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Review Article

# Precision Therapeutics for Alzheimer's Disease

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## Abstract

Alzheimer's disease are responsible for causing dementia and accounts for 60-70% of all cases, due to which millions of people worldwide were affected. Alzheimer's disease becomes economic burden on societies and to healthcare systems also. It is a progressive neurodegenerative disease that gradually destroys memory, thinking social and behaviour skills and eventually, the ability to carry out simple tasks. Other clinical characteristics include confusion, hallucination, agitation, and behaviour disturbance. Alzheimer's gets worse over time. It causes the brain to shrink and brain cells to eventually die. There is no cure for Alzheimer's diseases, but medications and therapies can help manage the symptoms and improve quality of life for people with the diseases. As the prevalence of AD continues to increases, understanding its pathogenesis, improving diagnostic methods, and developing effective therapeutics have become paramount. Effective therapeutics for Alzheimer's diseases are needed. It is believed that Alzheimer's diseases (AD) is a complex and heterogeneous neurodegenerative disorder with no definitive cure. Precision therapeutics aim to tailor treatments based on an individual's genetic, molecular, and lifestyle factors to enhance efficacy and minimize adverse effects. Advances in genomics have enabled targeted therapies, such as antisense oligonucleotides and CRISPER- based gene editing, particularly for patients with high- risk genetic variants like ApoE4 and familial AD mutations (APP, PSEN1, PSEN2). Biomarker – driven approaches, including amyloid and tau-targeting monoclonal antibodies (Aducanumab, Lecanemab), along with neuroinflammation modulators, are shaping personalized interventions. Additionally, emerging strategies in multi-omics integration, AI- driven drug repurposing, microbiome- based therapies, and digital biomarkers are revolutionizing early diagnosis and individualized treatment plans. By leveraging precision medicine, the future of AD therapeutics lies in personalized, proactive, and predictive approaches that may significantly alter disease progression and improve patient outcomes. Another important factor in this development is the emergence of precision therapeutics that aims to tailor treatment to specific patients or patient subgroups. This relatively new platform would categorize AD patients on the basis of parameters like clinical genetics, and epidemiological factors. This review enlarges on recent progress in the design and clinical use of antisense molecules, antioxidants, antibodies, small molecules, and gene editing to stop AD progress and possibly reverse the disease on the basis of relevant biomarkers.

**Keywords**: Precision Therapeutics; Alzheimer's Disease; Biomarker; Epidemiological Factors

## Introduction

Dementia is mostly caused by Alzheimer's disease (AD), a sickness that results in the degeneration of brain cells. It is typified by a decrease in thinking and independence in one's routine tasks. AD is regarded as a complex illness, and two primary theories- the cholinergic and amyloid hypotheses- have been put out to explain it. The illness is also influenced by a number of risk factors, including ageing, genetics, head trauma, vascular disorders, infection and environmental variables. The two kinds of approved mediations for AD that are now available are cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonist. These medications are only useful in treating the symptoms of AD; they neither pre-

vent nor cure the illness. These days, research is concentrating on understanding AD pathology by focusing on multiple mechanisms, including aberrant tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage, with the goal of creating effective treatments that can halt or alter the progression of AD. Drugs that are currently on the market as well as potential future developments for AD therapy, including disease-modifying therapeutics (DMT), chaperones, and natural substances. Cognitive deficits and a gradually worsening memory loss are clinal hallmarks of AD. Amyloid-beta (Aβ) deposition outside of neurons and within senile plaques, as well as intracellular buildup of microtube-associated Tau protein, are the main causes of the patient decline. The disruption of neuron-neuron contact- at synapses by Amyloid- beta is thought to lead to cell death, whereas Tau neurofibrillary tangles restrict the flow of vital nutrients and other substances within neurons. Alzheimer's disease pathogenesis [1]. These reasons are accompanied by error in the amount of the presynaptic protein α-synuclein and lipid-carrier protein apolipoprotein E, particularly linked to the ε4 allele. A-synuclein can self- aggregate into huge inclusions called Lewis bodies inside neurons, while apolipoprotein E4 contributes to the buildup of tau and Aβ peptides [2]. In honor of the German psychiatrist Alois Alzheimer, Alzheimer's disease (AD) was called. When analysing the brain of his first patient, who experienced memory loss and a change in personality before to passing away, Alois Alzheimer discovered amyloid plaques and a significant loss of neurons. He characterized the condition as a severe cerebral cortex disease. This illness was initially referred to as Alzheimer's disease by Emil Kraepelin in his psychiatric handbook, 8th edition [2]. Brain disorders like Alzheimer's disease (AD) or other conditions like intoxication, infections, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen reaching the brain, vitamin B12 deficiency, and nutritional deficiencies can all contribute to a progressive loss of cognitive abilities [1]. There are two types of AD: early-onset (AD in ages 30 to 65) and late-onset (AD in ages over 65). In terms of genetics, AD can be classified as either sporadic or familial. Relatively few patients are affected by family instances, which are characterized by early onset and mutation inheritance. Genes encoding proteins linked to Aβ aggregates, such as presenilin-1 or 2, which is found in the catalytic core of the enzyme γ-secretase, and amyloid precursor protein (APP), are characterized by hereditary autosomal mutations in these cases. Ten distinct isoforms can arise from the 18 exons that make up the APP gene, with APP 695 being the most prevalent in the central nervous system (CNS) [2].

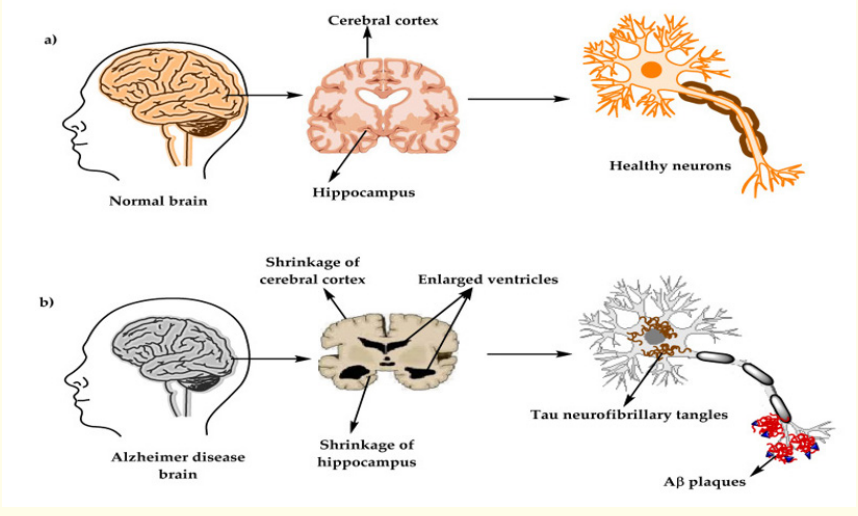


**Figure 1:** The physiological structure of the brain and neurons in (a) Healthy brain and (b) Alzheimer's disease (AD) brain [1].

## Need for Precision therapeutics

The National Institute of Health (NIH) and many other research institutions launched the Precision Medicine Initiative in 2015 as a new way to approach medicine with a patient-specific and targeted approach. According to these institutes, PM is defined as "developing approaches for treating and preventing disease that take account of individual heterogeneity in the environment, genes, and lifestyle for each person".

There is a lot of potential for this approach to medicine in addressing the distinct traits of individuals with different lifestyle, genetic, and related comorbidities that may change how they respond to treatment [5]. Predetermined by earlier clinical trials, such as a therapeutic technique or medication candidate, may not have anything to do with the main causes of the neurodegenerative process. Consequently, expanding the size of the data set to encompass the possible causes of cognitive decline for every patient and addressing the potential causes that have been found would be a more successful approach. The prevalence and costs of sickness are predicted to increase significantly by 2050, endangering the world's population. In order to prevent the disease from progressing in its early phases, while the neural and cognitive potential is still intact, it is imperative that pharmacological remedies be developed. The pharmaceutical market currently offers drug families including acetylcholinesterase inhibitors and non-competitive (NMDA) antagonists, which have been shown to only relieve symptoms of the disease and are only suitable for usage in the dementia stage of Alzheimer's. Degeneration of neuronal cells, extracellular accumulation of Aβ, and intracellular tau protein aggregation that results in the formation of neurofibrillary tangles (NFTs) are all potential pathogenic features linked to AD.

Many therapeutic options for the prevention and treatment of AD have been revealed by the growing body of evidence from preclinical and clinical research regarding the widespread role of neuroinflammation in AD and other neurodegenerative diseases. The innate immune response, or neuroinflammation, is a major mediator of disease aggravation and includes chemokines, microglia, cytokines, and astrocytes. Neuroinflammation and microglia activation have a major part in the Amyloid beta (Aβ) and tau hypothesis of AD. The healthcare paradigm has introduced the idea of precision medicine, a personalised approach to medicine that operates in accordance with the individual's genetic makeup and requirements, providing a medication that is specifically tailored for the individual. This approach aims to address both the prevention and treatment of AD [3].

Therefore, the goal of this strategy is to do away with the "one size fits all" standards for treating and preventing disease. A new paradigm for patient-centered and focused treatment has been made possible by the Precision Medicine Initiative, which was established by the National Institutes of Health (NIH) and other studies. The evolutionary approach to illness prevention and treatment that takes into account a person's unique genetic, environmental, and lifestyle factors is known as precision medicine [4]. Precision medicine has changed several different areas of healthcare research, including cardiology and oncology. It is intended to revolutionise the current healthcare system by widely disseminating the importance of this method. In order to encourage neurodegenerative researchers to concentrate on a specific, individual-specific approach to facilitate AD management, the manuscript highlights the neuroinflammatory mechanisms underlying AD and interventions affecting the disease therapeutics. This is followed by critical aspects of precision medicine, which may be a significant aspect of AD drug development [3,4].

