostic and therapeutic measures in drug development for AD. It is starting with the government recognizing that this disease is a public health concern and allocating more funds for research, to collaboration with private agencies to fund research that has discovered potential targets for treatment at every stage of this disease. Recent inclusivity of diverse race for clinical trial research has shown that there are more black people with Alzheimer's that have gone undiagnosed largely because of poor health access and being less insured. Efforts are being made to cover that gap. The Affordable Care Act has been instrumental in improving access to prescription drugs that has been used over the years to manage AD. Gene testing have had its significance in recruiting participants for clinical trials. However, this is an expensive venture that MCOs and other providers do not cover. Crispr technologies hold promise to eradicate AD at the genome. However, its major drawback has been regulatory concerns from international agencies. Making strict regulations on somatic cell gene editing would be helpful. Accelerated approval of Aducanumab has been a significant breakthrough. Those with beta amyloid plaques may benefit from this drug. However, worries about efficacy, safety concerns and price are a significant drawback. It has limited Medicare from covering the drug, and most people cannot afford out-of-pocket payments for the drug even if it eventually has an approved Medicare coverage. Applying Value Based Payment (VBP) system would go a long way to save cost and at the maximum intended output required. Three other drugs are still in the pipeline, and Lecanemab holds promise to be used for early-onset AD based on data available.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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