The late onset Alzheimer's disease (AD) that manifests beyond age 60 is called LOAD. Most cases of the disease are of this kind, which is the most prevalent. Age, heredity, and lifestyle choices like smoking, high blood pressure, and inactivity are risk factors for latent obstructive pulmonary disease (LOAD). Many research had looked at the role of genetics in the onset of LOAD; one study calculated those genetics was responsible for more than half of the phenotypic variable [5]. In terms of AD prevention, the shift from general risk-lowering tactics to targeted interventions that target specific risk factors—most notably genetics—has not yet been completed. This situation will allow the identification of unique biological mechanisms and signalling cascades in symptomless individuals at the highest risk for development to clinical benchmarks thanks to the complementary roles of genomic studies, investigation and analysis of fluid-based biological markers, and multi-modal brain imaging. As a result of the field's conjecture that the best chance of therapeutic success may be found in early biomarker-driven customized therapy, genomic research has identified genetic risk factors for Alzheimer's disease, which can help with early detection. Drug research's conventional "one size fits all" approach is being replaced by this paradigm change. This would enable the identification and characterization of disease states at the uniden-

tified preclinical stage, when pathophysiology and topographic abnormalities take place years or even decades before severe clinical symptoms appear. The PM approach enables the shift in AD and brain research toward biomarker-directed, "molecularly" customized therapy and preventative approaches that are very effective. In Figure, the PM concept is shown [4].

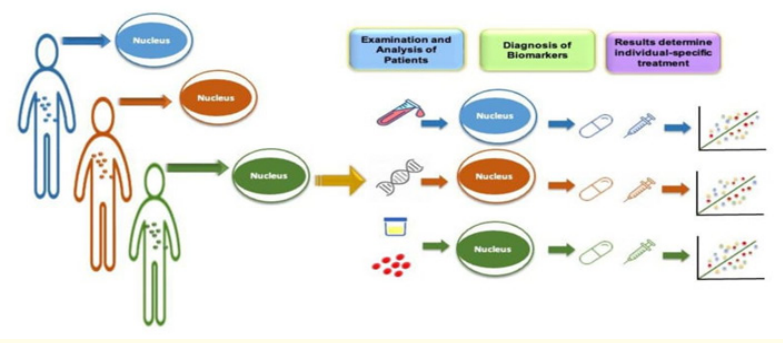


**Figure 2:** Precision medicine approach to prevention of disease. Precision medicine in Alzheimer's disease involves the use of biomarkers, such as genetic and imaging markers, to accurately diagnose and classify patients based on the specific subtype of the disease they have. This allows for more tailored treatment approaches and the development of targeted therapies [4].

Utilizing a PM paradigm to create innovative therapies, prophylactics, and therapeutic solutions for complicated illnesses is not a novel concept. Although the oncology community struggled for years to treat patients who died from advanced tumors in their late stages, today's mortality and treatment rates—particularly for some cancer types—are far higher than what was previously thought to be the case. Nevertheless, AD remains 100% fatal and has no known cure, even after over a century of scientific advancements. Current medicines offer only minor clinical benefits and are only licensed for late, possibly irreversible stages of clinical illness. Currently, a PM has been successfully adopted through the radical shift approach presented by the field of cancer [6].

Precision Medicine aims to tailor medical treatment to the distinct genetic, physiological, and clinical features of each patient's illness. It aims to tailor treatment and sickness prevention to each person's own biological makeup, which stands in stark contrast to the conventional "one pill fits all" strategy. Finding a single drug that will effectively treat every patient is, at best, impossible due to the enormous complexity of AD. Cardiology and oncology are two more disciplines that are similarly impacted. The cross-disciplinary, interdisciplinary, and investigative systems approach of SB (systems biology), supported by system neurobiology, must be incorporated into the PM in order for it to be employed effectively [7]. Drug discovery at the system level that considers the entire intricacy of disease pathophysiology is made possible by SB, which focuses on drug target identification, validation, and assay development. In recent years, biomarker-guided therapeutic approaches have been very successful in two cutting-edge translational research areas of biomedicine: oncology and cardio-vascular medications. The conventional reductionistic category nosology for "neurodegenerative illnesses" refer to fragmented late-stage clinical phenotypes and syndromes with different or overlapping histology patterns. Although there are some limitations to the current categorical diagnosis systems for neurodegenerative diseases, there have been continuous working group efforts to improve categorical criteria for diagnosis, particularly after adding biomarkers to the criteria [8]. The diagnostic accuracy and reliability have improved, depict fragmented late-stage clinical presentations and syndromes with different or overlapping histology findings. Although there are some limitations to the current categorical diagnosis systems for neurodegenerative diseases, there have been continuous working group efforts to improve categorical criteria for diagnosis, particularly after adding biomarkers to the criteria. The diagnostic accuracy and reliability have improved. The recent development of objective, agnostic biochemical classification for dementia and neurological illnesses to diagnose and assess risk in healthy older adults is a positive step. It is designed to identify the entire range of the particular biochemical anomalies in older persons who are at risk, long before the first clinical symptoms appear [4,6].

The application of PM in the domains of neurology, psychiatry, and neuroscience is expected to bring about a paradigm change in the way that brain disorders are treated, moving toward early identification and successful early therapies. With a strong focus on individualized care, preventative strategies can be employed before any notable disease development has occurred. Developing novel approaches for the early identification, categorization, diagnosis, treatment, and prophylactic measures of neurodegenerative diseases based on distinct physiological traits, as reflected by multifaceted possible biomarkers, is one of PM's main goals. In this regard, research in neurogenetics and neuro epigenetics has yielded developing results in AD biomarkers over the past 20 years. Neurochemistry has been studied on blood, and cerebrospinal fluid (CSF) as well as in structural, functional, metabolic imaging and neurophysiology.

Similar to the oncology approach, innovative biomarker studies are anticipated to uncover particular diagnostic, prognostic, and predictive biomarker characteristics in combination with SB to enable patient-specific therapeutic customization. Furthermore, biomarker-guided PM eliminates the present "trial-and-error" approach to pharmaceutical therapies, which has significant medical implications for patients and healthcare organizations [4]. As stated in the Institute of Medicine (IOM) Committee Recommendations for Advancing Appropriate Use of Biomarker Tests (Companion Diagnostics) for Molecularly Targeted Therapies, the ultimate goal of PM is to improve clinical outcomes as well as the quality of patient care.

## Challenges with current treatments

AD is a multifaceted illness. Genetic mutations create an uncommon (<0.5%) familial form of AD, whose symptoms usually appear between the ages of 30 and 50. This is in contrast to the great majority of AD cases, which are sporadic and affect those over 60. Furthermore, women and men have significantly different incidences of AD. Since women are thought to make up over two-thirds of AD patients, there is the intriguing possibility that there are biological factors underpinning the higher prevalence of AD cases in women that need more research. Progressive cognitive deterioration is the primary distinguishing feature of AD. Yet, when the illness worsens, other crippling non-cognitive symptoms appear, such as decreased food and sleep, as well as neuropsychiatric changes (such as apathy and depression). Further epidemiological research has also confirmed a connection between AD and metabolic problems [9]. Studies on AD etiology have mostly focused on how memory and cognitive failure develop because the disease has been regarded as a memory disease, generally ignoring other symptoms and co-morbidities. Thus, it is not surprisingly that precise and reliable biomarkers are still lacking for early disease diagnosis. Although conclusive diagnostics has mostly been confirmed through post-mortem examination, it is now widely accepted that pathophysiological changes begin to develop decades prior to initial cognitive symptoms, in a preclinical or presymptomatic stage. Further, the addition of novel biomarkers to diagnostic criteria has prompted a shift in how AD is considered as pathological entity, increasing the appreciation that it should not be regarded as having discrete and defined clinical stages, but rather as multifaceted process moving along a continuum. (Figure 3). Relatively accurate diagnosis and timely therapies will likely be achieved when neuropsychological, fluid and imaging biomarkers are used in combination [9].

Even medications with successful preclinical evaluation have failed to reverse or slow down the progression of AD in large clinical trials, despite improvements in animal and clinical research over the past few decades. This may be because clinical trials have mostly focused on anti-amyloid therapies, as the amyloid cascade hypothesis has been at the forefront of therapeutic prospection. Such disappointing results also point to issues in translating therapies from rodent model species to humans. This translational impedance is exacerbated by the fact that, although neuropathological features of AD are well known, the complexities of the mechanism involving central and peripheral derangements have not been well defined. Given that AD has a complex pathology, it is now thought that more effective treatments may be possible using disease-modifying therapies and drugs that target multiple molecular pathways, which should importantly take sex differences into consideration, as recently noticed. Potential therapies that work in a sex of one animal species (usually male rodents) also frequently fail to translate to human trials dominated by female participants (often 2:1 female: male in large trials).

Few effective treatments or methods to prevent or cure AD have been developed despite extensive research into its pathophysiology during the past three decades. In light of the fast increase in AD cases, if a cure is not created in the coming years, society will face many social and economic challenges. Notably, the worldwide burden of AD would be greatly reduced if improvements in treatment approaches resulted in even minor delays in the start or course of the illness. Since the science has undergone a conceptual shift in

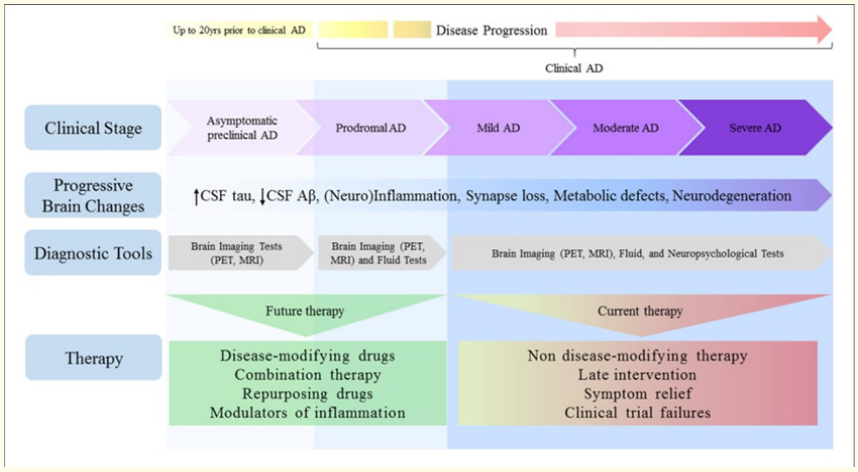


**Figure 3:** AD portrayed as a continuum: difficulties in treatment. In the AD brain, pathophysiological alterations start years before the disease's clinical symptoms appear and go from clinically asymptomatic to substantially impaired spectrum. Even if there are no cognitive symptoms in the preclinical stage, the patient may move to the prodromal stage of AD, which is marked by short-term memory loss that does not interfere with daily living activities, due to progressive amyloid accumulation. But as the illness worsens, numerous parts of the brain and their activities deteriorate, leading to significant memory loss and metabolic abnormalities that impact autonomy. As of yet, there are no reliable biomarkers; nonetheless, early detection will guarantee that people receive therapies in time. The current research pipeline for AD needs to change towards the use of disease-modifying approaches, combination and/or repurposing therapies, and the search for agents that selectively target particular modulators of inflammation, as therapies that were once thought to be promising have failed clinical trials [9].

recent years, AD is now seen as a complex process that progresses along a continuum rather than only having distinct and defined clinical stages. Since biomarker research has advanced, it is now understood that pathophysiological alterations start years before AD symptoms appear. Approximately 15 years prior to the onset of clinical AD, for instance, alterations in CSF tau levels have been demonstrated to occur, although CSF Aβ42 levels may decrease even sooner, up to 20 years before the onset of symptoms.AD ranges from clinically asymptomatic to profoundly incapacitated. Given that the distinction between preclinical AD and healthy ageing is not clearly defined in our current understanding, these borders are difficult to draw [9]. Future research will probably address this unanswered question because early detection biomarkers have emerged as a key area of interest. The majority of AD patients are women, making up about two-thirds of the affected population, hence sex differences should also be considered as a biological variable in the etiology of AD. One possible explanation for the high prevalence of AD in women is that women tend to live longer. Nevertheless, even after accounting for women's longer lifetime compared to men, their risk of developing late-onset AD is higher. We still don't fully understand the biologically elevated risk of AD in women. Nonetheless, it is now accepted that the perimenopause to menopause transition disrupts multiple estrogen-regulated systems, thereby affecting multiple domains of cognitive function. Indeed, recent preclinical studies have implicated that a shift in the bioenergetics system of the brain during menopause onset could serve as an early initiating mechanism for increased AD risk in the female brain. These biological variables may lead to increased fatty acid catabolism, Aβ deposition, and impaired synaptic plasticity, which could serve as a mechanism that triggers AD [12]. As a result, it is conceivable that disappointing outcomes in clinical trials may be partially explained by metabolic differences in women and men. Therefore, recommendations to include both female and male animals in preclinical research should be completely embraced by the research community. The development of disease-modifying drugs in the last ten years may be necessary to create strategies that disrupt the underlying disease processes, even if the

amyloid cascade hypothesis has dominated research for the previous 20 years. Additionally, combined pharmacotherapy may provide advantages for AD treatment. TB, HIV/AIDS, cardiovascular disease, and cancer are just a few of the illnesses for which this approach has shown promise. It may also improve the effectiveness of medications that are ineffective when taken alone but have additive or synergistic effects when taken together. Given, the well-known high failure rates in central nervous system drug research, repurposing already-marketed medications becomes an intriguing alternative to expedite AD drug discovery. Repurposing these molecules could speed up treatment development because metabolic disorders appear to be a major factor in AD and numerous medications for metabolic diseases have already been approved for use in humans. This is because evaluations of pharmacokinetics, human safety, tolerance, and preclinical toxicology might proceed more quickly. In the molecular pathophysiology of sporadic AD, impaired brain insulin signaling or brain-insulin resistance appears to be a key factor. Drugs that have already been licensed for the treatment of diabetes mellitus, such as insulin and medications that increase insulin sensitivity, may accelerate their development for the treatment of AD by focusing on brain insulin signaling. Anti-diabetic medications such as insulin, exenatide, and liraglutide have already been evaluated in ongoing clinical trials, which is noteworthy. Neuroinflammation, particularly in its early phases, promotes a vicious cycle of neuronal injury, pro-inflammatory factor production, and microglial activation. AD and peripheral metabolic dysregulation are likely linked to the coordination of inflammatory processes, including those triggered by TNF-α, between the brain and the periphery. Evidence that gene variations for immune receptors, particularly TREM2, are linked to increased AD-risk further supports the critical role of neuroinflammation in AD. A significant amount of data suggests that inflammation may be a target for AD treatment. Anti-inflammatory drug trials, including those involving non-steroidal anti-inflammatory drugs (NSAIDs), minocycline, peroxisome proliferator-activated receptor-γ (PPAR-γ) activators, and TNF-α signaling inhibitors, have not yet produced encouraging results, despite the fact that long-term NSAID use has been linked to a lower risk of AD. There are currently other therapeutic techniques being evaluated that involve intravenous immunoglobulins and/or monoclonal antibodies, but the results are still inconclusive. These ambiguous findings may be somewhat explained by the fact that anti-inflammatory medications target generic rather than particular neuroinflammatory components in AD. For this reason, understanding the potential of addressing inflammation in neurodegeneration will require an understanding of specific modulators of inflammation at early stages of the illness [9].

## Understanding Alzheimer's disease pathophysiology and the role of genetics

The full application of genetics to provide tailored guidance will be necessary for a Precision Medicine approach to AD treatment. In this part, the effects of genes on late-onset AD are discussed, along with examples of a targeted PM strategy that targets these genetic impacts.

### APOE gene

APOE, which codes for the apolipoprotein E (APOE) protein, is one of the most well-known genetic factors for late-onset AD. Studies have shown that the APOE-genotype has a significant impact on the risk of AD; specifically, the ε4 allele has been linked to an increased risk of AD, whereas the ε2 allele has been linked to a lower risk; additionally, individuals with two copies of the ε4 allele had an even higher risk of developing AD than those with just one copy. There are several pathophysiologic mechanisms that may explain why APOE ε4 is linked to a higher risk of AD, while APOE ε2 is linked to a lower risk of AD. First, of all, the alleles encode proteins with different molecular properties that influence how APOE binds with Aβ, which may explain the increased accumulation of Aβ plaques, one of the main characteristics of AD, observed in APOE ε4 individuals. Studies have shown that the associations of the APOE allele with both LDL and HDL receptors have a significant impact on the progression of atherosclerosis, one of the main risk factors for AD. Because the ε4 allele has been found to account for 27.3 percent of delayed AD risk and because recent research indicates that potential risk-reduction therapies may be selectively effective (or even less effective) based on the presence of the ε4 allele, it may be essential to incorporate this genetic makeup into the AD preventive approach. Depending on the APOE genotype, a variety of AD preventive strategies can be tailored. Within investigations of the APOE ε4 allele, it was found that a significant variance in some treatments compared with score of control specifically for individuals with "ε4 alleles." However, the FINGER trial showed negligible changes in cognition features among APOE genotypes with multimodal routine modifications [10]. The- effectiveness of

the therapies may have been impacted by an inherent difference between those who carry the APOE ε4 allele and those who do not. To determine the impact of APOE on multimodal therapies, large sample sizes and higher statistical power are needed in trials. According to other single-factor research studies, the APOE genotype can be used to focus preventative therapy for AD. Those with the APOE ε4 variant experienced the largest changes in LDL, HDL, and total cholesterol [11] in 15 of the trials, according to a comprehensive assessment of the studies that altered the dietary fat. In another study, researchers found that in the Mediterranean diet response, both individuals with and without the APOE ε4 allele demonstrated improved cognitive performance as measured by the Mini Mental State Exam (MMSE), while only those without the 4 allele primarily contributed to the clock drawing test, which assesses spatial reasoning and executive functioning. According to a different, research, improved cognitive performance was linked to aerobic fitness in ε4 homozygotes. Likewise, three RCTs with ε4 alleles showed that administering omega-3 fatty acids improved cognitive function in non-impaired individuals. Generally speaking, genotype-specific approaches can benefit people by using specific techniques and implementing tactics that have been proven to work well for persons with similar genotypes [12]. Generally, speaking, genotype-specific approaches can benefit people by using specific techniques and implementing tactics that have been proven to work well for persons with similar genotypes. As the PM strategy for AD prevention develops, more research will be needed to determine the impact of APOE on different physical activities, food preferences, and lifestyle modifications.

## Presenilin 1 and 2 gene

Given the identification of many pathogenic variants in amyloid precursor protein (APP), it would be clear that mutations only account for a portion of early-onset AD. Not even a year after the first APP mutation was identified, four other studies offer additional AD linkage region at 14q24. Three years after the initial mutation that caused AD, researchers found the related gene (PSEN1) [13]. The highly conserved polytopic membrane protein encoded by PSEN1 is necessary for intramembrane communication [14]. PSEN1 mutations enhance the APP's production of Aβ-42. Mutations where the γ-secretase cleaves APP are altered, as evidenced by the rising frequency of Aβ42/Aβ40. Ten exons of the PSEN1 gene code for proteins. The 5′-untranslated regions are also coded for by two or three additional exons [13].

Information suggests that PSEN2 is located soon after PSEN1. From the standpoint of proteins and genomics, PSEN1 and PSEN2 are similar. PSEN2 mutations are the cause of late-onset AD. As opposed to when there is an APP or PSEN1 mutation, the condition will progress more slowly. Protein-coding exons make up 10 of the PSEN-2 gene, while two more exons code for the 5′-untranslated region. Although the two PSENs have different codon mutations, they have a structural similarity. There are indications that only about one-third of dominantly inherited cases of AD are linked to known mutations in the PSEN or APP genes. It implies the existence of more disease loci.

Additionally, early-onset AD is associated with variations in PSEN1 and PSEN2. Presenilin's are intramembrane proteases that catalyze γ-secretase. The production of cleavage products such as Aβ is promoted by mutations in presenilin's. Seizures were significantly more common in AD patients with the most common PSEN2 mutation (N141I) (32 percent), despite the fact that these episodes are still only self-reported and that no complete persistent observation for electrographic (focal) seizures has even been conducted in this patient population. Furthermore, as certain PSEN2 mutations are associated with lower penetrance, episodes may inadvertently be mistakenly classified as sporadic AD, making PSEN2 especially pertinent to the study of AD hyperexcitability. PSEN2 appears to be a promising tool for defining the combined impact of aging and seizures on the disease load in AD. First, neuropsychiatric symptoms may be more significantly affected by PSENs. Second, PSEN2 is a key player in neuroinflammation. Loss of normal PSEN2 function disrupts canonical γ-secretase action, promoting a pro-inflammatory phenotype mediated by inflammatory cytokines and microglia [15].

## Molecular and cellular mechanisms

Neuronal dysfunction in AD is linked to the buildup of extracellular Aβ protein within and outside of nerve cells as well as the presence of hyperphosphorylated tau tangles [16]. It has been observed that the structure and function of tau and Aβ oligomeric forms are among the most compelling for understanding pathogenesis, establishing therapeutic interventions, and offering a theoretical synthesis of how their actions initiate and maintain pathogenesis Figure 4 illustrates the several components that have been connected to the development of AD, including mitochondrial dysfunction, oxidative stress, metal ion imbalance, genetic risk factors, an aberrant blood–

brain barrier (BBB), and more [17]. As a carrier function, the BBB exports metabolic end products from the central nervous system (CNS) and transports vital nutrients, hormones, and medications to the brain. Additionally, it acts as a barrier to keep circulating hazardous chemicals and proteins with osmotic activity out of the central nervous system. As people get older, the BBB becomes less stable, which leads to leakage. By allowing peripheral immune cells to enter the brain, AD exacerbates this BBB failing. It may also worsen the pathophysiology by encouraging detrimental neuroinflammation. Most evidence points to an accumulation of Aβ as the source of the spread of BBB damage. A possible role for tau in BBB degradation is suggested by the fact that tauopathies without Aβ pathology also exhibit BBB damage [18]. According to the immunological privilege model of the brain, the blood-brain barrier (BBB) was traditionally believed to prevent the blood from containing humoral and cellular immune system components. Nonetheless, it is becoming more and more obvious that T cells often travel to the brain. Despite not being fully matured effectors, the majority of T cells in the AD brain emit cytokines that may have an impact on the disease's pathogenic progression [19], Within the AD brain, T cells engage with astrocytes or microglia that operate as antigen-presenting cells (APCs) to carry out their effector functions, despite the decreased proliferation of T cells in this brain. Microglia are obviously important in the development of AD. Early tau and Aβ deposition causes, NLRP3 inflammasome assembly, cytokine and protein release, and microglial activation. However, ongoing microglial activation worsens AD pathogenesis and leads to increased protein accumulation and neuroinflammation since the initial triggers, such as tau and Aβ, are not removed.

Oxidative stress may promote the production and aggregation of Aβ and aid in the polymers and phosphorylation of tau, according to a number of studies. This could lead to a vicious loop that promotes the development and progression of AD. It is probable that oxidative stress is initiated and/or amplified by mitochondrial dysfunction during the start and progression of AD. Oxidative stress can damage the mitochondria's structure and functionality. Environmental or metabolic changes, as well as reactions to genetic deficits, can cause defects in mitochondrial dynamics. This may make it harder for the mitochondria to adjust to shifting cellular demands, which could be particularly harmful to nerve cells [19].

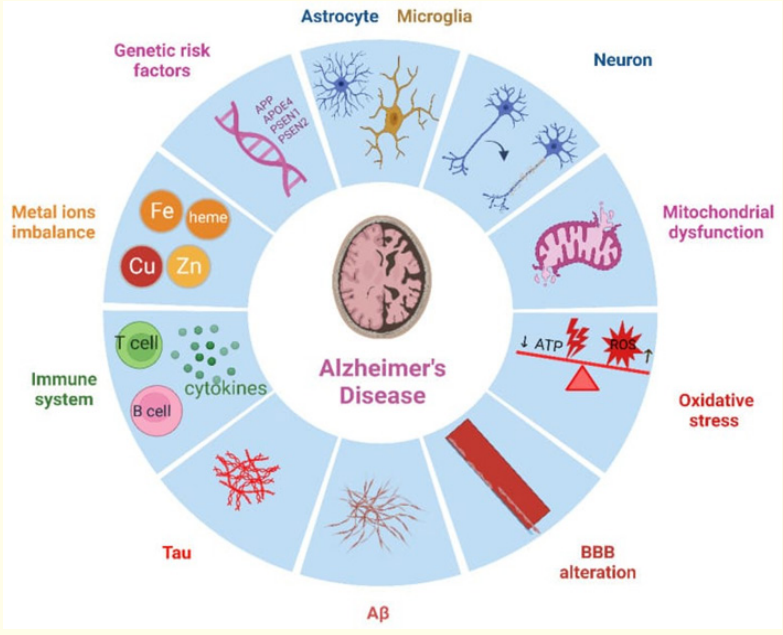


**Figure 4:** Defective blood-brain barrier, mitochondrial dysfunction, oxidative stress, metal ion imbalance, genetic risk factors, and the immune system are some of the causes linked to AD. Tau, microglia, astrocytes, T cells, and Aβ are also involved in the pathophysiology of AD. Developing successful treatments and expanding our knowledge of AD require a thorough grasp of these variables and how they interact [19].

Recently, it was shown that the apolipoprotein E (APOE) ε4 allele, the highest genetic risk factor for AD, is linked to a higher inflammatory response, however the precise mechanism is yet unknown. There are three common APOE alleles in the human population (ε2, ε3, and ε4), with ε2 being considered protective in comparison to ε3 and ε4 being a risk factor. Metal ions such as calcium, zinc, copper, and iron must maintain their equilibrium for the brain to continue functioning normally. A major contributing factor to the development of AD is the brain's imbalance of these metal ions. Tau hyperphosphorylation and excessive Aβ production can be promoted by incorrect iron, copper, zinc, or calcium deposition in different parts of the brain.

## Role of Aβ and neurofibrillary tau Tangle in AD

Because of their deposition in histopathological brain lesions—the neurofibrillary tangles (NFTs) for tau and the senile plaques for Aβ—the proteins Aβ and tau have been recognized as important contributions to the pathophysiology of AD. It is also discovered that AD patients' brains have higher levels of the soluble forms of tau and Aβ. Natural production of Aβ in the brain and its elimination from it occur at rates of 7.6% and 8.3% of total Aβ every hour in healthy persons, respectively. But this fraction drops by about 30% in late-onset AD (LOAD). Microglia and astrocytes are triggered as part of the inflammatory response due to Aβ accumulation in an effort to eliminate the plaque, but this also damages the closest nerve cells and neurites. Furthermore, NFTs cause neuronal death by blocking normal axonal transport, despite their normal involvement in intracellular activity [19].

## Effect of Aβ in AD

The primary energy source for brain cells to operate correctly is mitochondria. The membranes of mitochondria include Aβ and amyloid precursor protein (APP), which interact with other proteins within the mitochondria, enhance the production of reactive oxygen species (ROS), and injure the structure and functionality of the mitochondria. Normal brain function may be disrupted as a result of this. By raising intracellular Ca2+ levels and encouraging Ca2+ entrance into mitochondria, Aβ oligomers can also degrade mitochondria's structure and function. Damage to synapses in AD is correlated with cognitive deficits. Synaptic damage, poor neurotransmission, and cognitive impairment in aging and AD patients have been linked to mitochondrial failure and Aβ accumulation at synapses. It has been demonstrated that Aβ from APP is increased by dysfunctional mitochondria, and that Aβ leads to mitochondrial dysfunction. P-glycoprotein, is a vital gatekeeper and is necessary for the regular clearance of Aβ across the blood-brain barrier. Part of this process involves the brain's endogenous release of Aβ peptide, New data lend credence to the theory that impaired P-gp activity encourages Aβ buildup and plays a role in the pathogenesis of AD. Oxidative stress and inflammation are known to be facilitated by Aβ oligomers [20]. Additionally, there is evidence that oxidative stress and inflammation may possibly play a role in the production of Aβ oligomers. Anti-inflammatory and antioxidant medications taken together have been suggested as a potential treatment for AD. The heme complex, which is produced in the mitochondria and is a crucial functional form of iron in cells, binds to Aβ to prevent Aβ accumulation and cause heme deficit. Insufficient heme lowers the protein level and activity of mitochondrial complex IV, which leads to oxidative stress and disturbs Ca2+ homeostasis. Additionally, APP, mitochondrial complex IV, NO-synthase (NOS), and zinc and iron homeostasis are all impacted by heme depletion. Age-related alterations in the brain are similar to those seen in heme-deficient cells, and they are more noticeable in neurodegenerative illnesses like AD. Since brain cells lacking heme are unable to differentiate an entire cell cycle, it is possible that heme serves a special purpose beyond its conventional use in cell biology [21].

## Effect of tau in AD

In the human hippocampus of normal subjects and those with AD, in situ hybridization was used to examine the distribution of α-tubulin mRNA. The hybridization signal was significantly lower in NFT-rich regions, and NFT-containing neurons had a weaker hybridization signal than NFT-free neighboring neurons. The biological activities of the phosphoprotein tau are controlled by the amount of its phosphorylation. Tau is hyperphosphorylated in the AD brain, and tauopathies are linked to NFTs built up from hyperphosphorylated tau. NFT-bearing neurons exhibited decreased tubulin transcription, which may contribute to the cells' decreased microtubule count. Within the axons and dendrites, microtubules are grouped in paraxial rows. The microtubule arrays give axons and dendrites the structural backbone they need to grow and preserve their distinct morphologies [22]. The emergence of NFTs is thought to be linked to AD neuronal dysfunction. For a neuron to retain its form, microtubules are necessary. Tau's aberrant phosphorylation probably disrupts microtubules by lowering functional tau levels. Early microtubule instability was indicated by the decrease in acetylated α-tubulin immunoreactivity in the majority of NFT-bearing neurons, even in the neuronal population with a

smaller tau immunoreactivity. Oxidative stress is more likely to affect cells that overexpress tau, and there is evidence that oxidative stress may play a role in tau disease. Microtubule instability causes tau tangles, which are made up of tau monomers and oligomers. Neuroinflammation, compromised synaptic function, malfunctioning autophagy, and defective mitochondria are all associated with tau tangle buildup, and these conditions can all result in neuronal damage. Furthermore, tau oligomers are capable of spreading across neurons, investigated the spread of tau pathology in a mouse model and discovered that synaptic connections can help tau pathology spread between neurons. They also discovered that reducing synaptic connectivity led to a large drop in the total quantity of accumulated tau. Similar to this, Wu., *et al*. [23] examined the spread of tau disease in the brain using a mouse model and discovered that, via a trans-synaptic mechanism, neuronal activity in one region of the brain might promote the spread of tau pathology to related regions. Both results, taken together, show that tau oligomers can migrate trans-synaptic from one neuron to another. The NFTs are composed of hyperphosphorylated tau, which has been shown to impede mitochondrial transport. Neurodegeneration may eventually result from this because it causes oxidative stress and an energy deficit at the synapses [24].

## Neuroinflammation

Inflammation of the nerve cells is another fundamental mechanism of AD pathogenesis. Although the brain's healing systems depend on inflammation, chronic inflammation can harm brain function. There is still much to learn about the molecular processes that lead from low-grade, chronic systemic inflammation to neurodegeneration [25]. Neuroinflammation increases the severity of AD and is most likely caused by AD diseases and risk factors. Higher levels of proinflammatory cytokines and inflammatory markers are seen in AD brains, probably in reaction to the deposition of NFT and Aβ plaques, which cause damage or death to nerve cells [25]. The complement system, microglia, and astrocytes are activated by Aβ deposition, which also causes the release of inflammatory mediators such IL-1α, IL-1β, IL-6, and TNF-α, as well as reactive oxygen and nitrogen species [26]. These factors reduce phagocytosis and prolong neuroinflammation. In the pre-symptomatic phase of AD, proinflammatory mediators trigger microglia activation, which results in synaptic dysfunction and neuronal death. This suggests that the pathophysiology of AD begins with neuroinflammation. Furthermore, a prior study suggested that inflammation plays a role in AD by detecting activated microglia around amyloid plaques and higher levels of proinflammatory cytokines in the peripheral and central nervous systems (CNS). Therefore, a possible treatment approach for AD may involve inhibiting neuroinflammation. A variety of cytokines contribute to neuroinflammation in AD. β- and γ-secretase increases the production of Aβ from APP in response to TNF-α and IL-1. Through the p38-MAPK pathway, IL-1 also increases tau phosphorylation. Tight junction proteins are downregulated, astrocytic sonic hedgehog synthesis is suppressed, and astrocytic activation is increased by IL-1β, which leads to the generation of pro-inflammatory cytokines, disruption of the blood-brain barrier, and neuroinflammation. The cdk5/p35 pathway causes tau phosphorylation and increased APP expression in response to IL-6 [26], Moreover, circulating immune cells in the periphery may be drawn to AD brains by raised chemokine and cytokine levels, traversing the blood-brain barrier to the central nervous system and intensifying inflammation. Microglia may also be drawn to the edges of Aβ plaques by chemokines. It was discovered that AD patients' brains had higher expression levels of chemokine receptors on activated microglia. Higher levels of the chemokines MCP-1/CCL2 and CCL11 may also be indicative of pathology and memory function abnormalities in early AD patients.

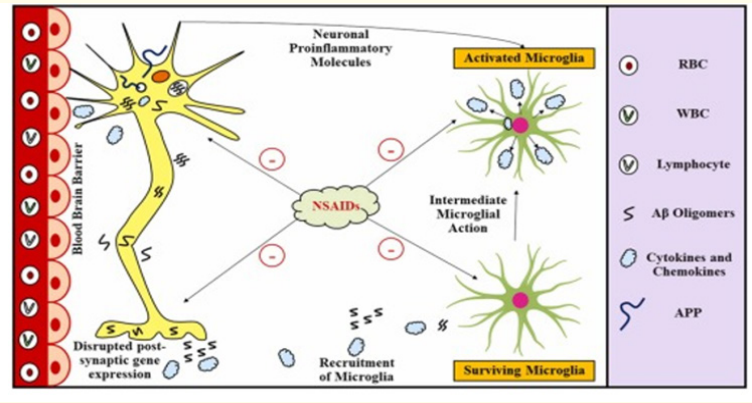


**Figure 5:** AD pathology at the initial stages associated with neuroinflammation and NSAID-mediated hindrance of the causative steps (RBS – red blood cells), WBC – white blood cells, Aβ- amyloid beta, APP- amyloid precursor protein, NSAID- non steroidal anti-inflammatory drugs) [3].

The chemokine SDF-1/CXCR4 can, however, decrease Aβ deposition and activate microglia. Tau protein levels in the cerebrospinal fluid (CSF) are negatively correlated with SDF-1 levels, which is consistent with its neuroprotective effect [27]. SDF-1 levels are low in early AD patients. RANTES levels were shown to be lower in a prior study, but other chemokines such as IP-10, IL-13, IL-8, MIP-1α, and fractalkine were found to be higher in the blood of AD patients [28]. To fully understand their significance in the course of AD, more research is necessary, as evidenced by the disagreement surrounding these chemokines in the literature. The outer membrane mitochondrial protein known as the translocator protein (TSPO) has been linked to neuroinflammation in AD and is a possible biomarker. Microglia and maybe astrocyte activation are closely correlated with increased TSPO expression in the brain's periphery. Neuroinflammation imaging has been performed *in vivo* using TSPO radiotracers [3]. In AD, it has also been discovered that CSF1R, COX-1, COX-2, CB2R, P2X7, and P2Y12 receptors are dysregulated proteins. These proteins have been made into radiotracers, but more research is needed to decide whether to use them as possible imaging biomarkers to identify neuroinflammation [3]. The complement system has also been studied as an inflammatory biomarker. A higher risk of AD is linked to lower plasma C3 levels, which are the keystone of complement system activation. Previous investigations have shown that AD patients have higher amounts of C3 and C4. C-reactive protein (CRP), an acute-phase inflammatory protein, may also encourage the production of Aβ42 and the activation of the complement system in the AD brain. In AD brains, serum CRP levels were shown to be higher in some studies but lower in others. The fact that its levels fluctuate as the illness worsens is probably the cause of this dispute. It may be possible to visualise neuroinflammation and track the evolution of AD *in vivo* by targeting inflammation biomarkers. This could be a promising approach for early diagnosis and treatment. Evidence suggests that diet and the development of AD are related. High in carbohydrates, salt, fat, and cholesterol, the Western diet (WD) can exacerbate systemic inflammation, brain amyloid buildup, tau protein phosphorylation, and memory, learning, and cognitive impairment. Moreover, WD has been connected to neuroinflammation. The hippocampal and entorhinal cortex of chronic WD-fed AD animal models exhibited increased numbers of activated macroglia and astrocytes. Furthermore, elevated levels of proinflammatory genes (Trem2, Treml2, Tyrobp, CX3CR1, Ccl3) and phagocytic microglial cell markers (Iba1, CD68, TREM2) surrounding the Aβ-plaques suggested neuroinflammation; WD-induced neuroinflammation appears to happen earlier, prior to the formation of Aβ plaques and brain deposition. A reduction in microglial phagocytic activity and astrocyte-dependent disruption of the glymphatic system can lead to poor amyloid clearance and neuroinflammation. In a prior study, APOE4 carriers also showed a greater effect of WD on the development of AD. A connection between food, obesity, and AD was shown in a number of studies. In midlife and adulthood, the chance of developing AD and cognitive impairment is increased sixfold by obesity [3]. Reduced cortical and hippocampus volume, poor memory function, executive functioning deficiencies, and an elevated rate of brain atrophy are all characteristics of obese people. Obesity brought on by diet has been linked in animal models of AD to deficits in cognitive functions, impaired hippocampal neurogenesis, and elevated APP, p-tau, and Aβ levels in the hippocampus. Experiments with diet-induced high cholesterol in mice revealed a worsened neuroinflammatory response, elevated p-tau levels, and the production and accumulation of toxic Aβ in nerve cells and astrocytes, all of which resulted in cognitive impairment. Other research has shown that diet-related dysbiosis and changes in the composition of the human gut microbiome may disrupt synaptogenesis, disrupt neurotransmitter production, cause systemic inflammation, compromise the BBB, and contribute to the development of AD and cognitive impairment [29]. Additionally, a number of studies have indicated that type 2 diabetes mellitus (T2DM) is a significant vascular risk factor and has a role in the development of AD. AD is twice as likely to occur in T2DM patients as in healthy people. The role and interplay of genetic and environmental risk factors in the onset and course of AD should be the focus of future research.

## Heterogeneity of disease progression

Based on genetic studies of autosomal dominant forms of AD, it is most likely that the disease process is initiated by processing of the amyloid-precursor protein (APP) and the significant amount of Aβ deposition caused by individual mutations. With the prevalent late-onset AD (LOAD), on the other hand, symptoms appear more than ten years after tau and Aβ depositions, followed by behavioral and cognitive abnormalities [30]. A number of factors, including neuroinflammation, increased glucose metabolism, oxidative stress, excitotoxicity, and synaptic disconnection—all of which are involved

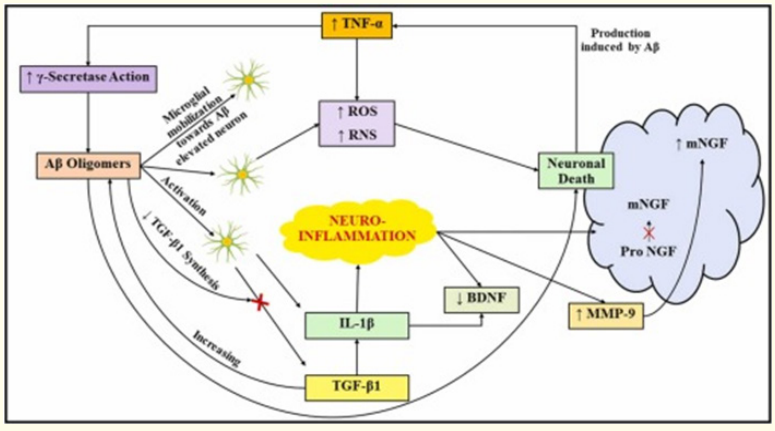


**Figure 6:** Neuroinflammation as a major driving factor in AD pathogenesis [TNF-α – tumour necrosis factor – alpha; ROS – reactive oxygen species; RNS – reactive nitrogen species; Aβ – amyloid beta; IL-1β -interleukin-1 beta; TGF-β1 – transforming growth factors-beta 1; BDNF – brain derived neurotrophic factor;MMP-9 – matrix metalloproteinase-9; NGF – nerve growth factor; mNGF – mature nerve growth factor] [3].

in normal ageing and longevity [30] appear to be present and situated in the ageing environment when the clinical syndrome in LOAD first appears. The clinical phenotype, age of onset, and rates of progression of LOAD may all be impacted by these variables. It is therefore not unexpected that the numerous therapeutic trials conducted on LOAD patients using antibodies to either remove Aβ from the brain or stop its deposition have yielded negligible, if any, clinically meaningful results. The genetic and nongenetic factors that drive the clinical syndrome after Aβ deposition in both LOAD and early-onset AD (EOAD) cases, such as neuroinflammation, neuronal and volume loss, amyloid angiopathy, and white matter changes found on imaging and pathology, therefore appear to need to be identified as targets for intervention. Apart from eliminating Aβ from the brain, the subsequent sections on genetic factors linked to LOAD might offer hints about which aspects should be the focus of upcoming treatment research.

The main cause of genetic heterogeneity in autosomal dominant AD (ADAD) is the particular mutations used in the pathophysiology of individual instances, which lead to an early and very rapid pathological buildup of Aβ protein in the brain. In ADAD, the main causes of clinical heterogeneity are point mutations on chromosomes 14, 21, and 1. Age at onset, phenotype, and rates of progression of ADAD are further influenced by the mean ages at onset for carriers of the same mutation, the age at onset of the parents of particular ADAD cases, and the epistatic effects of other genes, such as apolipoprotein E (APOE).Individual cases' beginning age seems to have the biggest impact on the advancement rates of ADAD cases [30]. It seems that the fastest rates of advancement are seen in individuals with earlier ages of onset (before the age of 35) and those with the oldest ages of onset (after the age of 65) [30].

The APOE ε4 allele is linked to an earlier age at onset and earlier Aβ deposition, although its association with the rate of cognitive decline is debatable and may vary depending on the stage of AD. Between around 65 and 70 years of age, APOE has the biggest impact on AD risk; by 85 years of age, survival effects cause it to significantly drop. A genetic variable that appears to alter the downstream consequences of a beta deposition and causes a rapid pace of cognitive deterioration has been found. This trait is characterised by phenotypic traits that include the emergence of psychotic symptoms early in the disease [31]. Once the effects of the APOE4 allele are taken into consideration, additional genes that have been discovered to alter the risk for LOAD include CLU, CR1, phosphatidylinositol-binding clathrin assembly protein (PICALM), BIN1, ABCA7, and CD33 [32]. The single-nucleotide polymorphism (SNP) (rs11136000) in CLU, which codes for the protein clusterin (expressed at higher levels in the brains of LOAD patients), which inhibits complement activation and prevents fibrillization of Aβ, was linked to a quicker rate of cognitive deterioration. A variant in the complement receptor CR1 (rs3818361), which is expressed in the cerebral cortex and contributes to neurodegeneration through

astrocyte-mediated mechanisms, was linked to a faster rate of longitudinal deterioration. While the pace of cognitive deterioration was unaffected by an SNP in PICALM, it was linked to an earlier age of onset [33].

Using GWAS research, at least 30 genes on 14 distinct chromosomes have been linked to LOAD, indicating the involvement of four biological pathways in the pathophysiology of AD. Immune response, endocytosis, transport of cholesterol, cell-to-cell adhesion, and proteasome-ubiquitin activity are a few of these. The APOE gene on chromosome 19q13.2 is known to play a role that has been extensively verified in a number of studies. Aβ deposition and aggregation are linked to ApoE. Through its apparent interaction with Aβ oligomers and fibrils, it can increase the buildup of Aβ in the brain and CSF, which in turn influences the risk of developing AD. In order to control the removal of soluble Aβ, APOE probably affects Aβ transport across the blood–brain barrier. Primary astrocytes synthesise APOE, and carriers of the APOE e4 allele have greater neuroinflammation, decreased Aβ clearance ability, and a higher density of Aβ deposition in the brain [20]. Nonetheless, AD is common in APOE4 noncarriers. An APOE4-independent mechanism for TOMM40 that raises the risk for AD has been suggested by the discovery that an SNP (rs2075650) in the TOMM40 gene, which is closely linked to APOE, is linked to AD in individuals without an APOE ε4 allele, even after controlling for age and sex. SNP rs2075650 in the TOMM40 gene is implicated in protein precursors transported into mitochondria and is associated with macular degeneration, lifespan, AD, and cholesterol levels.

The same four AD-related genes have been found to be the most significant risk factors in three large GWAS studies: the Framingham Heart Study (FHS), Cardiovascular Health Study (CHS), Health and Retirement Study (HRS), and Late-Onset Alzheimer's Disease Family Study (LOADFS) [34]. On chromosome 19, these genes are located in or close to the APOE gene. They are TOMM40, APOE, APOC1, and poliovirus receptor-related 2 (PVRL2). Due to its function in preserving the blood–brain barrier, including its permeability, and so avoiding viral infections that may contribute to the pathophysiology of AD, the SNP rs6859, found in PVRL2 (NECTIN2), may be most closely associated with AD. Thus, mutant versions of PVRL2 might permit the entry of specific mutant strains of the herpes and pseudorabies viruses as well as the transmission of viruses from cell to cell. Additionally, the combination of APOE and APOC genes has been implicated in the role of cell adhesion and the brain's vulnerability to viral infections. Additionally, in GWAS of African Americans with late-onset AD, SNPs linked to APOE, PVRL2, TOMM40, and APOC [35] were identified as having strong genome-wide correlations with AD. Crucially, despite controlling for the impact of APOE, the correlation between AD and PVRL2 (SNP: rs6859) remained statistically significant, confirming its independent function in AD. The risk of AD is significantly increased when APOC1 mutations are paired with those in the APOE e4 allele. A large risk reduction for AD is linked to a minor allele of rs157580 in the TOMM40 intron area, while a significant risk increase for AD is linked to a minor allele of rs2075650 in the same location [35]. Although the brain also expresses the APOC1 gene, the liver does so most frequently. In the metabolism of high-density lipoproteins (HDL) and very-low-density lipoproteins (VLDL), APOC1 encodes a member of the apolipoprotein C1 family. Type 2 diabetic mellitus (T2DM) and AD are linked to six SNPs in the APOC1 gene. These SNPs have also been found in GWAS of human longevity. These genes may be involved in the risk of other diseases or in biological processes that affect those risks, such as those related to lipid metabolism, information processing rate, cardiovascular risk, inflammation, cancer, and type 2 diabetes, given their association with human longevity. T2DM and AD share similar pathogenic characteristics, such as the aberrant behaviour of amyloid peptides in the pancreatic islets in T2DM and Aβ in the brain in AD patients. An increasing body of research suggests that AD is partially a metabolic disease brought on by the brain's gradual incapacity to react to insulin and insulin-like growth factor. A number of parallels between the progression of the two diseases further demonstrate the relationship between T2DM and AD. These include the direct impact of insulin on the metabolism of Aβ, oxidative stress, aberrant protein processing, inflammation, dyslipidaemia, and the generation of advanced glycation end products [36].

Since AD has been linked to various illnesses, systemic ageing mechanisms and the biological processes that affect these risks are probably involved. A meta-analysis of polymorphisms in the TOMM40 gene that convey risk for sporadic AD suggests that mitochondrial dysfunction caused by TOMM40 mutations may be the most significant of these. Aβ deposition, synaptic degeneration, NFT formation, neuronal dysfunction, and death through the accumulation of reactive oxygen species are all caused by mitochondrial dysfunction [36].

Several single-nucleotide polymorphisms (SNPs) that implicate one or more biological pathways in AD are combined to create polygenic risk scores (PRS) obtained from genome-wide association studies (GWAS) based on previously identified SNPs. As anticipated, PRSs demonstrate superiority over single-gene analysis in distinguishing AD from cognitively normal people. A number of studies have compared PRS with (APOE-PRS) vs without APOE (non-APOE-PRS) in order to determine genetic risk greater than that of APOE alone [37]. Age at onset of Alzheimer's disease symptoms, elevated tau and amyloid-beta load in the brain, decreased Aβ and increased tau in CSF, and greater atrophy are all linked to APOE-PRS. In Alzheimer's disease patients [37]. APOE-PRS is also linked to plasma inflammatory markers. By combining APOE-PRS with a rare variant of TREM2 (triggering receptor expressed on myeloid cells 2), it was possible to distinguish between people with Alzheimer's disease dementia and those with normal cognition. This was shown to increase diagnostic accuracy using a pathologically confirmed Alzheimer's disease cohort, and higher PRS scores were linked to declining age at onset and CSF amyloid-b42. This suggests that heritability in AD has a significant polygenic contribution beyond the recognised genetic variables related with AD risk. The combined contribution of APOE and non-APOE-PRS to the variability in age at onset, however, was less than 6%.

## AD biomarker

Both the selection of participants and the assessment of the efficacy of the treatment procedures under test are done using biomarkers. Along with their disease-modifying qualities, they are used to investigate the safety limits of innovative therapeutic approaches and to clearly increase target occupancy [38]. Their use in clinical trials to enhance the basis for illness therapy is still restricted, nevertheless, since only 40% of biomarker studies included functional, cognitive, neuropsychiatric, and other clinical parameters as their primary endpoints. With advancements in brain imaging and fluid biomarker testing, the clinical basis of AD has been transformed. Blood and CSF biomarkers, along with PET imaging, help detect AD in its early stages and pinpoint the neuropathological changes linked to the illness [39]. With advancements in brain imaging and fluid biomarker testing, the clinical basis of AD has been transformed. In addition to identifying the neuropathological changes linked to AD, blood and CSF biomarkers and PET imaging help diagnose the illness in its early stages. In order to address a number of issues, including invasiveness, assay repeatability, and cost inefficiency, certain innovative PET methods and blood tests are presently being developed for AD biomarkers. In a short amount of time, the steady advancement of biomarkers facilitates the accurate, early, routine, and trustworthy identification of AD. The four main categories of biomarkers created for AD are blood tests, CSF, PET, and MRI. In addition, the formation of biomarkers has been linked to five pathological hallmarks, including tau pathology, synaptic dysfunction, Aβ pathology, glial cell activation, and neurodegeneration. In addition, some cognitive tests help identify memory impairment early on. These include the Memory Impairment Screen (MIS), General Practitioner Assessment of Cognition (GPCOG), Mini-Mental State Exam (MMSE) for dementia detection, Mini-Cog test, Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), and Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) [26]. To diagnose pre-clinical cognitive impairment, composite cognitive tests have also been devised. Cognitive tests are dependable methods and instruments for early AD diagnosis and tracking of treatment outcomes, but they cannot detect the disease before symptoms appear until they are more sensitive, which delays their use from the perspective of early personalised medicine.

## Anti- amyloid therapies (Monoclonal antibodies)

Several therapeutic trials have used monoclonal antibodies to target Aβ in recent years. The lead in this regard has been the amyloid cascade hypothesis, however sporadic AD may not be as well suited to this model. The effectiveness of antibody targeting is well documented [40]. According to the Clinical Dementia Rating Scale, patients with mild to moderate AD who get bapineuzumab treatment report improvements in their cognition and function. However, Salloway., *et al*. [41] reported the findings of two phase 3 studies in 2014, which showed no clinical difference between the treatment and a placebo in mild to moderate instances of AD. However, rising plasma Aβ levels indicated that the drug was removed from the brain. A total of 1,331 noncarriers and 1121 APOE4 carriers participated in their two study groups. When comparing the ADAS-cog11 and DAD scores (bapineuzumab group minus placebo group) at week 78, the between-group differences were -0.2 ($p = 0.80$) and -1.2 ($p = 0.34$), respectively, from baseline. However, the FDA did approve lecanemab (Leqembi®) and aducanumab (Aduhelm®), two more anti-amyloid monoclonal antibodies, for the treatment of Alzheimer's disease, despite the lack of strong statistical support

[42]. An example of this new therapeutic option is the FDA's recent approval of lecanemab-irmb in 2024. The medication seems to delay the pace of cognitive deterioration in early-stage AD patients by roughly 27% over the course of 18 months in a multicenter, double-blind phase III research that used this antibody in 898 patients and a placebo in 897 patients. Patients who took the medication outperformed those who received a placebo in four cognitive and functional assessments ($p < 0.001$) [43]. Furthermore, Cohen., *et al*. [44], the same research team, came to the conclusion that "Lecanemab was associated with a relative preservation of the Quality of Life and less increase in carer burden, with consistent benefits seen across different quality of life scales and within scale subdomains. "Patient-reported outcomes are valuable because of these advantages. Lecanemab treatment may, in fact, provide significant advantages to patients, care partners, and society, as evidenced by previously documented advantages across a variety of measures of cognition, function, disease progression, and biomarkers [44]. It should be noted in this regard that disease-modifying antibodies are unique in that they interfere with the fundamental pathophysiologic mechanism, resulting in a reduced clinical decline. Additionally, it has been shown that a local low dose of ultrasound can enhance the effects of the controversial anti-amyloid antibody aducanumab by partially opening the blood-brain barrier and increasing its delivery to specific brain regions of interest. These advancements may open the door to more research on monoclonal antibodies, but their side effects may prevent their widespread usage at this time [45].

## Stem cell therapy

Stem cells are distinguished by their capacity for self-renewal, clonality, and differentiation into any type of cell. As totipotent stem cells have the highest capacity for differentiation, while unipotent stem cells have the lowest capacity, the various types of stem cells are distinguished from one another by this capacity [46]. Alzheimer's disease-induced anatomical and functional deficits in the brain may be partially compensated for by stem cell transplantation, which replaces cells in the patient's brain. Stem cells must not develop into tumours and be safe and compatible with the patient. Totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells are the five distinct types of stem cells. The inner cell mass is made up of pluripotent stem cells, which are created from these cells. Additionally, this structure contains pluripotent cells [47]. Although pluripotent cells can develop into all three germ layers, they cannot develop into extraembryonic structures. One instance of it consists of pluripotent cells created by embryonic stem cells, which can be produced from the embryo's regular epiblasts. Similar to pluripotent stem cells, these are derived from somatic cells [48]. It is possible for multipotent cells to produce a particular cell line [54]. An outstanding illustration of these cells that can differentiate into many types of blood cells is haematopoietic stem cells. A wide variety of cell lines can be produced from oligopotent stem cells. Myeloid stem cells, which are capable of producing several types of WBCs, are one example of it [49]. The ability of unipotent stem cells to differentiate into numerous types of cells is highly limited; they can only differentiate into one type of cell. Their ability to create a single type of cell is limited [50]. The source from which stem cells originate is another factor used to classify them. Embryonic stem cells, neural stem cells, adult stem cells (including MSCs), and induced pluripotent stem cells are the different types of stem cells [56]. The ESCs found in the inner cell mass of the blastocyst on days five and six following fertilisation have the ability to produce all cells originating from the three germ layers, including ectoderm, mesoderm, and endoderm. Pluripotency is assigned to ESCs by transcription factors (TFs) such as Oct-4 and Nanog [51]. Adult stem cells do not provide an immunological barrier during transplantation and use MSCs that were taken from the patient. Wharton's jelly, bone marrow, amniotic fluid, menstrual blood, and the umbilical cord are among the various sources from which these MSCs are isolated. By altering the somatic cells' genetic composition, iPSCs can be produced from patients' normal somatic cells. These were initially produced in a mouse model by Takahashi and Yamanaka by introducing the oncoproteins c-Myc and Kruppel-like factor-4 (Klf-4), as well as the octamer binding TF 3/4 (Oct-3/4), and SOX-2 [52]. The term Yamanaka TFs refers to these transcription factors. In 2007, the same process was carried out again using these four Yamanaka TFs and human fibroblasts from the skin's dermis. This process produced iPSCs that successfully replicated the ESCs' high differentiation power, epigenetics, pluripotent genes, and telomerase enzyme expression [51]. The stem cell-based treatment for AD is depicted in Figure 7.

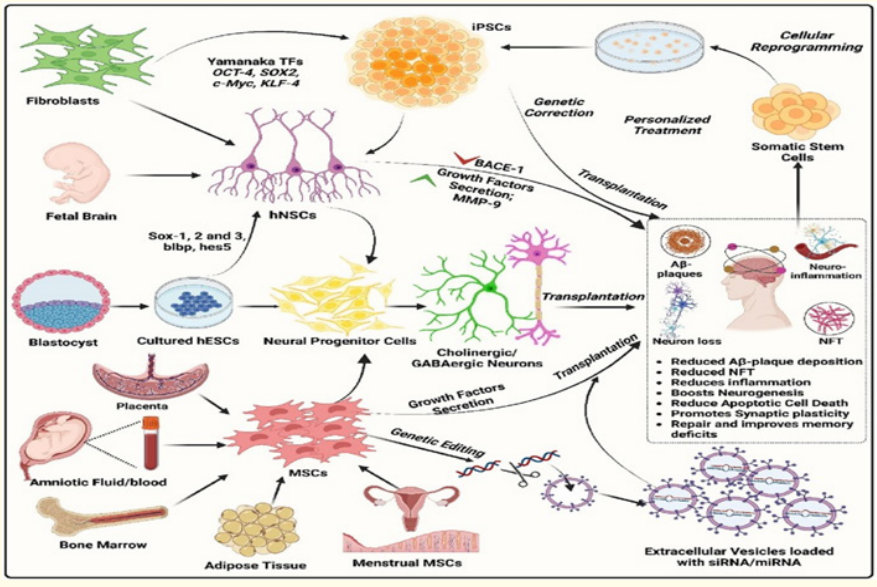


**Figure 7:** Therapeutic intervention for AD using stem cells. The foundation of stem-cell therapy is in the multipotency and self-renewal capacity of stem cells. Neuronal stem cells (NSCs), neural progenitor cells (NPCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) are being investigated for their potential as therapeutics. In vitro, stem cells can be obtained and propagated using a variety of techniques. These stem cells can come from a variety of cells and tissues, including the placenta, fibroblasts, foetal tissues, adipose tissue, and embryonic stem cells. In vitro culture is possible when specific growth factors are present. Additionally, patients' own differentiated cells can be reprogrammed to produce iPSCs. Furthermore, it is possible to convert MSCs to release extracellular vesicles that contain siRNA or miRNA that specifically targets amyloid β plaques. Lastly, these altered or generated stem cells that are put back into the patient have anti-inflammatory and anti-amyloidogenic properties and can increase the metabolic activity of nerve cells [51].

## CRISPER/Cas 9: Gene editing tool

Recently identified and promising, CRISPR/Cas9 is a new genome editing tool that can be used to cure diseases for which there are few or no available treatments. Ishino first recognized this instrument in 1987 (Figure 9). Subsequent research has revealed that the CRISPR/Cas9 system is a crucial component of a bacterium's defenses against the unwanted integration of mobile genetic components like viruses and plasmids. Additionally, CRISPR/Cas9 was introduced to laboratory settings to explore its potential because to the groundbreaking work of Doudna and Charpentier. Recent in-depth study on CRISPR/Cas9 has shown that it greatly increases editing efficiency and reduces off-target effects, and it is widely employed for both fundamental and translational research.

The Cas9 enzyme and single-guide RNA (sgRNA) are the two primary parts of CRISPR/Cas9. The sgRNA recognises the target DNA sequence; different characteristics are taken into account throughout the design process to increase specificity [58]. The Cas9-protein, on the other hand, functions as an endonuclease and cuts DNA double strands like a pair of molecular scissors (Figure 3). The two categories of CRISPR/Cas systems are Class 1 (type I, type III, and type IV) and Class 2 (type II, type V, and type VI). While Class 2 uses a single Cas protein, which makes it easy and desirable for genome editing, Class 1 has many Cas proteins that cooperate. One of the most studied and applied Class 2 CRISPR/Cas9 systems in drug development is type II. The Cas9 protein recognises the target gene sequence and then produces a double standard break. To fix this break, two different approaches might be used: non-ho-

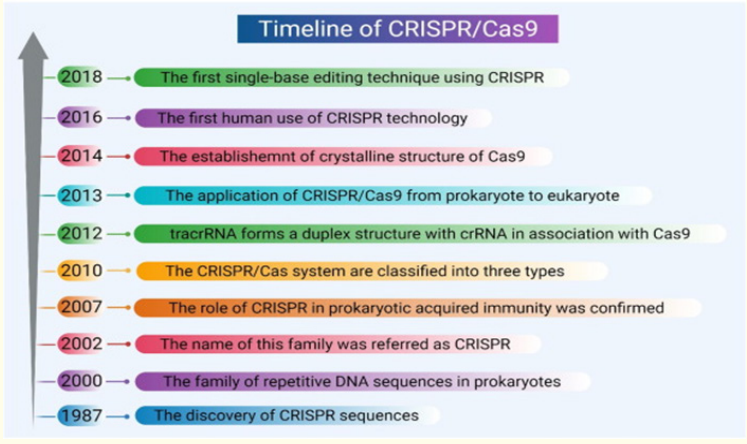


**Figure 8:** The CRISPR/Cas9 timeline, crRNA: CRISPR-derived RNA; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated proteins 9 system [53].

mologous end joining (NHEJ) or homology-directed repair (HDR). While NHEJ causes insertion and deletion, which can result in premature stop codons and/or DNA frameshifts, ultimately leading to gene inactivation, the HDR pathway assists in substituting the right sequence for the altered or defective one. The appropriate DNA sequences are inserted into the targeted location to start HDR with the help of a donor DNA template. Furthermore, NHEJ can occur in any phase of the cell cycle, whereas HDR is restricted to the G or S phase. Although it is less effective than the NHEJ pathway, the HDR pathway generally offers a very dependable DNA repair mechanism. The CRISPR/Cas9 system can be used in three different ways to modify the desired gene: via plasmid-borne CRISPR/Cas9, purified Cas9/sgRNA complexes, or a combination of Cas9-mRNA and sgRNA [53,59].

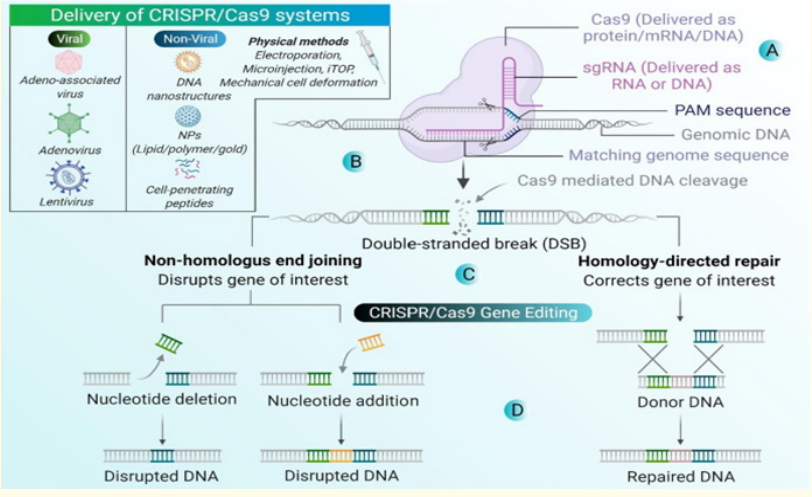


**Figure 9:** A cartoon schematic that shows the steps of the CRISPR/Cas9 technology. (A) A specially made sgRNA (guide RNA) bonds with Cas9 (CRISPR-associated endonuclease), a DNAase that can cause a double strand break, to produce a Cas9-sgRNA complex after matching with a genomic DNA sequence that contains mutations. (B) The target genomic DNA is associated with the Cas9-sgRNA complex. Using sgRNA, Cas9 looks for the right sequence in the target DNA and uses PAMs (protospacer adjacent motifs) to identify it. These sequences are typically 2–6 base pairs long and are located 3–4 nucleotides downstream from the cut site, where they typically act as a tag. (C) DNA cleavage mediated by Cas9 results in double strand breaks (DSB). (D) When a double strand break (DSB) occurs, the DNA repair process is triggered to fix the break by closing the gap via either homology directed repair (HDR) or non-homologous end joining (NHEJ) [53].

## Lifestyle and non-pharmacological interventions

According to research, dementia risk may be elevated by the same heart disease risk factors. It's unclear whether these variables increase risk via causing blood vessel abnormalities in the brain or by exacerbating Alzheimer's disease-related brain changes. Among the causes is a lack of physical activity. Fatigue, smoking or coming into contact with smoke, elevated blood pressure elevated cholesterol. Type 2 diabetes is not well controlled.

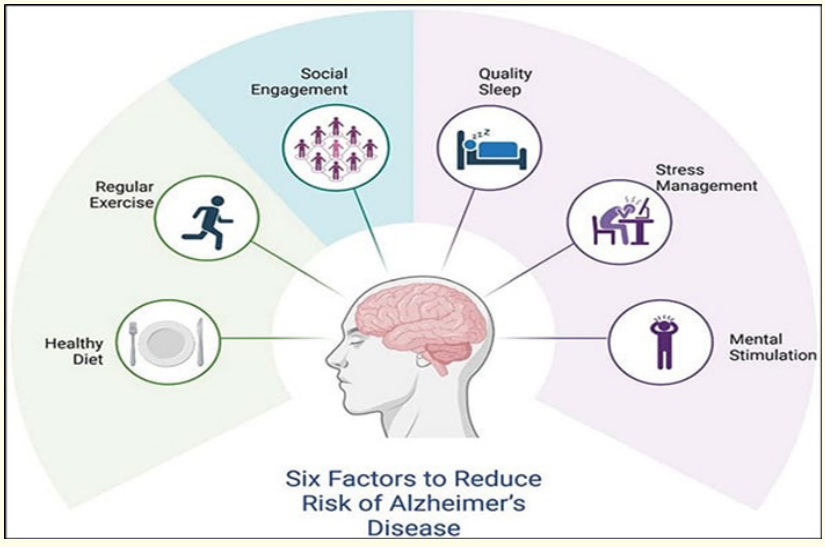


**Figure 10:** Six factors to reduce risk of Alzheimer's Disease [60].

The risk of dementia is increased in middle age, especially when there are high levels of low-density lipoprotein, or LDL, cholesterol. According to research, those under 65 who have elevated LDL cholesterol are more likely to develop dementia. Taking medications to reduce LDL cholesterol, however, did not increase the risk. To some extent, altering your living behavior can change your risk because all of these factors are modifiable. A low-fat, fruit-and vegetable-rich diet and frequent exercise, for instance, are linked to a decreased risk of Alzheimer's disease. There is no way to avoid Alzheimer's. But altering your way of living can reduce your chance of contracting the illness. There is evidence to show that reducing your risk of cardiovascular disease may also lessen your chance of dementia. Maintaining a heart-healthy lifestyle can help reduce the risk of dementia. Do frequent exercise. Follow a Mediterranean diet that emphasizes meals low in saturated fat, fresh produce, and healthy oils. Cooperate with your physician to control diabetes, high blood pressure, and excessive cholesterol. Keep an eye on your cholesterol levels, especially those of low-density lipoprotein, or LDL. For those under 65, high LDL cholesterol increases the risk of dementia. The risk is not increased, however, by taking medications to reduce LDL cholesterol. If you smoke, seek assistance from a healthcare provider to stop. According to a big, long-term study conducted in Finland, changing one's lifestyle can assist those at risk of dementia experience less cognitive loss. Participants in the study received both individual and group sessions with an emphasis on social activities, exercise, and food. A Mediterranean diet has been shown in numerous studies to improve cognitive performance and delay the ageing process. A Mediterranean diet emphasizes plant-based foods such almonds, olive oil, fish, poultry, fruits, vegetables, and grains. Foods high in trans and saturated fats, such as cheese, butter, margarine, red meat, fried foods, and pastries, are reduced in the diet. Treating eyesight and hearing impairments is also crucial. According to studies, untreated eyesight loss increases the risk of dementia and cognitive impairment. Additionally, research has shown that dementia risk is increased in those with hearing loss. On the other hand, dementia risk was reduced in those who wore hearing aids. According to other research, maintaining mental and social engagement is associated with intact cognitive abilities in later life and a decreased risk of Alzheimer's disease. Reading, dancing, playing board games, making art, playing an instrument, attending social gatherings, and other pursuits are all included in this.

## Conclusion

Memory loss and cognitive dysfunction are hallmarks of AD, a neurodegenerative illness that progresses over time. It is commonly known that patients have pathological characteristics including NFTs and Aβ plaques. The specific effects of these changes on the onset and progression of AD or the intricate relationships between different pathogenic episodes, however, are not adequately explained by the current theory. Current treatment methods are not curative; rather, they are meant to halt the progression of AD. Since the disease's earliest lesions begin at an early preclinical stage and proceed subtly over years, preventative strategies are crucial for the primary prevention of cognitive symptoms. Tau-related neurodegeneration and amyloidosis are the primary pathophysiological processes of AD, and they follow distinct temporal and topographical routes. For example, amyloidosis in the brain begins in neocortical areas and progresses to subcortical areas. Conversely, neurodegeneration begins on the locus coeruleus and continues into the neocortical and transentorrinal areas. The topography of neurofibrillary tangles is strongly associated with cognitive and behavioral characteristics of AD.

Body fluids, imaging investigations, and clinical biomarkers are some of the criteria that have been put out for a more precise diagnosis of AD. The prognosis of AD does not change despite treatment, which just addresses symptoms. It is thought to be the first-line treatment for all AD patients. Numerous studies have demonstrated that changing lifestyle choices like diet and exercise can enhance brain health and lessen AD without the need for medicinal intervention. More recently, studies have been concentrating on addressing the pathogenic characteristics of AD, namely p-tau and Aβ. Although there has been progress in recent decades, the precise etiology of the disease remains unclear due to its complex nature. In addition to the well-known pathological features (neurofibrillary tangles resulting from Tau hyperphosphorylation and aggregates of Aβ due to a malfunction in its removal), oxidative stress, neuroinflammation, metal ion imbalance, and mitochondrial dysfunction have also been shown to be significant contributors to the illness.

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